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Concentrations of phthalates and DINCH metabolites in pooled urine from Queensland, Australia

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Abstract

Dialkyl phthalate esters (phthalates) are ubiquitous chemicals used extensively as plasticizers, solvents and adhesives in a range of industrial and consumer products. 1,2-Cyclohexane dicarboxylic acid, diisononyl ester (DINCH) is a phthalate alternative introduced due to a more favourable toxicological profile, but exposure is largely uncharacterised. The aim of this study was to provide the first assessment of exposure to phthalates and DINCH in the general Australian population. De-identified urine specimens stratified by age and sex were obtained from a community-based pathology laboratory and pooled (n = 24 pools of 100). Concentrations of free and total species were measured using online solid phase extraction isotope dilution high performance liquid chromatography tandem mass spectrometry. Concentrations ranged from 2.4 to 71.9 ng/mL for metabolites of di(2-ethylhexyl)phthalate, and from <0.5 to 775 ng/mL for all other metabolites. Our data suggest that phthalate metabolites concentrations in Australia were at least two times higher than in the United States and Germany; and may be related to legislative differences among countries. DINCH metabolite concentrations were comparatively low and consistent with the limited data available. Ongoing biomonitoring among the general Australian population may help assess temporal trends in exposure and assess the effectiveness of actions aimed at reducing exposures.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC or the views of the Australian Department of the Environment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2015.12.016.

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Keywords

Biomonitoring; Urine; Phthalates; DINCH; Plasticizers; Population monitoring; Children; Australia

1. Introduction

Dialkyl phthalate esters (phthalates) are man-made chemicals produced in excess of 1 million tonnes globally per year, and are extensively-used in plastics manufacture (Koch and Calafat, 2009). Phthalates, which vary in molecular weight and physical–chemical properties according to their carbon alkyl chain and branching pattern, can be loosely grouped into low-molecular-weight (LMW) and high-molecular-weight (HMW), each with different industrial uses (Alves et al., 2014). HMW phthalates are commonly used as plasticizers in flexible polyvinyl chloride (PVC) (CPSC, 2014); LMW phthalates are generally used in solvents, adhesives, waxes, inks, cosmetics, perfumes, insecticides and pharmaceuticals (Alves et al., 2014; Frederiksen et al., 2007) (Table S1). Phthalates are continuously released into the environment due to the absence of covalent bonding with the products in which they are used (NRC, 2008). Diet is the major route of exposure to HMW phthalates (Fromme et al., 2004), while for LMW phthalates exposure occurs primarily through use of personal care products such as cosmetics (CPSC, 2014; Takaro et al., 2010). 1,2-Cyclohexane dicarboxylic acid, diisononyl ester (DINCH) is a complex mixture of nine-carbon branched-chain isomers. DINCH was introduced in 2002 as a replacement for some HMW phthalates in many PVC products, including medical devices, toys and food packaging (CPSC, 2010) due to lower migration rate (Welle et al., 2005) and more favourable toxicological profile (Fromme et al., 2016; Bhat et al., 2014) than traditional phthalates.

Phthalates have received considerable attention because of their ubiquitous presence in the environment, frequent detection in human biomonitoring studies, and demonstrated toxicity in rodents and humans (Alves et al., 2014; CPSC, 2014; Frederiksen et al., 2007; Hannon and Flaws, 2015; Kay et al., 2014; Miodovnik et al., 2014). Phthalates are rapidly metabolized via hydrolysis and subsequent oxidation reactions, with metabolites excreted in the urine and faeces (Silva et al., 2003). The phthalate monoesters, formed during the phase I biotransformation, can be excreted unchanged or they can undergo phase II biotransformation to produce glucuronide-conjugated monoesters. The phthalate monoesters may be further metabolized to produce oxidative products and their glucuronide conjugates (Silva et al., 2003, 2006, 2007b). Human metabolism studies have shown that monoesters are the major urinary metabolites of LMW phthalates, whereas oxidized metabolites are the dominant metabolites of HMW phthalates, and these metabolites are commonly used as biomarkers of exposure to phthalates (Anderson et al., 2001; Wittassek et al., 2011; Wittassek and Angerer, 2008). Similarly, oxidative metabolites of DINCH have been identified, and serve as effective biomarkers to assess environmental exposures to DINCH (Koch et al., 2013a; Silva et al., 2013). The parent compounds, their major urinary metabolites and abbreviations are summarised in Table 1.

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Several large-scale population based biomonitoring studies have been undertaken to evaluate phthalate exposures internationally, such as the National Health and Nutrition Examination Survey (NHANES) in the USA (CDC, 2015), and the Canadian Health Measures Survey in Canada (Health Canada 2015; Saravanabhavan et al., 2013), but little information exists of DINCH exposure. Two recent Australian studies presented data on phthalates metabolites concentrations for small, specific populations of South Australian men (Bai et al., 2015) and pregnant women (Hart et al., 2013), but no broad surveillance programmes for non-persistent environmental chemicals exist in Australia at this time. The aim of this study was to provide a preliminary characterisation of phthalates and phthalate alternative DINCH exposure in a convenience sample of the general Australian population using pooled urine samples, and to generate some of the first data on phthalate and DINCH exposures in children <5 years.

