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Urinary metabolites of organophosphate esters: Concentrations and age trends in Australian children

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ABSTRACT

There is growing concern around the use of organophosphate esters (OPEs) due to their suspected reproductive toxicity, carcinogenicity, and neurotoxicity. OPEs are used as flame retardants and plasticizers, and due to their extensive application in consumer products, are found globally in the indoor environment. Early life exposure to OPEs is an important risk factor for children's health, but poorly understood. To study age and sex trends of OPE exposures in infants and young children, we collected, pooled, and analysed urine samples from children aged 0–5 years from Queensland, Australia for 9 parent OPEs and 11 metabolites. Individual urine samples (n = 400) were stratified by age and sex, and combined into 20 pools. Three individual breast milk samples were also analysed to provide a preliminary estimate on the contribution of breast milk to the intake of OPEs. Bis(1-chloroisopropyl) phosphate (BCIPP), 1-hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP), bis(1,3-dichloroisopropyl) phosphate (BDCIPP), dibutyl phosphate (DBP), diphenyl phosphate (DPHP), bis(2-butoxyethyl) phosphate (BBOEP), bis(2-butoxyethyl) 3-hydroxyl-2-butoxyethyl phosphate (3OH-TBOEP), and bis(2-butoxyethyl) hydroxyethyl phosphate (BBOEHEP) were detected in all urine samples, followed by bis(methylphenyl) phosphate (80%), and bis(2-ethylhexyl) phosphate (BEHP, 20%), and bis(2-chloroethyl) phosphate (BCEP, 15%). Concentrations of tris(2-chloroethyl) phosphate (TCEP), BCEP, tris(2-ethylhexyl) phosphate (TEHP), and DBP decreased with age, while bis(methylphenyl) phosphate (BMPP) increased with age. Significantly higher concentrations of DPHP (p = 0.039), and significantly lower concentrations of TEHP (p = 0.006) were found in female samples compared to males. The estimated daily intakes (EDIs) via breastfeeding, were 4.6, 26 and 76 ng/kg/day for TCEP, TBP and TEHP, respectively, and were higher than that via air and dust, suggesting higher exposure through consumption of breast milk.

1. Introduction

For more than four decades flame retardants (FRs) have been added to a variety of consumer products to delay combustion and meet flammability standards. Prior to 2004, polybrominated diphenyl ethers (PBDEs) were the most commonly used FRs worldwide (Ma et al., 2013). Due to their persistence, bioaccumulation, and toxicity, several major commercial mixtures of PBDEs, including Penta-BDE, Octa-BDE, and Deca-BDE were banned in parts of Europe and North America in the 2000's (Alaee et al., 2003). The phase-out of PBDEs led to increasing use and production of alternative flame retardants, such as organophosphate esters (OPEs) (van der Veen and de Boer, 2012; Butt et al., 2014), some of which are also used as plasticizers (van der Veen and de Boer, 2012). There is evidence that certain OPEs are reproductive toxins, carcinogenic, and neurotoxic (World Health Organization, 1991a, b, 1998; van der Veen and de Boer, 2012), with comparable

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toxicity to some traditional FRs (i.e. 3,3′,5,5′-tetrabromobisphenol A, and 2,2′,4,4′-brominated diphenyl ether) (Behl et al., 2015). Only limited epidemiological studies of human exposure are available, but these have reported an association between OPE exposure and decreased free thyroxine levels and semen quality parameters in adults (Meeker and Stapleton, 2010; Egloff et al., 2014).

Since OPEs are additive FRs, they are not chemically bound to the carrier material and can leach over time into indoor and outdoor environments (Marklund et al., 2003; van der Veen and de Boer, 2012). We have recently reported high concentrations of tris(2-butoeyethyl) phosphate (TBOEP) and tris(2-chloroisopropyl) phosphate (TCIPP) in Australian indoor air and dust, and high detection frequencies for other OPEs (He et al. under review). As people spend > 90% of their time indoors, they are exposed to a broad range of OPEs, and dermal exposure via dust is generally regarded as a primary exposure pathway. Children may be more highly exposed due to their proximity to the ground, lower breathing zone, and hand-to-mouth behavior (Brasche and Bischof, 2005; Xue et al., 2007; Toms et al., 2009; Heffernan et al., 2013).

Due to the short half-lives of many OPEs (World Health Organization, 1998; van der Veen and de Boer, 2012), it may be difficult to detect parent compounds in biological matrices. Therefore, the presence of OPE metabolites in urine offers more suitable targets for analysis. In vitro studies with human liver microsomes have shown that OPEs are readily metabolized to their dealkylation and hydroxylation metabolites (Van den Eede et al., 2013a; Ballesteros-Gómez et al., 2015b; Van den Eede et al., 2015a, 2016). These metabolites have recently been detected in human urine (Cooper et al., 2011; Butt et al., 2014; Van den Eede et al., 2015b; Butt et al., 2016). Further, there is a good correlation between concentrations of major OPE metabolites in urine and their respective parent compounds measured in dust (Meeker et al., 2013; Fromme et al., 2014; Cequier et al., 2015), with some exceptions (Carignan et al., 2013; Dodson et al., 2014), suggesting that these metabolites can be used as suitable biomarkers of exposure to specific OPEs. Although, some studies (Carignan et al., 2013; Dodson et al., 2014) observed weak correlations or non-correlations for OPEs in dust and urine, most studies considered dermal absorption as a primary exposure pathway for OPEs (Abdallah and Covaci, 2014; Hoffman et al., 2015b; Abdallah et al., 2016). The target parent and metabolite OPEs and their acronyms are listed in Table 1.

