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REVIEW ARTICLE

Recent biomonitoring reports on phosphate ester flame retardants: a short review

Anne-Marie Saillenfait[1] · Sophie Ndaw[1] · Alain Robert[1] · Jean-Philippe Sabaté[1]

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Abstract

Organophosphate triesters (PEFRs) are used increasingly as flame retardants and plasticizers in a variety of applications, such as building materials, textiles, and electric and electronic equipment. They have been proposed as alternatives to brominated flame retardants. This updated review shows that biomonitoring has gained incrementally greater importance in evaluating human exposure to PEFRs, and it holds the advantage of taking into account the multiple potential sources and various intake pathways of PEFRs. Simultaneous and extensive internal exposure to a broad range of PEFRs have been reported worldwide. Their metabolites, mainly dialkyl or diaryl diesters, have been used as biomarkers of exposure and have been ubiquitously detected in the urine of adults and children in the general population. Concentrations and profiles of PEFR urinary metabolites are seen to be variable and are highly dependent on individual and environmental factors, including age, country regulation of flame retardants, and types and quantities of emissions in microenvironments, as well as analytical procedures. Additional large biomonitoring studies, using a broad range of urinary diesters and hydroxylated metabolites, would be useful to improve the validity of the biomarkers and to refine assessments of human exposure to PEFRs.

Keywords Flame retardant · Organophosphates · Exposure assessment · Human biomonitoring · Health

Introduction

Organophosphorous flame retardants are one of the most common groups of flame retardants (FRs). They primarily consist of organophosphate triesters (PEFRs). The total global consumption of organophosphorous compounds used as FRs was estimated to be about 207,000 tons in 2004. In 2006, chlorinated phosphate and non-chlorinated organophosphorous FRs represented 11 and 10% of FR consumption in Europe, respectively (NEG 2009; Arcadis 2011; EFRA 2007). Since the early 2000s, brominated flame retardants such as certain polybrominated diphenyl ethers (PBDE), have been progressively phased out or seen their use restricted in many regions of the world (e.g., North America, Japan, and Europe), because of their bioaccumulation, persistence, and potential health effects. The halogen-free PEFRs are considered as possible alternatives to PBDE, and their production and use have been increasing over the past few years. PEFRs are also applied as plasticizers in polymers such as PVC (e.g., aryl phosphates), cellulosic fibers, polyurethane foams (e.g., chlorinated phosphate), and engineering plastics (e.g., polycarbonate/acrylonitrile butadiene styrene-PC/ABS, and polyphenylene oxide/high impact polystyrene-PPO/HIPS). Other applications of phosphate esters are as anti-foam agents, additives in hydraulic fluids, and lubricants. PEFRs have a broad application field and are extensively used alone or in combination with other FRs in a variety of industries, including plastics, furniture, textiles, construction, electrical engineering and electronics, transportation (e.g., road and rail vehicles), and the petroleum industry (NEG 2009; ATSDR 2012). Triphenyl phosphate (TPHP) is also present in personal care products such as nail polish (Mendelsohn et al. 2016).

PEFRs are frequently applied as chemical additives and they are not chemically bound to the polymers (i.e., unlike reactive FRs). They can be released from treated industrial and commercial products by abrasion, leaching and/or

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✉ Anne-Marie Saillenfait
anne-marie.saillenfait@inrs.fr

[1] Institut National de Recherche et de Sécurité, Rue du Morvan, CS, 60027, 54519 Vandoeuvre Cedex, France

volatilization during their lifetime. They have been detected in a wide range of environmental samples around the world (e.g., indoor dust) and concern about human exposure to PEFRs is increasing. In addition, some recent epidemiological studies have suggested that certain PEFRs may have possible health effects, such as interference with endocrine and reproduction functions. Tris(2-chloroethyl) phosphate (TCEP), tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), and tris(2,3-dibromopropyl)phosphate (TDBPP) are listed as carcinogenic substances under California's proposition 65 (OEHHA 2017). In Europe, several PEFRs have been classified as substances suspected of causing cancer (e.g., TCEP, TDCIPP, tributyl phosphate—TNBP) and/or that may damage fertility (e.g., TCEP, tri-ortho-cresyl phosphate-ToCP) (ECHA 2018).

While the occurrence of PEFRs in indoor dust has been extensively described across the world, less is known about internal exposure to PEFRs in humans. Several human studies have used urinary biomarkers of PEFRs to monitor exposure to these FRs among workers and the general population.

This short review compiles the available data on PEFRs in human urine published from 2011 to May 2018. A comprehensive search was performed in the Pubmed database using the search terms "organophosphate flame retardant" and "exposure", or "flame retardant" and "urine". Only full text articles were reviewed. Studies were included if the PEFRs were measured in a biological matrix (e.g., urine, hair, milk). There were no restrictions on the size and age of the study population, geographical region, or study design (e.g., pooled data).

Environmental occurrence and routes of exposure

PEFRs have been found worldwide in diverse outdoor environments, including river water, groundwater, and wastewater, with individual concentrations ranging from several ng/l to tens of µg/l (Van der Veen et al. 2012; Wei et al. 2015; Ali et al. 2017). They have been ubiquitously detected in floor and surface dust from various indoor environments, including private houses, vehicles, and various public and work places (e.g., offices, daycare centers, electronic equipment stores and recycling plants, and hospitals). PEFRs concentrations in floor and surface dust were in the range of 0.02 ng/g to tens of µg/g. The concentrations of PEFRs measured in indoor air were generally around tens to hundreds of ng/m^3. Higher PEFR levels in indoor air or dust have occasionally been reported in occupational settings (e.g., recycling of electronics) or microenvironments (e.g., cars) (Wu et al. 2016; Ali et al. 2017; Zhou et al. 2017; Bello et al. 2018; Björnsdotter et al. 2018). Concentrations in outdoor air are approximately 1–4 orders of magnitude less than in indoor air (Wei et al. 2015). The ubiquity of PEFRs in the environment indicates that the general population is likely to be exposed to several of these chemicals, through multiple sources, on a daily basis.

PEFRs can enter the human body via several routes. Recent studies have shown that dermal absorption may contribute substantially to the total body burden of PEFRs (Abdallah et al. 2016; Mendelsohn et al. 2016; Liu et al. 2017; Bello et al. 2018; Frederiksen et al. 2018). Ingestion of dust and dermal exposure to dust and treated materials (e.g., clothes and furniture) are considered primary sources of exposure to PEFRs. For volatile or semi-volatile PEFRs (e.g., TCEP, tris(1-chloro-2-propyl) phosphate—TCIPP), air and suspended particles inhalation may be a significant intake pathway (Schreder et al. 2016; Xu et al. 2016; He et al. 2018c). Ingestion of contaminated food (e.g., by migration from plastic packaging) may contribute to oral intake of PEFRs, but its contribution appears to vary substantially between compounds, as well as between and within populations (Zhang et al. 2016; Zheng et al. 2016; Xu et al. 2017; Poma et al. 2017, 2018).

Human health effects

The toxicological profiles of halogenated and non-halogenated PEFRs have been reviewed by several (environmental) agencies, in particular to evaluate their suitability as alternatives for PBDE FRs (NEG 2009; ATSDR 2012; Van der Veen et al. 2012; US EPA 2015; Ministry of Environment and Food of Denmark 2016). Assessments almost entirely relied on experimental studies. Critical effects were found to differ from one compound to another. A few PEFRs were identified as being toxic to the male reproductive system (i.e. TCEP, TDCIPP, ToCP), potentially carcinogenic (i.e., TCEP and TDCIPP), and/or toxic to specific organs (i.e., kidney for TCEP). Because of their toxic potential, the chlorinated PEFRs TCEP and TDCIPP are presently subject to regulations in several countries (mainly Northern America, Europe, Japan) (OEHHA 2017; Canada Safety Consumer Act 2018; ECHA 2018). The US EPA has established an oral reference dose of 0.01 mg/kg/day for TCIPP, tris(2-ethylhexyl) phosphate (TEHP) and TNBP; 0.02 mg/kg/day for TmCP and TDCIPP; and 0.007 mg/kg/day for TCEP (US EPA 2017).