2. Materials and methods

2.1. Study population and sample collection

De-identified specimens were obtained from a community-based pathology laboratory (Sullivan Nicolaides Pathology, Taringa, QLD, Australia) from surplus stored urine that had been collected and analysed as part of routine testing in Queensland, Australia. These samples may have been first morning voids, or samples of convenience collected at any time of the day. Urine specimens were collected from November 2012 to November 2013 in sterile polyethylene urine specimen containers, refrigerated for up to three days, and frozen immediately following collection. As this was a pre-existing, convenience population no specific sampling protocols were employed. This work was approved by the University of Queensland ethics committee (approval number 2013000397). The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

2.2. Pooling protocol

Descriptive information about each specimen included date of birth, date of sample collection and sex. Before pooling, samples were stratified by age and sex into the following strata: 0–4, 5–14, 15–29, 30–44, 45–59, >60 years. The mean age of each pool was calculated from the average age of the individuals making up that pool. A total of 2400 individual specimens were combined into 24 pools, with 100 individual specimens contributing to each pool, and a replicate pool for each strata (n = 24 pools of 100). Specimens were pooled based on volume, where each individual in the pool contributed the same volume to the pool, thus the concentration measured in each pool is equivalent to the arithmetic mean of the concentration in each individual sample contributing to the pool (Caudill, 2010; Mary-Huard, 2007). During pooling, individual urine specimens were thawed, homogenised and aliquoted, after which the pooled sample was homogenised, divided into smaller aliquots and frozen until analysis. A synthetic urine sample was included as a procedural blank (Calafat and Sampson, 2009. Refer to SI for further information). No measures of creatinine or specific gravity were available for individual samples.

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2.3. Chemical analysis

The 14 phthalate and phthalate alternative metabolites measured in urine at the CDC (Atlanta, USA) were monoethyl phthalate (MEP), mono-n-butyl phthalate (MBP), mono-3-carboxypropyl phthalate (MCPP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-carboxypentyl phthalate (MECPP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), monobenzyl phthalate (MBzP), mono-isobutyl phthalate (MiBP), monomethyl phthalate (MMP), mono-isononyl phthalate (MNP), mono carboxyisooctyl phthalates (MCOP), mono carboxyisononyl phthalates (MCNP), and cyclohexane-1,2-dicarboxylic acid, monohydroxy isononyl ester (MHINCH) (Table 1). Concentrations of the free and total (sum of free and conjugated) species of these compounds were measured using online solid phase extraction-high performance liquid chromatography isotope dilution tandem mass spectrometry as described previously (Silva et al., 2007a). Concentrations of free species were obtained by omitting the enzymatic hydrolysis. To monitor for accuracy and precision, each analytical run included calibration standards, reagent blanks, and quality control materials of high and low concentrations. The limits of detection (LOD) ranged from 0.2 to 0.6 ng/mL and are listed in Table 2.

2.4. Statistical analysis

The influence of age (in years) and sex on chemical concentration was assessed via linear regression on ln-transformed urinary concentration, as follows:

$$\mathrm{Ln}(concentration) = I + \beta_1 * Age + \beta_2 * Sex\,.$$

An interaction term between age and sex was included in the models, but was not significant. We summed the concentrations of DEHP metabolites (MEHP, MEOHP, MEHHP and MECPP) to create a summary measure (∑DEHP). All analyses were conducted using IBM SPSS Statistics, version 22 for Windows, (IBM, New York, USA, www.ibm.com). Criteria for significance were set as $p < 0.05$. Outliers in the ln-transformed values were identified using the outlier labelling rule (Hoaglin and Iglewicz, 1987). Concentrations beneath the LOD were replaced with LOD/$\sqrt{2}$.

3. Results

Results for the 14 phthalate and DINCH metabolites and ∑DEHP concentrations for samples pooled by age and sex (n = 24) are summarised in Table 2. With the exception of MMP (7 of 24 pools had concentrations <LOD), all other biomarkers were detected in all pooled samples. Concentrations varied by two orders of magnitude for the different compounds, ranging from 2.4 to 71.9 ng/mL for metabolites of DEHP; (Fig. 1) 50.5 to 147 ng/mL for ∑DEHP; 1.2 to 16.2 ng/mL for MHINCH; and <0.5 to 775 ng/mL for all other metabolites. The highest concentrations were detected for MEP (geometric mean [GM] 127 ng/mL), MECPP (GM 41.6 ng/mL) and MCOP (GM 38.9 ng/mL), followed by MEHHP (25.6 ng/mL), MBP (24.4 ng/mL) and MiBP (20.6 ng/mL), which reflect exposure to diethyl phthalate (DEP), DEHP, di-isononyl phthalate (DINP), DEHP, di-n-butyl phthalate (DnBP) and di-iso-butyl phthalate (DiBP) respectively (Table 1). Extreme values were observed for MCOP, MCNP (124 and 6.1 ng/mL respectively, pool 9) and MEP (775 ng/mL, pool 19)