Human biomonitoring using pooled biological samples of serum or urine is an established paradigm for cross-sectional monitoring of population exposure (Heffernan et al., 2014; Drage et al., 2017; Thomas et al., 2017). Van den Eede et al. (2015b) used pooled urine samples to assess exposure to OPEs in an Australian population and reported an inverse association between urinary concentrations of DPHP, BCIPHIPP, and BDCIPP and age. However, child-specific exposure pathways, and estimated daily intakes (EDIs) were not examined. The aim of this study was to further investigate the age and sex trends of OPEs in infants and young children < 5 years in Australia using pooled urine samples, and to provide the first preliminary EDI assessment of OPEs via breastfeeding.

2. Materials and methods

2.1. Materials

TDCIPP, TBP, TEHP, TBOEP, TPHP, TMPP, DPHP standards were purchased from Sigma-Aldrich (St Louis, MO, USA). TCIPP was purchased from Dr. Ehrenstorfer (Augsburg, Germany). BCEP, BCIPP, BDCIPP, DBP, BEHP, BBOEP, and BMPP were purchased from TRC (Toronto, Canada). TCIPP-d18, TBP-d27 and TPHP-d15 were purchased from Cambridge Isotope laboratories Inc. (Andover, MA, USA). BCIPHIPP, BBOEHEP, 3OH-TBOEP, TBOEP-d6, DPHP-d10, BCEP-d8 and BDCIPP-d10 were provided by the Toxicological Center (University of Antwerp, Belgium). Ultra-pure water was obtained from a Milli-Q system (Merck Millipore, MA, USA), β-glucuronidase, triethyl amine, sodium acetate, and acetate acid were purchased from Sigma; StrataX-AW cartridges, RC-cellulose syringe filters (0.2 μm) were purchased from Phenomenex Inc. (Torrance, CA, USA), and acetonitrile was purchased from Merck (Darmstadt, Germany).

2.2. Study population and sample collection

Sample collection was undertaken using a methodology described previously (Heffernan et al., 2016). Briefly, de-identified individual specimens were obtained from a community-based pathology laboratory (Sullivan Nicolaides Pathology, Taringa, Queensland, Australia)

Table 1
Summary statistics for concentrations of OPE parent and metabolites in pooled urine samples.

Full name	Abbreviation	DF[a] (%)	MDL[b] (ng/mL)	Pooled mean (ng/mL)	Range (ng/mL)	
Parent OPE						Target metabolites
Tris(2-chloroethyl) phosphate	TCEP	45	0.022	< 0.022	< 0.031–0.90	BCEP
Tris(2-chloroisopropyl) phosphate	TCIPP	0	1.3	< 1.3	n.d.	BCIPP, BCIPHIPP
Tris(1,3-dichloroisopropyl) phosphate	TDCIPP	45	0.014	< 0.014	< 0.022–0.069	BDCIPP
Tributyl phosphate	TBP	0	7.5	< 7.5	n.d.	DBP
Tris(2-ethylhexyl) phosphate	TEHP	45	0.030	< 0.030	< 0.040–0.61	BEHP
Tris(2-butoxyethyl) phosphate	TBOEP	0	0.26	< 0.26	n.d.	BBOEP, 3OH-TBOEP, BBOEHEP
Triphenyl phosphate	TPHP	5	0.31	< 0.31	< 0.50–0.56	DPHP
2-Ethylhexyl diphenyl phosphate	EHDPHP	25	0.16	< 0.16	< 0.44–1.4	DPHP
Tris(methylphenyl) phosphate	TMPP	35	0.010	< 0.010	< 0.010–0.020	BMPP
OPE metabolites						Specific metabolite
Bis(2-chloroethyl) phosphate	BCEP	15	0.014	< 0.014	< 0.014–0.036	Yes
Bis(1-chloroisopropyl) phosphate	BCIPP	100	0.039	0.85	0.063–3.2	Yes
1-Hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate	BCIPHIPP	100	0.0020	0.43	0.11–2.1	Yes
Bis(1,3-dichloroisopropyl) phosphate	BDCIPP	100	0.0034	2.6	1.6–19	Yes
Dibutyl phosphate	DBP	100	0.051	0.18	0.013–0.55	Yes
Bis(2-ethylhexyl) phosphate	BEHP	10	0.16	< 0.16	< 0.41–0.61	Yes
Bis(2-butoxyethyl) phosphate	BBOEP	100	0.0033	0.32	0.085–0.78	Yes
Bis(2-butoxyethyl) 3-hydroxyl-2-butoxyethyl phosphate	3OH-TBOEP	100	0.0027	0.029	0.016–0.063	Yes
Bis(2-butoxyethyl) hydroxyethyl phosphate	BBOEHEP	100	0.0025	0.075	0.014–0.15	Yes
Diphenyl phosphate	DPHP	100	0.22	25	0.33–58	No
Bis(methylphenyl) phosphate	BMPP	80	0.0022	0.024	< 0.0039–0.093	Yes

[a] DF = detection frequency; n.d. = not detected.
[b] MDL = method limits of detection.