Despite the increasing use of a wide range of PEFRs and the ubiquitous exposure to PEFRs among the general population, human data on the potential health effects of PEFRs are still limited, especially regarding long-term exposure and the risks for children. The epidemiological studies published since 2010 mainly addressed respiratory outcomes (asthma, rhinitis), and endocrine and reproductive effects (Table 1). Results of a few studies have raised concern about

Table 1 A summary of recent epidemiological studies on the potential health effects of PEFRs

Author, location	Subjects and study period	Sampling	Exposure assessment	Health effects related to PEFRs exposure
Hormonal and reproductive effects				
Carignan et al. (2018a) USA	201 couples from the Environment and Reproductive Health (EARTH) prospective cohort study[a] 2005–2015	One or two spot urine samples per in vitro fertilization cycle	Urinary metabolites in males: BCIP, BDCIPP, DPHP, ip-PPP, tert-butylphenylphenyl phosphate (tb-PPP)	*Paternal exposure and partner's pregnancy outcome* Association between paternal preconception BDCIPP levels and reduced probability of oocyte fertilization No association between PFR metabolites and the proportion of cycles resulting in implantation, clinical pregnancy and live birth
Carignan et al. (2018b) USA	211 women from the Environment and Reproductive Health (EARTH) prospective cohort study[a] 2005–2015	One or two spot urine samples per in vitro fertilization cycle	Urinary metabolites in females: BCIP, BDCIPP, DPHP, ip-PPP, tb-PPP	*Maternal exposure and pregnancy outcome* Association between the levels of two individual metabolites (i.e., DPHP and tb-PPP) and of total metabolites, and reduced probability of successful fertilization, implantation, clinical pregnancy, and live birth
Ingle et al. (2018) USA	220 men from the Environment and Reproductive Health (EARTH) cohort study[a] 2005–2015	One to five urine and sperm samples	Urinary metabolites in males: BCIP, BDCIPP, DPHP, ip-PPP, tb-PPP	*Exposure in men and semen parameters* No consistent association between individual metabolites and semen parameters
Preston et al. (2017) USA	26 men and 25 women as a part of the Flame Retardant Exposure Study (FlaRE) 2010–2011	Spot urine and blood samples at 1, 6 and 12 months	Urinary DPHP	*Adult exposure to TPHP and circulating thyroid hormones* No association between DPHP levels and thyroxine (free T4), triiodothyroxine (free and total T3) or thyroid stimulating hormone (TSH) concentrations in serum Association between DPHP levels and increased total T4, especially in women
Soubry et al. (2017) USA	67 men as a part of the Gametic Epigenetic Reprogramming (TIEGER) cross-sectional study 2012–2013	Spot urine and sperm samples on the same day	Urinary metabolites: BCIP, BDCIPP, DPHP, ip-PPP, tb-PPP	*Exposure in men and DNA methylation at imprinted genes in sperm* Association between PEFRs metabolites (i.e., BDCIPP, DPHP, ip-PPP) and small methylation differences (hyper- or hypo-methylation of different genes specific to the metabolites)

Table 1 (continued)

Author, location	Subjects and study period	Sampling	Exposure assessment	Health effects related to PEFRs exposure
Meeker et al. (2013a) USA	33 men from couples who were infertile due to a male factor, a female factor, or both (subset of a parent study: Meeker et al. 2007) 2003–2004	One urine, blood, and semen sample	Urinary BDCIPP and DPHP	*Exposure in men, and semen parameters, and reproductive and thyroid hormones* Association between BDCIPP levels and decreases in sperm quality parameters, and concentrations of total T3 and FSH in serum Association between DPHP levels and decreased sperm concentration (no significant changes in hormones, e.g., prolactin)
Meeker et al. (2007, 2010) USA	50 men from couples who were infertile due to a male factor, a female factor, or both (subset of a parent study: Meeker et al. 2007)	Dust collected at the homes of men who participated in the parent study in 2002–2007 One blood and semen sample (38 samples for semen)	TDCPP and TPHP in dust	*Exposure in men and semen parameters and reproductive and thyroid hormones* Association between TDCPP levels and changes in serum concentrations of hormones (decrease in free T4 and increase in prolactin) Association between TPHP and increased prolactin and decreased sperm concentration
Effects at birth and in childhood				
Hoffman et al. (2018) USA	349 mothers and their children from the cohort of the Pregnancy Infection and Nutrition study (PIN) 2002–2005	Single spot urine samples from the mothers during late-second or early-third trimester (24–30 weeks of pregnancy)	Urinary metabolites: BCIP, BDCIPP, DPHP, ip-PPP, tb-PPP, 1-hydroxy-2-propyl phosphate (BCIPH-IPP)	*Maternal exposure and birth outcomes* Higher levels of BDCIPP and ip-PPP associated with decreased gestational duration and increased preterm births (<37 weeks gestation) among female infants
Castorina et al. (2017a) USA	310 mothers and their 7-year-old children from a longitudinal birth cohort study (Center for the Health Assessment of Mothers and Children of Salinas-CHAMACOS) 1999–2000	Single spot urine samples from the mothers at 26 weeks of pregnancy	Urinary metabolites: BCIP, BDCIPP, DPHP, ip-PPP, tb-PP (Castorina et al. 2017b)	*In utero exposure and neurodevelopmental outcome (associations analyzed: total PEFR metabolites, TDCIPP, TPHP, ip-PPP)* Association between DPHP and total PEFR metabolites levels, and decreased cognitive function (full scale IQ and working memory) No association between prenatal BDCIPP and ip-PPP levels and neurobehavioral development

Table 1 (continued)