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(Table 2), but these were not deemed statistical outliers (Hoaglin and Iglewicz, 1987). It should be noted that MCPP is a major metabolite of DnOP, but it is also a minor metabolite of DBP and other HMW phthalates like DINP and DIDP. Therefore, it is possible that the concentrations of MCPP in humans reflect exposure not only to DnOP, but to other phthalates (Kochet al., 2012; Calafat et al., 2006). We did not detect the target compounds in the synthetic urine sample.

The concentration of free phthalate species are shown in Table S2. For the relatively more lipophilic phthalate metabolites namely MBP, MiBP, MBzP, MEHP, MEHHP and MEOHP conjugates are the major urinary metabolites and percentage of free species is relatively low (2–20%). By contrast, MEP, MMP and MCPP, the most hydrophilic metabolites, along with MECPP, MCOP and MCNP are largely excreted in their free form (37–100% free).

The results of the regression model are summarised in Table 3. There was a small but significant inverse association between age and concentration for MECPP ($p = 0 < 0.001$), MEOHP ($p = 0.003$), MiBP ($p < 0.001$), MBP ($p = 0.002$) and MBzP ($p = 0.014$); but there was no association for MEHHP, MEHP, MCOP, MNP, MHINCH or MCPP. For MEP the opposite trend was observed, with increasing concentration with age ($p = 0.001$, Fig. S1). There were no significant differences between male and female pools for all phthalate metabolites except MBzP, where male pools had concentrations 1.4 times higher than female pools ($p = 0.008$). There was no significant interaction between age and sex for MBzP.

4. Discussion

4.1. Concentration and age/sex trends

The highest biomarker concentrations were measured in the youngest age groups for MECPP, MEOHP, MiBP, MBP and MBzP, and these were the compounds for which the age * sex regression model provided the best fit (R^2 0.241 to 0.569, Table 3). Overall the model was a poor fit for MEHHP, MEHP, MCOP, MCPP and MNP ($R^2 < 0.15$, Table 3) where there was considerable scatter in the data (e.g. for MCPP, Fig. S1) or where the measured concentrations were relatively consistent across the age profile (e.g. for MEHP, Fig. S2). In this case, it is likely that factors other than age and sex — such as behaviour or exposure source e.g. consumer product use — may affect concentration. For example, for MCOP and MHINCH urinary concentrations are highest in the 15–29 and 30–44 year age groups, compared to other age groups, which may be the result of diet, as this is the primary source of exposure to DINP (Wormuth et al., 2006) and may also be important for DINCH, although the exposure pathways for DINCH remain largely understudied (EFSA, 2006; Schütze et al., 2015).

Higher urinary phthalate metabolite concentrations are generally measured in children than in adolescents and adults (Frederiksen et al., 2007; Schütze et al., 2014, 2015; Wormuth et al., 2006; Silva et al., 2004; Wittassek et al., 2011), likely due to children’s higher energy requirements per kilogramme body weight (WHO, 2011), resulting is greater exposure via contaminated food. Exposure sources differ significantly between young children and adults due to age-dependant behaviours — hand-to-mouth activity and higher dust exposure in children; and the use of specific personal care products in adolescents and adults (e.g. for

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relatively higher exposure to DEP and DnBP). Oxidative phthalate metabolism seems to be slightly favoured in neonates and young children compared with adults (Koch et al., 2006; Koch and Calafat, 2009), and the relatively higher concentrations of monoester phthalates in children could be due to different metabolic pathways compared with adults, who mainly excrete the high molecular weight phthalates as secondary metabolites (Frederiksen et al., 2007).

Interestingly the trend for MEP is opposite to what is observed for the other phthalate metabolites, as concentration increases with increasing age ($p < 0.001$). MEP, a metabolite of DEP, is a chemical commonly used in fragrances and other personal care products, which may be used in greater amounts and with greater frequency in adolescents and adults, than in children. However, DnBP is also used in products with volatile components such as perfumes, nail polishes, and hair sprays (Wormuth et al., 2006); and MBP has an inverse association between concentration and age, so this may not be the case. Further, air and dust are additional exposure sources to DnBP (Koch et al., 2013b), and we would expect exposure from these sources to be greater in children (WHO, 2011). A possible explanation is the use of some low molecular weight phthalates, such as DEP and DnBP in coatings for oral medications such as omeprazole (CPSC, 2014; Hernández-Díaz et al., 2009), consumed by adults but not children.

Some studies report significantly higher concentrations of the monoester metabolites of short-chain phthalates, particularly DiBP and DnBP, in women (Silva et al., 2004; Wittassek et al., 2011; Trasande et al., 2013). This may be related to more frequent use of personal care products and cosmetics containing such phthalates by women compared with men (Wittassek et al., 2011). However, in this study there were no significant differences between urinary concentrations in male and female pools for MiBP or MBP, or for any of the other phthalate metabolites. The exception was MBzP, where male pools had urinary concentrations approximately 1.4 times higher than females (Table 3). MBzP is used in PVC flooring, paint, adhesives and food packaging (CPSC, 2014, Wormuth et al., 2006, Table S1), and the main exposure sources are dust for infants and children, and contaminated food for adults (CPSC, 2014, Wormuth et al., 2006). Exposure to these sources is unlikely to vary by sex.

4.2. Comparison with international data

The results of the current study are compared with select biomonitoring data for phthalate and DINCH metabolites from international populations in Table 4. Concentrations of DEHP metabolites were generally consistent with studies from Germany (Kasper-Sonnenberg et al., 2012; Koch and Calafat, 2009) and Canada (Saravanabhavan et al., 2013), but were higher than concentrations in pregnant women from Puerto Rico (Cantonwine et al., 2014), and were approximate two times higher than the general US population (CDC, 2015). Noteworthy is that concentrations of MECPP in Australian children 0–5 years (GM 49.4 ng/mL) were similar to children in Germany (GM 41.8 ng/mL, n = 145) (Kasper-Sonnenberg et al., 2012; Koch and Calafat, 2009), substantially higher than children in Denmark (GM 23 ng/mL, n = 145) (Frederiksen et al., 2013), but significantly lower than children in Spain (GM 115 ng/mL, n = 19) (Casas et al., 2011) (Table 4).

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In addition to DEHP metabolites, overall the mean urinary concentrations of MBP, MiBP, MCOP, MCPP and MEP are higher in the Australian pools compared with NHANES data from the United States (CDC, 2015) (Table 4). In the case of MiBP, MCOP and MCPP specifically, Australian concentrations are at least three times greater than the USA (20.6, 38.9 and 6.5 ng/mL versus 6.00, 19.7 and 3.01 ng/mL respectively). Measured concentrations of MCOP in Australia (GM 38.9 ng/mL) are higher than in Denmark (5.4 ng/mL, n = 145) (Frederiksen et al., 2013), Germany (5.6 ng/mL, n = 103 (Kasper-Sonnenberg et al., 2012) and 5.6 ng/mL, n = 45 (Koch and Calafat, 2009)), Puerto Rico (16.4 ng/mL, n = 139) (Cantonwine et al., 2014), Spain (4.0 ng/mL, n = 118) (Casas et al., 2011) and USA (19.7 ng/mL, n = 2489) (CDC, 2015). MCOP is a metabolite of DINP, which is the most important substitute for DEHP in its applications today (Zota et al., 2014; Wormuth et al., 2006). The MCOP concentration differences by country may be the result of different legislative measures across countries. For example, in Australia there are regulations in place limiting DEHP content in children's plastic products (ACCC, 2010; Australian Government, 2011), but not DINP. On the contrary, in the USA, Europe and Canada there are restrictions for the use of DINP in certain toys and childcare items (CPSIA, 2008; EU, 2005; CCPSA, 2010). However, as there is not a linear age–concentration profile for MCOP concentrations in the pools (Fig. S2), we speculate that the higher average concentrations of MCOP may be due to the use of DINP in building materials such as flooring and wall coverings in Australian buildings compared with elsewhere.

MEP is the metabolite detected at the highest mean concentration in many different populations globally (Table 4). In the USA there have been significant reductions in DEP exposures in recent years — geometric mean concentrations of its metabolite MEP were 42% lower in the NHANES 2009–10 survey cycle compared with the 2001–02 cycle (CDC, 2015). DEP is not regulated in the USA, but the success of advocacy efforts by public health and environmental organizations such as the Campaign for Safe Cosmetics (2014) (see www.safecosmetics.org) may explain some of these findings (Zota et al., 2014). Additionally the USA has observed a decline in the general population exposure to those phthalates that have been the focus of legislative activities, including bans on DEHP, butyl benzyl phthalate (BBzP) and DnBP in children's products (CPSIA, 2008; US EPA, 2012). A similar decline may be observed in DEHP exposures in Australia following a recent ban (March 2010) by the Australian Government prohibiting use of DEHP above 1% w/w in children's plastic products that are intended for use by children up to and including 36 months of age and can readily be sucked and/or chewed (e.g. toys, dummies, teething rings, feeding bottles) (ACCC, 2010; Australian Government, 2011); but no historical phthalate exposure data exist to assess any temporal trends. This decline may be accompanied by a subsequent increase in exposure to phthalate alternatives like DINCH, such as the 19% and 98% increases in detection frequency noted in USA (Silva et al., 2013) and Germany (Schütze et al., 2014), respectively over a 12–13 year period. Ongoing biomonitoring among the general Australian population may help assess temporal trends in exposure and assess the effectiveness of actions aimed at reducing exposures.