Author, location	Subjects and study period	Sampling	Exposure assessment	Health effects related to PEFRs exposure
Lipscom et al. (2017) USA	72 children (aged 3–5 years) 2012–2013	Passive wristband samplers worn continuously for 7 days	FRs in wristbands, including brominated diphenyl ethers (BDEs) and total PEFRs	*Child exposure and social behavior* Cross-sectional association between total PEFRs levels and poorer social skills in a few domains (e.g., externalizing behavior)
Respiratory outcomes and immunotoxicity				
Sun et al. (2018) China	180 participants (130 adults, 27 students, and 33 children) 2016–2017	Single spot urine sample	9 urinary metabolites including BCEP, BCIPP, BDCIPP, DNBP, DPHP, BBOEP, BEHP	*Indoor exposure and allergy* Association between DNBP levels and self-reported symptoms of allergy
Canbaz et al. (2016) Sweden	110 children who developed asthma at 4 or at 8 years, matched with 110 controls from a large prospective study 1994–1996	Dust collected from the mother's mattress two months after child birth	PBDEs and PEFRs in dust, including TECP, TCIP, TDCIPP, TPHP, TBOEP, EHDPHP, mmp-TCP	*FRs in mother's mattress dust and the development of childhood asthma* No association between higher concentrations of PEFRs and the development of childhood asthma
Araki et al. (2014) Japan	516 inhabitants (adults and children) in 156 different homes Cross-sectional study 2004–2006	Indoor floor and multi-surface dust collected in each family's home in 2004, 2005, and 2006	11 PEFRS such as TBOEP, TCIPP, TDCIPP, TPHP (most frequently detected) in dust	*Indoor exposure and asthma and allergy* Association between TNBP levels and the inhabitant's medical treatment for asthma and allergic rhinitis Association between TCIPP and TDCIPP levels and the inhabitant's recent medical treatment for atopic dermatitis
Bergh et al. (2011) Sweden	Adults (men and women) Part of a larger study, the Healthy Sustainable Houses study in Stockholm (3H) Frequency of SHS studied in 481 multi-family buildings with 10,506 dwellings (Engvall et al. 2010) 2006	Indoor air from 169 apartments in buildings with a high or low incidence of reported SHS (2–4 apartments/buildings)	Phthalates and 15 organophosphorous flame retardants	*Indoor exposure and sick house syndrome (SHS) (i.e., irritation of the eyes, nose, throat, skin and coughing)* No association between PEFR levels and reported SHS symptoms
Kanazawa et al. (2010) Japan	134 inhabitants (64 men and 70 women) of 41 dwellings Cross-sectional study 2006–2007	Indoor air and dust (surface, floor) from the dwelling	Semi-volatile organic compounds including 11 PEFRs	*Indoor exposure and sick house syndrome (SHS)* Association between TBNP levels (floor dust) and reported mucosal symptoms of SHS Inverse association between TBEP concentrations (floor dust) and reported mucosal symptoms of SHS

Table 1 (continued)

Author, location	Subjects and study period	Sampling	Exposure assessment	Health effects related to PEFRs exposure
Others				
Deziel et al. (2018) USA	100 cases and 100 controls Cases: Patients newly diagnosed with papillary thyroid cancer (PTC) (women) 2010–2013	Single spot urine samples	6 urinary metabolites: BCIPP, BCIHPP, BDCIPP, ip-PPP, DPHP and tert-butyl phenyl phenyl phosphate (tb-PPP)	*Adult exposure and PTC* No association between urinary PEFR metabolites concentrations measured at the time of diagnosis and risk of PTC Tb-PPP was only detected in 6% of samples and was therefore excluded for analysis
Hoffman et al. (2017c) USA	70 cases and 70 controls Cases: Patients newly diagnosed with papillary thyroid cancer (PTC) (men and women) 2014–2016	Dust collected at each participant's home	FRs in household dust, including BDEs, TCEP, TCIPP, TDCIPP and TPHP	*Adult exposure and PTC* Higher levels of TCEP associated with increased odds of PTC, especially larger and more aggressive tumors
Lu et al. (2017) China	221 adults and children 2014	Single spot urine samples	8 urinary metabolites: BCEP, BCIPP, BDCIPP, BBOEP, DBP, DPHP, DoCP, DpCP	*Adult exposure and oxidative stress (8-OHdG in urine)* Association between PEFR metabolite levels (i.e., DCEP, DNBP, DPHP) and a higher concentration of 8-OHdG, in e-waste dismantling sites
Zhao et al. (2016) China	154 men and 101 women 2012	One blood sample	TCIPP, TBOEP, TPHP, TEP, TNBP, EHDPP in blood	*Adult exposure and changes in sphingolipid homeostasis* Association between levels of the six PEFRs and increased sphingomyelin concentration Negative association between EHDPP, TPHP, and TNBP levels and sphingosine 1-phosphate concentration

[a]Participants originated from couples whose infertility diagnosis was either male factor, female factor, or a combination of both

the possible association between exposure to some PEFRs, and alteration of thyroid hormone regulation and male reproduction (e.g., sperm quality) (Meeker et al. 2010, 2013a; Hoffman et al. 2017c; Preston et al. 2017; Soubry et al. 2017; Carignan et al. 2018a). However, at present, there is not enough consistent information from which to draw firm conclusions about the adverse health effects of PEFRs (as a class or specific) in humans.

The isomer ToCP has proven to be neurotoxic and to inhibit both cholinesterase and neuropathy target esterase (NTE) activity (NEG 2009; ATSDR 2012; US EPA 2015; Ministry of Environment and Food of Denmark 2016). Worldwide, it has been associated with numerous cases of delayed neuropathy and paralysis of the extremities in humans (Petroianu et al. 2016). Consequently, there has been a significant reduction in the commercial use of ToCP, e.g., in aircraft engine oil.

Biomarkers of exposure

Cholinesterase activity

The neurotoxic properties of ToCP have mainly been attributed to its metabolite cresyl saligenin phosphate. This reactive intermediate binds covalently to a serine moiety of butyrylcholinesterase in blood. The resulting adducts can be determined by mass spectrometry and have been proposed as a biomarker for measuring exposure to ToCP (Schopfer et al. 2014; Tacal et al. 2014; Johnson et al. 2015). In addition, the American Conference of Governmental Industrial Hygienists (ACGIH) recommended erythrocyte cholinesterase activity as a biological exposure index (BEI) for ToCP. However this biomarker is not specific and can be inhibited by other OPs, such as organophosphorous pesticides (NEG 2009; ATSDR 2012).

Urinary biomonitoring

Urinary PEFRs or their metabolites appear to be the preferred non-invasive biomarkers for identifying and quantifying human exposure to PEFRs. They provide integrated information on total body burden, covering all types of sources and exposure pathways (i.e., inhalation, dermal absorption, and oral uptake), and they can be used to quantify an individual's exposure.

Diester metabolites

Information on the metabolism of PEFRs in humans is still limited and there are differences in the information available for different compounds. A common metabolic pathway has been proposed for the three types of PEFR triesters, i.e., trialkyl, triaryl, and trihaloalkyl/aryl phosphate esters. This was mainly based on in vivo studies in rodents and in vitro studies using human hepatocytes or liver fractions (Ballesteros-Gomez et al. 2015a, b; Hou et al. 2016; Van den Eede et al. 2013a, 2015a, 2016a, b, c). The first steps in the biotransformation of these triesters lead to the rapid formation of diesters or monoesters by hydrolysis of one or two ether bonds between the phosphate group and the substituent, and to a variety of hydroxylated metabolites that undergo glucuronide and sulfate conjugation. Indeed, several dialkyl or diaryl phosphates have been detected in human urine, including bis(2-chloroethyl) phosphate (BCEP), bis(1-chloro-2-propyl) phosphate (BCIPP), bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), dibutyl phosphate (DNBP), and diphenyl phosphate (DPHP) (Table 1). These diesters are expected to be important and stable metabolites of TCEP, TCIPP, TDCIPP, TNBP, and triphenyl phosphate (TPHP), respectively (Table 2). Hence, most biomonitoring studies have focused on the determination of dialkyl or diaryl phosphate metabolites in urine to quantify human exposure levels to PEFRs.

However, there have been concerns regarding the use of urinary DPHP as a biomarker of exposure levels of the parent TPHP. DPHP may lack specificity since other aryl organophosphate esters containing at least two phenyl substituents [e.g., bisphenol A bis(diphenyl phosphate) and resorcinol bis(diphenyl) phosphate] have the potential to form DPHP after being hydrolysed and may contribute to DPHP urinary levels (Ballesteros-Gomez et al. 2015b; He et al. 2018a). In addition, DPHP itself is currently a commercially available product (e.g., as catalyst for resin manufacturing). Therefore, Van den Eede et al. (2016b) recommended using DPHP as a biomarker of aryl-PFRs rather than of TPHP only. In contrast with TPHP, the production of DPHP from 2-ethylhexyl diphenyl phosphate by human serum hydroxylase in vitro was found to be minor and thus it was not considered to be likely a confounding factor (Van den Eede et al. 2016b).