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4.3. Strengths and limitations

4.3.1. Study population—The study population consisted of samples collected during the course of routine pathology testing which were surplus to requirement. Because collection was not randomised, the samples are not statistically representative of the Australian population as a whole. However there is no reason to expect exposure to the target compounds to be different in this community pathology-sourced population than in the general Australian population. As discussed above, because this was a convenience population no specific sampling protocols (e.g., collection containers, collection protocol, sample storage) were employed. However, synthetic urine was collected, stored and processed under conditions simulating real sample conditions during pooling and extraction, and in these synthetic urine samples concentrations of all biomarkers were <LOD. Moreover, the percentage of the target analytes excreted in their conjugated form are consistent with the expected percentages based on the physicochemical properties of each biomarker, and with results reported previously (Silva et al., 2003, 2006, 2007b; Frederiksen et al., 2007). Together these findings suggest that there was no systematic contamination resulting from the sampling and pooling protocols. No creatinine or specific gravity data were available for the samples used in this study. However, for the interpretation of pooled measurements as representative measures of average concentration, variation in individual sample hydration status is expected to be averaged out and not introduce significant bias to the estimated average concentrations and excretion rates. The use of pooled pathology specimens is advantageous as it saves significantly on analytical costs, reduces the time and resources required for participants' recruitment, and may avoid ethical difficulties associated with reporting individual results (reviewed in Heffernan et al., 2014).

This study provides the first data on exposure to phthalates and DINCH for the general Australian population, and is one of the few studies conducted on this scale globally. The highest concentrations were measured in the youngest age groups for some phthalate metabolites (MECPP, MEOHP, MiBP, MBP, MBzP) but not others (MCOP, MHiNCH). For MEP, the highest concentrations were measured in the oldest age groups. There were no significant differences between males and females. In general, phthalate metabolite concentrations in Australia are at least two times higher than in other countries, including the United States and Germany, and this may be due to differences in legislation restricting the use of some compounds. DINCH concentrations were relatively low and consistent with the limited data available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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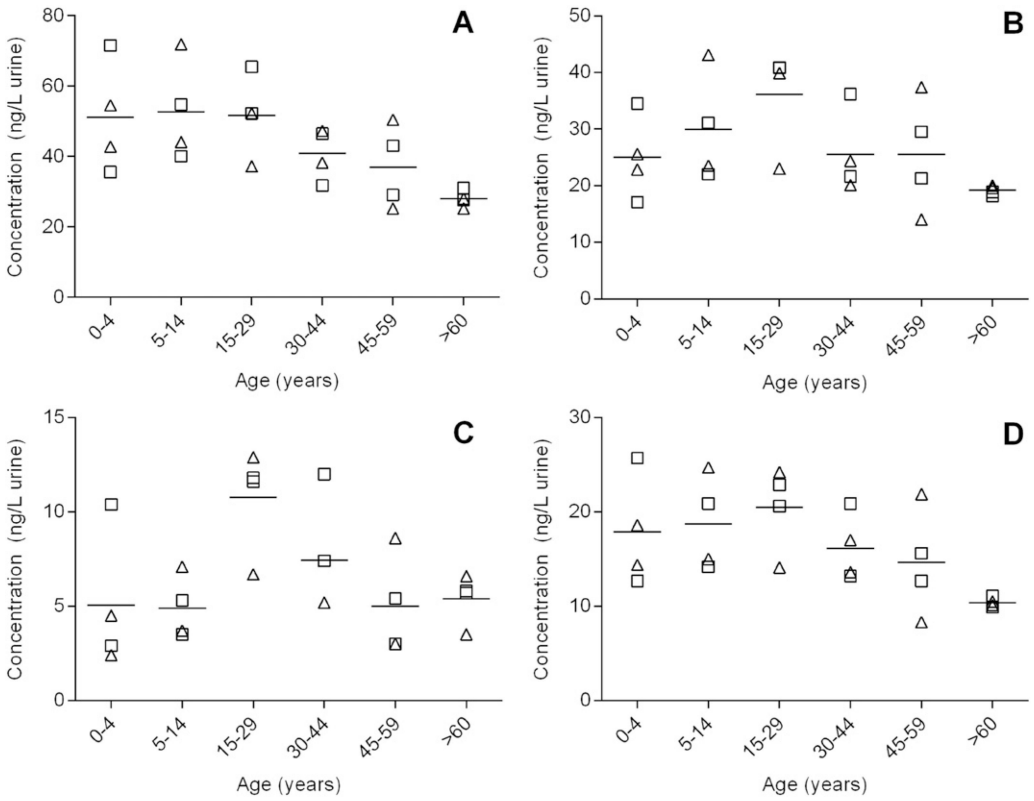

Fig. 1.

Urinary total concentration (ng/mL) versus age (years) for DEHP phthalate metabolites (MECPP (A), MEHHP (B), MEHP (C) and MEOHP (D)). Triangles denote female pools, squares denote male pools. Horizontal line indicates mean concentration of four pools in each age strata.

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Table 1

Main urinary biomarkers of phthalates and phthalate alternative DINCH.

Parent compound	Abbreviation	Urinary biomarker	Abbreviation
Low molecular weight phthalates			
Di-n-butyl phthalate	DnBP[a]	Mono-butyl phthalate	MBP
Diisobutyl phthalate	DiBP	Mono-isobutyl phthalate	MiBP
Diethyl phthalate	DEP	Monoethyl phthalate	MEP
Dimethyl phthalate	DMP	Monomethtyl phthalate	MMP
High molecular weight phthalates			
Butyl benzyl phthalate	BBzP	Monobenzyl phthalate	MBzP
Di(2-ethylhexyl) phthalate	DEHP	Mono(2-ethylhexyl) phthalate	MEHP
		Mono(2-ethyl-5-hydroxyhexyl) phthalate[b]	MEHHP
		Mono(2-ethyl-5-oxohexyl) phthalate[b]	MEOHP
		Mono(2-ethyl-5-caboxypentyl) phthalate[b]	MECPP
Diisononyl phthalate	DINP[a]	Monocarboxyoctyl phthalate[b]	MCOP
		Mono-isononyl phthalate	MNP
Di-n-octyl phthalate[c]	DnOP	Mono(3-carboxypropyl) phthalate[a,b]	MCPP
Diisodecyl phthalate	DIDP[a]	Monocarboxy-isononyl phthalate[b]	MCNP
Other			
1,2-Cyclohexane dicarboxylic acid, diisononyl ester	DINCH	Cyclohexane-1,2-dicarboxylic acid-mono(hydroxy-isononyl) ester	MHINCH

[a]MCPP is also a minor metabolite of DBP and other HMW phthalates like DINP and DIDP.

[b]Secondary (oxidized monoester) phthalate metabolites. Remaining metabolites are primary (hydrolytic monoesters) phthalate metabolites.

[c]In addition to other high molecular weight phthalates.

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Table 2

Summary of pool characteristics and chemical concentrations (ng/mL) per strata for phthalate and DINCH metabolites. Each pool represents 100 individuals.