Other metabolites

A few hydroxylated metabolites of PEFRs have recently been identified in urine samples from adults and children (Dodson et al. 2014; Van den Eede et al. 2015b; Hammel et al. 2016; Kosarac et al. 2016, Su et al. 2016; Bui et al. 2017; He et al. 2018a; Hoffman et al. 2017a, 2018; Phillips et al. 2018; Völkel et al. 2018). Urinary bis(2-butoxyethyl)-(2-hydroxyethyl) phosphate (BBOEHEP) was used to monitor exposure to tris(2-butoxyethyl) phosphate (TBOEP) (Van den Eede et al. 2015b; He et al. 2018a; Völkel et al. 2018). Hydroxylated metabolites of TPHP (i.e., 4-hydroxyphenyl diphenyl phosphate, 4-hydroxyphenyl phenyl phosphate) have been considered as potential specific urinary biomarkers of TPHP exposure (Van den Eede et al. 2013a, 2015b;

Table 2 Parent compounds and metabolites

Parent PEFR		PEFR metabolite	
Full name (CAS number)	Abbreviation	Full name	Abbreviation
Halogenated organophosphorous compounds			
Tris(2-chloroethyl) phosphate (115-96-8)	TCEP	Bis(2-chloroethyl) phosphate	BCEP
Tris(1-chloro-2-propyl) phosphate (13674-84-5)	TCIPP	Bis(1-chloro-2-propyl) phosphate Bis(1-chloro-2-propyl) 1-hydroxy-2-propyl phosphate	BCIPP BCIPHPP
Tris(1,3-dichloro-2-propyl) phosphate (or isopropyl) (13674-87-8)	TDCIPP	Bis(1,3-dichloro-2-propyl) phosphate	BDCIPP
Non-halogenated organophosphorous compounds			
Tri-*n*-butyl phosphate (126-73-8)	TNBP	Di-n-butyl phosphate	DNBP
Tris(2-ethylhexyl) phosphate (78-42-2)	TEHP	Bis(2-ethylhexyl) phosphate	BEHP
Mono-substituted isopropyl triphenyl phosphate (Isopropylphenyl diphenyl phosphate) (several isomers: 55864-04-5, 69515-46-4, 64532-94-1)	Mono-ITP	Isopropylphenyl phenyl phosphate	ip-PPP
Tris(2-butoxyethyl) phosphate (78-51-3)	TBOEP	Bis(2-butoxyethyl) phosphate Bis(2-butoxyethyl)-(2-hydroxyethyl) phosphate	BBOEP BBOEHEP
Triphenyl phosphate (115-86-6)	TPHP	Diphenyl phosphate	DPHP
Tricresyl phosphate (1330-78-5) Ortho, meta, and para isomers (78-30-8, 563-04-2, 78-32-0, respectively)	TCP ToCP, TmCP, TpCP	Dicresyl phosphate	DCP
2-ethylhexyl diphenyl phosphate (1241-94-7)	EHDPP	5-hydroxy-2-ethylhexyl diphenyl phosphate	5-OH-EHDPHP

Chemical structures of PEFR metabolites are given in Supplementary material S1

The commercial mixtures TCP, TCIPP, and tri-isopropylated phenyl phosphate contain varying amounts of their isomers, e.g., the most abundant isomer in commercial products of TCIPP is generally the completely branched isomer, CAS: 13674-84-5

Dodson et al. 2014; Su et al. 2016). However, they were only occasionally detected, and at very low levels, in human urine samples (glucuronide and sulfate conjugates, or the sum of free form and conjugates) (Van den Eede et al. 2015b, 2016b; Su et al. 2016). In several studies, the hydroxylated metabolite of TCIPP, bis(1-chloro-2-propyl) 1-hydroxy-2-propyl phosphate (BCIPHPP), appeared to be a major urinary metabolite and therefore a candidate biomarker of human exposure to this PEFR (Van den Eede et al. 2015b; Butt et al. 2016; Hammel et al. 2016; Hoffman et al. 2017a; Bello et al. 2018; He et al. 2018a; Phillips et al. 2018). Total hydroxylated metabolite (i.e., the sum of free and conjugated forms) was usually measured after enzymatic deconjugation treatment of the urine samples with sulfatase and β-glucuronidase. The free form of BCIHPP was reported to be barely detectable (Kosarac et al. 2016).

Unmetabolized PEFRs

The parent compounds have also been tested as potential urinary biomarkers of exposure to the OP triester FRs. Considering their notable presence in urine, monitoring of the unchanged TCPE and TEHP along with their corresponding diester metabolites was considered useful for better estimation of the actual exposure (Dodson et al. 2014; He et al. 2018a). With the exception of TCEP and TEHP, unchanged PEFRs were detected in lower frequencies and concentrations than their related diester metabolites, suggesting that they were less suitable biomarkers (Van den Eede et al. 2015b; He et al. 2018a). Furthermore, additive PEFRs can leach from treated rubber and plastic storage materials and possible background contamination of collected samples must therefore be considered.

Chemical analysis

Sensitive methods are being developed to improve the limits of detection and concurrently quantify a broad number of chlorinated and non-chlorinated diester and/or selected hydroxylated OP metabolites in human urine samples. Typical analytical techniques, including gas chromatography–tandem mass spectrometry (GC–MS/MS) (Schindler et al. 2009a, b), high- or ultra-performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS or UPLC–MS/MS), with electrospray or atmospheric pressure chemical ionization (ESI or APCI) have been used successfully in numerous biomonitoring studies (Cooper et al. 2011; Reemtsma et al. 2011; Van den Eede et al. 2013b, Su et al. 2015; Kosarac et al. 2016; Petropoulou et al. 2016; Jayatilaka et al. 2017), as has high resolution mass spectrometry

(UPLC-HRMS) (Cequier et al. 2014). These same sensitive methods are also being developed for use with other non-invasive matrices such as hair, nails and human milk (Sundkvist et al. 2010; Kucharska et al. 2014; Liu et al. 2015; Alves et al. 2017).

Occurrence of PEFRs metabolites in human urine

General population

Metabolites of PEFRs, essentially the diesters, were omnipresent in the urine samples collected from the general population across different countries, and there was simultaneous exposure to several PEFRs (Table 3). Reported occurrences and concentrations varied substantially between individual PEFR compounds.

BDCIPP and DPHP were the most commonly detected diester metabolites in the urine of children, mothers, and the general population, and were also the most frequently analyzed (Table 3). Median levels of BDCIPP and DPHP were generally in the range of µg/l (about 0.1–3 µg/l), but values of hundreds of µg/l were reported in urine samples of a few individuals from various geographic areas. Within each of the different studies, concentrations were highly variable between individuals and could differ by two orders of magnitude. DPHP was consistently found at high frequencies (in most cases > 90%) in the general population in Europe, the United States and China, suggesting ubiquitous exposure to DPHP or its parent compounds (e.g., TPHP or other aryl-PEFRs such as 2-ethylhexyl diphenyl phosphate) around the world.

Highly variable detection frequencies were reported for BCIPP, DNBP, and BBOEP. In general, their median levels were around, or less than, 0.3 µg/l.

Information on the occurrence of BCEP and isopropylphenyl phenyl phosphate (ipPP) is more limited. These were detected in more than half of the urine samples in the large majority of studies that monitored these metabolites. In most studies, their median concentrations were in the range of 0.2-2 µg/l.