Pool #	Sex	Age strata (years)	Av. age (years)	MBP	MiBP	MEP	MMP	MBzP	MEHP	MEHHP	MEOHP	MECPP	ΣDEHP	MCOP	MNP	MCPP	MCNP	MHINCH
1	M	0–4	2.93	38.2	33.3	74.1	6.5	9.2	10.4	34.5	25.7	71.6	142	29.1	1.0	16.7	3.0	3.3
2	M		2.74	23.6	21.1	108	1.4	4.3	2.9	17.1	12.7	35.6	68.3	29.4	3.1	4.6	2.6	2.0
3	F		3.33	37.2	31.5	71.4	7.6	6.1	4.5	25.6	18.6	54.6	103	27.0	1.3	4.3	2.3	2.4
4	F		3.24	23.1	22	29.2	<LOD	3.8	2.4	22.9	14.4	42.8	82.5	36.5	1.3	4.4	2.9	1.9
5	M	5–14	8.83	42.9	34.8	47	3.6	10.1	5.3	31.1	20.9	54.8	112	42.0	2.4	5.3	3.1	2.7
6	M		9.21	21.6	23.2	84.8	2.1	5.2	3.5	22.0	14.2	40.1	79.8	30.1	1.8	3.5	2.7	1.8
7	F		8.74	31.3	32.6	95.3	4.0	5.3	7.1	43.1	24.7	71.9	147	31.5	1.6	4.2	3.2	3.1
8	F		9.54	29.4	30.5	65.9	2.0	4.6	3.7	23.5	15.0	44.1	86.3	40.5	2.7	5.9	2.7	3.5
9	M	15–29	24.28	20.5	18.1	80.1	3.5	4.4	11.8	40.9	20.6	65.5	139	124	12.3	15.9	6.1	9.8
10	M		23.98	23.6	21.6	93.8	2.6	6.9	11.6	40.8	22.9	52.3	128	51.8	4.4	7.6	3.7	3.7
11	F		24.05	30.9	31.1	181	1.6	7.8	12.9	39.9	24.2	52.2	129	52.1	3.9	6.4	3.6	4.2
12	F		23.39	24.6	20.3	131	<LOD	5.2	6.7	23.0	14.1	37.2	81.0	47.2	7.3	4.5	2.7	2.0
13	M	30–44	37.77	25.4	24	144	1.5	7.9	12	36.2	20.9	46.5	116	54.1	5.3	7.2	3.2	14.4
14	M		37.33	23.5	19.7	248	1.7	6.7	7.4	21.6	13.2	31.8	74.0	45.9	2.8	8.9	2.4	5.4
15	F		36.73	16.7	15.5	140	7.3	4.6	5.2	20.1	13.6	38.2	77.1	25.2	2.0	4.1	1.9	1.2
16	F		36.78	20.2	18.8	105	<LOD	5.1	5.2	24.4	17.0	47.3	93.9	58.2	3.7	18.5	3.3	16.2
17	M	45–59	52.94	17.5	12.7	239	2.1	4.9	3.0	21.3	12.7	29.1	66.1	45.5	2.4	6.4	2.8	10.8
18	M		53.15	26.5	21.6	142	21.5	5.8	5.4	29.5	15.6	43.0	93.5	50.0	2.3	6.2	3.1	6.0
19	F		53.29	44.8	11	775	3.5	3.1	8.6	37.4	21.9	50.4	118	41.9	7.1	11.2	2.6	1.9
20	F		53.05	15.2	13.8	218	<LOD	3.2	3.0	14.0	8.3	25.2	50.5	33.8	2.1	18.8	2.1	2.4
21	M	>60	73.71	16.1	13.6	242	1.1	4.3	5.8	18.2	9.9	27.6	61.5	26.7	2.4	3.9	2.3	7.3
22	M		71.91	35.7	16.3	107	<LOD	5.9	5.7	18.9	11.1	31.1	66.8	26.6	2.2	5.1	2.0	2.9
23	F		75.07	15.5	17.8	187	<LOD	3.4	6.6	19.6	10.5	28.0	64.7	29.9	1.2	3.8	2.3	13.2
24	F		76.08	13.8	14.8	266	<LOD	3.1	3.5	20.0	10.1	25.2	58.8	27.0	1.7	4.1	2.4	2.7
		Average	21.43	24.4	20.6	127	3.1	5.2	5.7	25.6	15.6	41.6	88.5	38.9	2.7	6.5	2.8	3.9
		LOD (ng/mL)		0.4	0.2	0.6	0.5	0.3	0.5	0.2	0.2	0.2	N/A	0.2	0.5	0.2	0.2	0.4

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Table 3

Regression parameters (β (95% CI)) for log-transformed urinary total concentrations (ng/mL) of phthalate and DINCH metabolites and ΣDEHP (sum of MEHP,MEOHP,MEHHP, MECPP) (n = 24 pooled samples).

Compound	Intercept	Age (years)	Sex	R^2
MBP	3.377 (3.120 to 3.634)	−0.006 * −0.021 to −0.001	0.062 −0.200 to 0.325	0.241
MiBP	3.346 (3.156 to 3.535)	−0.01 *** (−0.014 to −0.006)	0.15 (−0.178 to 0.208)	0.569
MEP	4.282 (3.863 to 4.700)	0.019 *** (0.010 to 0.027)	− 0.129 (−0.555 to 0.298)	0.497
MMP	0.695 (−0.223 to 1.614)	−0.017 (−0.036 to 0.002)	− 0.72 (−0.217 to 1.656)	0.224
MBzP	1.679 (1.463 to 1.896)	− 0.006 * (−0.010 to −0.001)	0.311 ** (0.090 to 0.532)	0.430
MEHP	1.642 (1.215 to 2.068)	0.000 (−0.009 to 0.009)	0.185 (−0.250 to 0.620)	0.036
MEHHP	3.37 (3.113 to 3.628)	− 0.005 (−0.010 to 0.001)	0.059 (−0.204 to 0.322)	0.148
MEOHP	2.979 (2.750 to 3.204)	− 0.008 ** (−0.012 to −0.003)	0.047 (−0.184 to 0.278)	0.358
MECPP	4.007 (3.810 to 4.205)	− 0.009 *** (−0.013 to −0.005)	0.019 (−0.182 to 0.220)	0.484
Σ DEHP	4.694 (4.469 to 4.918)	− 0.007 ** (−0.011 to −0.002)	0.046 (−0.183 to 0.275)	0.313
MCOP	3.651 (3.342 to 3.960)	− 0.002 (−0.008 to 0.005)	0.139 (−0.175 to 0.454)	0.054
MNP	0.873 (0.339 to 1.407)	0.001 (−0.010 to 0.012)	0.159 (−0.386 to 0.703)	0.018
MCPP	1.838 (1.373 to 2.302)	0.000 (−0.010 to 0.009)	0.079 (−0.395 to 0.553)	0.006
MCNP	1.083 (0.894 to 1.273)	− 0.004 (−0.007 to 0.000)	0.12 (−0.074 to 0313)	0.200
MHINCH	0.812 (0.235 to 1.388)	0.011 (−0.001 to 0.023)	0.383 (− 0.205 to 0.971)	0.203

* $p < 0.05$.