In almost all available studies, di-ortho-cresyl phosphate (DoCP) and/or di-para-cresyl phosphate (DpCP) (determined alone or together) were detected only occasionally, and/or at relatively low levels (i.e., median levels < 0.02 µg/l) in recent studies in China and USA, suggesting limited exposure to the precursors of these metabolites in these general populations (Schindler et al. 2013; Fromme et al. 2014; Kosarac et al. 2016; Lu et al. 2017; Romano et al. 2017; Chen et al. 2018; Ospina et al. 2018). However, higher frequencies were reported in some occupationally exposed populations (Jayatilaka et al. 2017; Tao et al. 2018). DpCP was more abundant than di-meta-cresyl phosphate (DmCP) and DoCP. The synthesis and commercial compositions of TCP have in fact changed over time. Because of its neurotoxic properties, efforts have been made to minimize the amount of the ortho isomer present in commercial products containing TCP (NEG 2009; ATSDR 2012; US EPA 2015).

Other PEFRs metabolites were more rarely analyzed. Tert-butyl phenyl phenyl phosphate (tb-PPP) and bis(2-ethylhexyl) phosphate (BEHP) were detected infrequently (Su et al. 2015; Butt et al. 2016; Castorina et al. 2017b; Hoffman et al. 2017a, 2018; Soubri et al. 2017; Carignan et al. 2018a, b; Deziel et al. 2018; He et al. 2018a; Ingle et al. 2018; Sun et al. 2018). Dibenzyl phosphate (DBzP) was not detected in urine samples collected in the USA (Romano et al. 2017; Jayatilaka et al. 2017; Ospina et al. 2018).

Workers

In addition to the general population, urinary biomarkers have been used to assess exposure to PEFRs in a number of workplaces (Table 4). There are some indications that internal exposure may be higher than the background exposure of the general population during several types of occupational activity. For exemple, a recent study conducted in Australia showed that urinary levels of BCIPHPP among spray polyurethane foam applicators were approximately 50 times higher than urinary levels found in the general population (Bello et al. 2018). Numerous other worker groups are expected to be more heavily exposed than the general population, especially when workers are in direct contact with large volumes of PEFRs as pure chemicals or at high concentrations in technical formulations at industrial sites and in manufacturing (e.g., at electronics dismantling facilities or electronic goods recycling areas). Measurements of PEFRs in air and dust in various occupational settings have also shown that the work environment may noticeably contribute to external exposure to PEFRs (Makinen et al. 2009; Ali et al. 2014; Wei et al. 2015; Zheng et al. 2017; Zhou et al. 2017; Muenhor et al. 2017; Bello et al. 2018; Ceballos et al. 2018; Shen et al. 2018). Nevertheless, information on the nature and extent of occupational exposures to PEFRs, especially in terms of measurements of an individual's internal exposure, is still limited and warrants further investigations (characterization, quantification, and contribution to total PEFR burden).

Possible bias, limitations and strengths of the reviewed studies

The available biomonitoring data should be analyzed in the context of several influencing factors that have already been identified in a number of studies on the evaluation of human internal exposure to PEFRs.

Table 3 Urinary concentrations of the principal metabolites of PEFRs in general populations (μg/l)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	BBOEP	DPHP
Australia										
He et al. (2018a)	2014–2015	Children (0–5 years) Pooled urine samples (20 children/pool, 20 pools) Not adjusted for specific gravity	< 0.01[a] (0.036) **15**	0.85[a] (3.2) **100**	0.43[a].(2.1) **100**	2.6[a] (19) **100**	0.18[a] (0.55) **100**	–	0.32[a] (0.78) **100**	25[a] (58) **100**
He et al. (2018b)	2015–2016	51 children (3–29 months, average 13 months) Two urine samples from two consecutive days Not adjusted for specific gravity	< 0.01 (nr) **33**	< 0.68 (nr) **86**	0.93 (nr) **96**	3.3 (nr) 100	–	–	0.10 (nr) **75**	1 (nr) **94**
Van den Eede et al. (2015b)	2010–2011	Adults and children Pooled urine samples Not adjusted for specific gravity Campaign 1: 28 pools of 7 individuals and 44 pools of 7 individuals	–	–	nr (9.43) **100**	nr (8.90) **92**	nr (2.15)**18**	–	nr (0.53) **6**	nr (727) **97**
	2012–2013	Campaign 2: 23 pools of 100 individuals	–	–	nr (7.17) **100**	nr (3.41) **96**	nr (0.94)**4**	–	n.a. **0**	nr (225) **100**

Table 3 (continued)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	BBOEP	DPHP
Asia										
Chen et al. (2018) China	2015	411 children (212 aged 8–12 years and 199 aged 6–14 years) First morning void Specific gravity adjusted	1.04 (86.9) **91**	0.15 (3.11) **66**	–	0.05 (4.73) **29**	0.12 (2.67) **77**	–	0.05 (0.37) **84**	0.28 (6.18) **99**
Sun et al. (2018) China, Shanghai	2016–2017	180 participants (130 adults, 27 students, and 33 children) First morning void Not adjusted for specific gravity	nr (22.60) **5**	nr (8.83) **16.7**	–	nr (2.09) **21.1**	0.008 (1.48) **51.7**	–	0.097 (2.19) **68.3**	0.066 (4.0) **67.8**
Feng et al. (2016) China, Shanghai	2015	23 pregnant women Spot urine Specific gravity adjusted	–	–	–	1.58 (2.2) **17**	–	–	–	0.83 (7.3) **100**
Lu et al. (2017) China	2014	221 adults and children First morning void Not adjusted for specific gravity	1.1 (57) **71**	0.097(23) **56**	–	0.11 (4.5) **76**	0.15 (7.8) **99**	–	0.071 (2.1) **93**	0.53 (36) **100**
Yoshida et al. (2012) Japan	nr	5 individuals (16–48 years) Spot urine Not adjusted for specific gravity	–	–	–	–	<LOQ (< LOQ) **40**	–	–	n.a. (9.8) **20**

Table 3 (continued)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	BBOEP	DPHP
Europe										
Larsson et al. (2018) Sweden	2015	113 children (4 years) First morning void Presumably not ajusted for specific gravity	–	–	–	–	–	–	–	1.8 (35) **100**
Völkel et al. (2018) Germany	2011–2012	Children (20–80 months) 54 urine samples Spot urine Not adjusted for specific gravity	–	–	–	–	–	–	0.16 (nr) 80	–
Cequier et al. (2015) Norway	2012	48 mothers 2 to 8 samples over a period of 24 h (244 samples) Specific gravity adjusted Same population as Cequier et al. 2014	–	–	–	0.08 (2.1) **52**	<MDL (0.35) **8**	–	<MDL (0.27) < **1**	0.63 (60) **97**
		54 paired children (6–12 years, median 10 years) 2 or 3 samples over a period of 24 h (112 samples) Specific gravity adjusted	–	–	–	0.23 (3.3) **61**	<MDL (1.0) **15**	–	<MDL (1.0) **32**	1.0 (129) **97**
Cequier et al. (2014)	nr	42 mothers Spot urine Specific gravity adjusted	–	–	–	<LOQ (nr) **57**	<LOQ (nr) **5**	–	n.a. **0**	nr (nr) **100**