** $p < 0.01$.

**** $p \leq 0.001$.

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Table 4

Summary of GM urinary concentrations (ng/mL) of phthalate and DiNCH metabolites for select biomonitoring studies.

Reference	Country	Year	Population age (years) (n)	DnBP	DiBP	DEP	DMP	BBzP	DEHP				DiNP		DnOP	DiDP	DINCH
				MBP	MiBP	MEP	MMP	MBzP	MEHP	MEHHP	MEOHP	MECPP	MCOP	MNP	MCPP	MCNP	MHINCH
This study	Australia	2012–13	0 to >60 (24 pools)	24.7	21.0	130	1.7	5.3	6.0	26.4	16.1	42.9	39.9	2.8	6.7	2.9	N/A
			0–5 (4 pools)	29.7	26.4	63.9	2.2	5.5	4.2	24.3	17.2	49.4	30.3	1.5	6.2	2.7	N/A
Dirtu et al. (2013)	Belgium	2009–12	18–84 (152)[a,b,c]	38	58	74	11	8	3	15	6	16	–	–	–	–	–
			18–84 (43)[b,c,d]	37	65	51	8	6	3	13	6	15	–	–	–	–	–
Saravanabhavan et al. (2013)	Canada	2007–09	6–49 (3236)	23.2	–	56.0	N/A	11.5	3.6	23.5	14.2	–	–	N/A	1.4	–	–
Frederiksen et al. (2013)	Denmark	2011	31–52 (145)	26	48	74	–	6.1	4.7	21	10	15	9.8	0.30	5.4	–	–
			6–11 (145)	39	74	28	–	11	4.5	32	16	23	22	0.88	16	–	–
Philippat et al. (2012)	France	2002–06	22–38 (287)[b,e]	58.1	64.7	105.3	–	0.2	10.5	48.3	36.0	67.2	3.9	–	3.2	3.1	–
Kasper-Sonnenberg et al. (2012)	Germany	2007–09	29–49 (103)	32.8	44.5	50.5	1.3	6.6	4.4	16.8	12	21.2	5.6	–	0.6	–	–
			6–8 (104)	48.1	66.2	39.1	4.9	12.5	3.9	29.3	26.2	41.8	10.2	–	2.6	–	–
Koch and Calafat (2009)	Germany	2007	>18 (45)[b]	12.6	13.8	77.5	N/A	2.5	1.8	11.5	8.2	13.9	5.3	–	0.7	0.7	–
Fromme et al. (2016)	Germany	2011–12	2–7 (208)	–	–	–	–	–	–	–	–	–	–	–	–	–	< 0.1
Schütze et al. (2014)	Germany	1999–2012	20–30 (300)	–	–	–	–	–	–	–	–	–	–	–	–	–	< 0.1
Ha et al. (2014)	Korea	2012	6–19 (342)[b]	52.5	–	–	–	–	–	29.0	23.0	–	–	–	–	–	–
Romero-Franco et al. (2011)	Mexico	2007	32–79 (108)[c]	72.4	8.3	83.2	–	4.3	5.1	45.8	31.8	71.9	–	–	3.9	–	–
Cantonwine et al. (2014)	Puerto Rico	2010–12	18 – 40 (139)[e]	19.2	10.9	102	–	3.9	3.3	10.7	8.9	19.6	16.4	–	2.3	2.3	–
Casas et al. (2011)	Spain	2004–08	17 – 43 (118)[b,e]	29.9	41.9	324	–	10.5	4.4	17.3	15.7	32.2	4.0	–	1.5	2.8	–

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Reference	Country	Year	Population age (years) (n)	DnBP	DiBP	DEP	DMP	BBzP	DEHP				DiNP		DnOP	DiDP	DINCH
				MBP	MiBP	MEP	MMP	MBzP	MEHP	MEHHP	MEOHP	MECPP	MCOP	MNP	MCPP	MCNP	MHINCH
			4 (19)[b]	27.5	30.2	755	–	33.0	6.2	57.4	44.6	115.0	7.5	–	6.1	4.0	–
CDC (2015)	USA	2011–12	6 to >20 (2489)	7.61	6.00	37.90	N/A	4.52	1.36	7.91	5.08	12.9	19.7	N/A	3.01	2.49	N/A
Silva et al. (2013)	USA	2000–12	>18 (527)[b]	–	–	–	–	–	–	–	–	–	–	–	–	–	< 0.4

GM: geometric mean; N/A: not calculated, proportion of results below limit of detection was too high to provide a valid result.

[a]Overweight and obese.

[b]Medianconcentration.

[c]Creatininecorrected.

[d]Health controls.

[e]Pregnantwomen.