Table 3 (continued)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	BBOEP	DPHP
		42 paired children Spot urine Specific gravity adjusted	–	–	–	nr (nr) **79**	<LOQ (nr) **14**	–	<LOQ (nr) **33**	nr (37) **100**
Fromme et al. (2014) Germany	2011–2012	312 children (22–80 months, mean 54 months) Spot urine Not adjusted for specific gravity	0.2 (13.1) **65**	<0.2 (8.4) **21**	–	–	0.2 (6.6) **71**	–	2.0 (24.9) **90**	0.8 (23.2) **91**
Van den Eede et al. (2013b) Belgium	nr	59 adults (23 men and 36 women) Spot urine Not adjusted for specific gravity	nr (9.5) **27**	nr (6.2) **3**	–	nr (3.5) **25**	nr (3.5) **5**	–	nr (7.0) **31**	nr (13) **93**
Reemstma et al. (2011) Germany	nr	19 urine samples from males and females (14–85 years) Spot urine Not adjusted for specific gravity	–	–	–	–	–	–	–	1.3 (nr) nr
North America										
Carignan et al. (2018a) USA Massachusetts	2005–2015	201 men (whose partners were undergoing in vitro fertilization) Spot urine (1 sample) Specific gravity adjusted	–	n.a. **0**	–	0.46 (12.39) **84**	–	0.21 (3.60) **76**	–	0.57 (8.54) **87**

Table 3 (continued)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	BBOEP	DPHP
Carignan et al. (2018b) USA Massachusetts	2005–2015	211 women undergoing in vitro fertilization Spot urine (1 or 2 samples) Specific gravity adjusted	–	n.a. **0**	–	0.69 (63.4) **87**	–	–	–	0.75 (616) **94**
Deziel et al. (2018) USA Connecticut	2010–2013	200 women (100 population-based controls and 100 women diagnosed with thyroid cancer in a case–control study) Spot urine Specific gravity adjusted	–	nr (nr) **44**	0.19 (nr) **99**	0.65 (nr) **97**	–	2.35 (nr) **100**	–	0.82 (nr) **97**
Hoffman et al. (2018) North Carolina	2002–2005	349 pregnant women (24–30 weeks) Spot urine Specific gravity adjusted	–	nr (6.1) **49**	0.42 (98.0) **98**	1.85 (140) **93**	–	7.06 (69.0) **99**	–	1.31 (112) **84**
Ingle et al. (2018)	2005–2015	220 men Spot urine (1–5 samples/man) (255 samples) Specific gravity adjusted	–	–	–	0.61 (20.24) **85**	–	<MDL (4.08) **67**	–	0.70 (15.55) **86**

Table 3 (continued)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	BBOEP	DPHP
Ospina et al. (2018) National Survey US population	2013–2014	2666 spot urine samples, a random 1/3 sample of participants from the NHANES 2013–2014 Not adjusted for specific Age group: 6 years old and older	0.39 (110) **89**	0.16 (46.7) **61**	–	0.88 (169) **92**	0.25 (70.3) **81**	–	–	0.82 (193) **92**
		Age group: 6–11 years (n = 421)	0.66 (nr) **nr**	0.25 (nr) **nr**	–	2.31 (nr) **nr**	0.34 (nr) **nr**	–	–	1.70 (nr) **nr**
		Age group: 12–19 years (n = 427)	0.57 (nr) **nr**	0.16 (nr) **nr**	–	1.43 (nr) **nr**	0.27 (nr) **nr**	–	–	1.44 (nr) **nr**
		Age group: 20–59 years (n = 1266)	0.37 (nr) **nr**	0.16 (nr) **nr**	–	0.85 (nr) **nr**	0.22 (nr) **nr**	–	–	0.73 (nr) **nr**
		Age group: 60 years and older (n = 552)	0.30 (nr) **nr**	0.13 (nr) **nr**	–	0.43 (nr) **nr**	0.28 (nr) **nr**	–	–	0.65 (nr) **nr**
Phillips et al. (2018)	2014–2016	203 children (38–73 months) Three spot urine samples collected over a 48-h period Specific gravity adjusted	–	nr (31.9) **80**	nr (19.2) **97**	nr (80.7) **100**	–	nr (61.5) **100**	–	nr (50.9) **99**
Castorina et al. (2017b) USA California	1999–2000	310 pregnant women (26±2.4 weeks) Spot urine Specific gravity adjusted	–	n.a. **0**	–	0.41 (53.1) **77.7**	–	0.34 (5.47) **71.6**	–	0.93 (54.1) **79.4**

Table 3 (continued)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	BBOEP	DPHP
Hoffman et al. (2017a) USA North Carolina	2001–2006	349 pregnant women (24–30 weeks) Spot urine Specific gravity adjusted	–	0.7 (6.1) **48.7**	0.4 (98) **98.3**	1.9 (140) **92.8**	–	7.1 (69) **99.4**	–	1.3 (112) **83.7**
Preston et al. (2017) USA Massachusetts	2010–2011	51 adults (office workers, 26 men and 25 women) Spot urine, three sampling rounds, interval 6 months 135 samples Specific gravity adjusted	–	–	–	–	–	–	nr (0.17–142) **nr**	–
Romano et al. (2017) USA Rhode Island	2014	58 pregnant women (spot urine samples collected at 12, 28 and/or 35 weeks of gestation) Specific gravity adjusted	0.31 (nr) **74**	nr (nr) **53**	–	1.18 (nr) **93**	nr (nr) **33**	–	–	0.93 (nr) **95**
Thomas et al. (2017) USA Washington	2012–2014	41 children (15–18 months) Spot urine Specific gravity adjusted **Lab 1** N = 21	–	–	–	5.47 (64.66) **95**	–	0.48 (2.68) **81**	–	2.71 (16.56) **100**
		Lab 2 N = 20	–	–	–	2.01 (202.4) **85**	–	–	–	7.72 (26.93) **100**
Butt et al. (2016) USA California	2015	28 mothers Spot urine Specific gravity adjusted	–	n.a. (4.0) **11**	2.4 (104) **100**	2.8 (14.3) **100**	–	2.0 (14.8) **100**	–	1.2 (3.5) **100**

Table 3 (continued)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	BBOEP	DPHP
		33 paired children (2–70 months, mean 44 months) Spot urine Specific gravity adjusted	–	n.a. (3.4) **9**	2.0 (23.2) **100**	7.4 (798) **100**	–	2.1 (8.5) **100**	–	2.5 (82.0) **100**
Carignan et al. (2016) Eastern United States	2012	11 female gymnasts (older than 15 years in age) Several samplings on practice day Specific gravity adjusted	–	–	–	0.76 (3.99) **100**	–	–	–	8.71 (58.4) **100**
Hammel et al. (2016) USA North Carolina	2015	40 adults (15 men and 25 women) First morning void on 3 separate days Specific gravity adjusted	–	n.a.(0.57) **18**	1.12 (16.99) **100**	2.06 (21.21) **100**	–	–	–	1.16 (26.77) **100**
Kosarac et al. (2016) Canada	2010–2012	20 pregnant women (second and third trimester of pregnancy) and 4 post-partum women Spot urine Not adjusted for specific gravity	0.46 (1.25) **37**	0.46 (2.41) **54**	n.a. (0.53) **4** (free form, without enzymatic deconjugation)	0.26 (1.77) **29**	–	–	< 0.08 (1.02) **17**	2.94 (25.7) **92**
Petropoulou et al. (2016) USA California	nr	13 adults (8 women and 5 men) Spot urine Not adjusted for specific gravity	1.3 (15.0) **100**	0.3 (3.5) **100**	–	2.4 (7.3) **100**	–	–	–	1.5 (5.6) **100**

Table 3 (continued)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	BBOEP	DPHP
Hoffman et al. (2015a) USA North Carolina	2014–2015	43 children (2–18 months, mean 7.9 months) Spot urine Specific gravity adjusted	–	nr (7.5) **19**	–	nr (541) **100**	–	nr (6.1) **35**		nr (26.5) **93**
Hoffman et al. (2015b) USA North Carolina	2012	53 adults (26 men and 27 women) Spot urine Specific gravity adjusted	–	–	–	nr (4.46) **83**	–	–	–	nr (9.09) **91**
Su et al. (2015) Canada	2014	12 urine samples from 4 individuals Spot urine, 3 consecutive days Not adjusted for specific gravity	nr (12.33) **100**	nr (0.68) **42**	–	nr (1.17) **83**	nr (<MDL or <LOQ) **42**	–	<MDL	nr (1.29) **75**
Butt et al. (2014) USA New Jersey	2013–2014	19 mothers Spot urine Specific gravity adjusted	–	nr (0.64) **14**	–	nr (11.0) **100**	–	nr (2.3) **100**	–	nr (68.7) **95**
		23 paired children (1–5 years) Spot urine Specific gravity adjusted	–	nr (0.46) **4**	–	nr (251) **100**	–	nr (10.1) **92**	–	nr (140) **100**
Dodson et al. (2014) USA California	2011	16 adults Spot urine Not adjusted for specific gravity	0.63 (2.1) **75**	n.a. (0.97) **31**	–	0.09 (3.9) **94**	0.11 (0.45) **56**	–	n.a. (0.71) **12**	0.44 (6.8) **62**

Table 3 (continued)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	BBOEP	DPHP
Hoffman et al. (2014) USA North Carolina	2011–2012	8 pregnant women (18th and 28th week of pregnancy: 24-h urine and first morning voids. After birth of child: 1 spot urine) 39 urine samples Not adjusted for specific gravity	–	–	–	1.1 (19.9) **97**	–	–	–	1.6 (37.3) **97**
Meeker et al. (2013b) USA Massachusetts	2002–2007	45 men Spot urine Presumably specific gravity adjusted	–	–	–	0.12 (25.0) **91**	–	–	–	0.27 (9.84) **96**
Cooper et al. (2011) North America	nr	3 adults 9 urine samples Spot urine Specific gravity adjusted	–	–	–	0.37 (3.47) **100**	–	–	–	1.81 (63.8) **100**

50th percentile (max) % ≥ **limit of detection (LOD)**

nr not reported, n.a. not applicable

– Not analyzed

[a]Mean

[b]In most studies, the metabolite method limit of detection (MLOD) was in the range of 0.01–0.6 µg/l, depending on the method used. It was lower for BDCIPP and BBOEP (3 ng/l) in the study of He et al. (2018a) and for BCEP, BDCIPP, and DPHP in the study of Sun et al. (2018) (2–5 ng/l). The MLOD was in the range of 1.0–2.7 µg/l for BCIPP in the study of Hammel et al. (2016), for BCIPP and DPHP in the study of Kosarac et al. (2016), and for DNBP and DPHP in the study of Yoshida et al. (2012). The limit of quantification (LOQ) of BCEP, BCIPP, BDCIPP, and DNBP was in the range of 0.8–1.6 µg/l in the study of Chen et al. (2018). The LOQs of BCEP and BCIPP were 1.2, and 3.7 µg/l, respectively, in the study of Van den Eede et al. (2013b). The LOQ of DNBP and DPHP were 2.3, and 2.6 µg/l, respectively, in the study of Yoshida et al. (2012)

Table 4 Urinary concentrations of the principal metabolites of PEFRs in workers (μg/L)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	DPHP	Other
Bello et al. (2018) USA	nr	12 spray polyurethane foam applicators (construction insulation) Spot urine pre- and post-shift (24 samples) Specific gravity adjusted	–	6.2[a] (51.4) **100**	88.8[a] (703) **100**	5.3[a] (33.4) **100**	–	27.9[a] (134) **100**	6.5[a] (36.1) **100**	–
Tao et al. (2018) China	2016–2017	26 hotel room attendants (52 samples) Morning void and post-shift urine Specific gravity adjusted	–	–	–	0.23 (2.4) **79**	0.048 (1.3) **38**	–	0.24 (1.8) **87**	BBOEP: 0.11 (9.0) **59** DoCP&DpCP: 0.17 (1.1) **79** and **87**
Yan et al. (2018) China	nr	*E-waste recycling site* 88 workers (men and women) First morning void Not adjusted for specific gravity	1.77 (48.3) **94**	nr (0.31) **16**	–	0.23 (31.8) **82**	nr (0.96) **41**	–	0.70 (26.6) **93**	BBOEP: nr (21.0) **35** DNBP: nr (0.96) **41**
		Incineration plant 30 workers (men and women) First morning void Not adjusted for specific gravity	1.44 (22.5) **97**	nr (0.97) **40**	–	0.22 (3.56) **93**	–	–	0.11 (3.39) **90**	BBOEP: nr (26.2) **43** DNBP: 0.30 (34.8) **100**
Jayatilaka et al. (2017) USA	2010–2011	146 firefighters Spot urine collected within 3 h after firefighting Not adjusted for specific gravity	0.86 (10) **90**	0.24 (2.9) **63**	–	3.4 (44) **100**	0.18 (2.4) **92**	–	2.9 (28) **100**	DpCP: < LOD (0.31) **34**
	2015	76 adults from the general population Not adjusted for specific gravity	<LOD (4.1) **10**	<LOD (0.98) **5**	–	0.69 (6.8) **100**	< LOD (0.26) **5**	–	0.89 (5.6) **100**	n.a. **0**
Schindler et al. (2014) Germany	nr	5 aircraft maintenance technicians Spot urine Not adjusted for specific gravity Pre-shift/post-shift	0.5/0.3 (1.7)/ (0.5) **100**	0.2/0.2 (0.3)/ (0.3) **70**	–	–	12.5/23.5 (37.2)/(51.6) **100**	–	2.9/3.5 (7.4)/ (7.9) **100**	DoP, DmCP, or DpCP < LOD (i.e. 0.5)

Table 4 (continued)

Author, location	Sampling year	*N* (population)	BCEP	BCIPP	BCIPHPP	BDCIPP	DNBP	ip-PPP	DPHP	Other
Carignan et al. (2013) USA	2009	29 office workers (women and men) Spot urine during afternoon of a work day Specific gravity adjusted	–	–	–	408[a] (1760) **100**	–	–	–	–
Schindler et al. (2009a, b, 2013) (Anderson 2015; Weiss et al. 2015) Germany	nr	332 urine samples from air crews Spot urine collected within 12 h after exposure Not adjusted for specific gravity	0.33 (20.3) **82**	0.16 (6.87) **65**	–	–	0.28 (9.72) **100**	–	1.10 (302) **100**	DoP: < LOD (i.e. 0.5) DmCP: < LOD (0.62) **0.3** DpCP < LOD (0.55) **0.3**
		30 individuals from the general population (11–68 years) Spot urine Not adjusted for specific gravity	< 0.1[b] (27.5) **50**	< 0.25[b] (0.85) **12**	–	–	< 0.25[b] (0.26) **4**	–	0.52 (5.47) **68**	DoP, DmCP, or DpCP < LOD (i.e. 0.5)

50th percentile (max) % ≥ **limit of detection (LOD)**

nr not reported

– Not analyzed

[a]Geometric mean

Concentrations of urinary PEFR metabolites varied greatly both between the populations studied and from individual to individual within cohorts (Hoffman et al. 2017a; Preston et al. 2017). Except for BDCIPP and DPHP which were typical worldwide contaminants, there was no strong common pattern for the compositional profile of urinary PEFR metabolites. This may be explained by differences in FR regulations, dietary habits, lifestyle, and use of PEFRs in household products and indoor environments (e.g., building material), between the various countries and/or study locations (Carignan et al. 2013; Butt et al. 2016; Lu et al. 2017; Chen et al. 2018; He et al. 2018b). Other factors were reported to have an impact on urinary PEFR metabolite concentrations, including timing (e.g., season of collection) (Hoffman et al. 2017a, b; Deziel et al. 2018; Ingle et al. 2018; Phillips et al. 2018), sex (e.g., women tend to have higher levels of DPHP than men, Hoffman et al. 2015b; Preston et al. 2017; He et al. 2018a; Ospina et al. 2018), behavior and activity patterns (e.g., hand washing and cleaning routines, nail painting) (Abdallah et al. 2016; Mendelsohn et al. 2016; He et al. 2018b) and age (Van den Eede et al. 2015b; Lu et al. 2017; He et al. 2018a; Ospina et al. 2018; Sun et al. 2018). Urinary concentrations of the main PEFR metabolites were generally higher in toddlers than in adults (Butt et al. 2014, 2016; Cequier et al. 2015; Hoffman et al. 2015a; Van den Eede et al. 2015b; Chen et al. 2018; He et al. 2018a, b; Ospina et al. 2018). This is an international trend, generally attributed to the tendency of young children to crawl on the floor and to their elevated hand-to-mouth contact behavior, both of which result in increased oral and dermal contact with indoor settled dust and with products containing these chemicals (e.g., plastic toys). Differences in pharmacokinetics with age cannot be excluded.

Long-term temporal trends in the urinary levels of some PEFR metabolites have been reported among adults and/or children in the United States. Concentrations of BDCIPP in urine samples collected in 2014–2015 were 16.5 times higher than those collected in 2002–2003, while concentrations of DPHP increased at much lower rates until 2011 (Hoffman et al. 2017b). This may be related to changes in the use of specific PEFRs to meet the more stringent regulation of certain FRs, and improvements in the fire safety standards required for finished consumer products (e.g., furniture and textiles). For example, TCEP and TDCPP have recently been restricted or banned in children's products in several states in the USA (Vermont General Assembly 2013, US EPA 2015; Council of Columbia 2016, Department of Ecology State of Washington 2016).

In addition to the studied populations and the sources of PEFR emissions, sampling strategies may affect the study results. Human observations (Carignan et al. 2016) and in vitro and in vivo rat studies suggest that PEFRs are rapidly metabolized and eliminated in urine. PEFR half-lives in humans are generally estimated to be on the order of a few hours. The use of single spot urine samples in most studies may not represent metabolite concentration over time and may contribute to the variability in the metabolite concentrations. However, a slower urinary elimination of some metabolites (i.e., BBOEP) was recently observed in volunteers following an oral administration of TBOEP (Völkel et al. 2018). Several studies collected multiple samples over one day or the course of the study to limit within-subject variability (Meeker et al. 2013b; Hoffman et al. 2015b; Cequier et al. 2015, Su et al. 2015; Carignan et al. 2016; Hammel et al. 2016; Preston et al. 2017; He et al. 2018b; Phillips et al. 2018).

Analytical treatment of the biological samples may be critical for the measurement of PEFR urinary metabolites, e.g., conditions of urine collection and storage (Petropoulou et al. 2016; Carignan et al. 2017). Differences in the detection and quantification limits of the analytical methods employed to quantify urinary metabolites may also account for the broad range of detection rates of some metabolites within and/or across studies. Van den Eede et al. (2013b) showed that improvement of the LOQ method resulted in a higher detection frequency of BCEP and BDCIPP. In several studies, the method limit of detection (MLOD) of the hydroxylated metabolite of TCIPP, BCIPHPP, was much lower than that of the diester, BCIPP (at least tenfold—Butt et al. 2016; Hammel et al. 2016; Hoffman et al. 2017a; He et al. 2018a). BCIPHPP was in fact found at a higher incidence than BCIPP in recent biomonitoring studies that measured both metabolites in urine samples from the general population (Butt et al. 2016; Hammel et al. 2016; Hoffman et al. 2017a, 2018).

The biotransformation of PEFRs has not been extensively investigated in animals and humans and their potential metabolic pathways are principally based on qualitative in vitro analyses. In vivo, the triesters may undergo very little transformation, and/or several major metabolites other than diesters may be formed (Hou et al. 2016; Völkel et al. 2018). In addition, urine may not be the sole excretion pathway for certain PEFRs. Diester metabolites were the main metabolites targeted in urine for all PEFRs. However, there may be qualitative and quantitative metabolic differences between the compounds and/or between the metabolite kinetics. If the measured metabolite was not the best urinary biomarker of exposure, this would lead to underestimation of exposure for some PEFRs. For example, the diester metabolites of TBOEP and TCIPP were not always the main metabolites formed in vitro by human liver preparations. Several potential hydroxylated derivatives have been considered for urinary monitoring of certain PEFRs (e.g., BBOEHEP for TBOEP and BCIPHPP for TCIPP) (Van den Eede et al. 2015b; Butt et al. 2016; Hammel et al. 2016; Hoffman et al. 2017a, 2018; Bello et al. 2018; He et al. 2018a, b; Phillips

Table 5 PEFR concentrations in hair and nails (ng/g dry weight)

Author Location *N* (population) Sampling year	TCEP	TCIPP	TDCIPP	TNBP	TEHP	EHDPP	TPHP	TBOEP	Other
Europe									
Alves et al. (2017) Belgium A woman and a man Year nr									
Hair (scalp segment, one sample)	–	–	–	–	–	–	–	–	*DPHP* Woman[c]: *0.25* Man[c]: *0.23*
Fingernails (4 or five collections over 2 months	–	–	–	–	–	–	–	–	Woman[c]: *40,002* Man[c]: *80.5*
Toenails (4 or five collections over 2 months	–	–	–	–	–	–	–	–	Woman[c]: *6815* Man[c]: *18.5*
Kurcharska et al. (2015a) Norway 48 mothers and their 54 children (6–12 year old) 2012									
Hair (scalp segment) *Mothers*	72 (< 33[a]–163) **16**	–	30 (< 9[a]–3744) **91**	22 (5-672) **100**	12 (< 1[a]–53) **96**	27 (5 -265) **100**	52 (5-1256) **100**	65 (14-1253) **100**	*TCP*[b] 8 (< 2[a]–134) **78**
Hair (scalp segment) *Children*	59 (< 33[a]–118) **26**	–	31 (< 9[a]–2698) **92**	11 (3–150) **100**	8 (< 1[a]–118) **90**	21 (2[a]–346) **100**	63 (6-363) **100**	318 (34-2411) **100**	*TCP*[b] 8 (< 2[a]–74) **62**
Martin et al. (2015) Germany 4 women Year n.r									
Hair (scalp segment)		nr (0.18–1.70) **100**	–	**0**	–	–	nr (0.10–0.91) **100**	–	–
Kurcharska et al. (2014) Belgium 20 adults Year nr									
Hair	55 (34–404) **70**	–	42 (10-2969) **95**	32 (7-5032) **95**	10 (2-322) **75**	15 (5-105) **100**	59 (7-237) **100**	37 (7-338) **100**	*TCP*[b] 5 (3–73) **65**
China									
Qiao et al. (2016) 49 adults (27 man and 22 woman) 2014									
Hair (two segments)	3.61 (< 3.50[a]–64.9) **57**	43.9 (< 6.53[a]–141) **98**	4.14 (< 1.04[a]–73.8) **86**	3.30 (< 0.61[a]–25.4) **98**	24.1 (< 0.05[a]–151) **98**	11.8 (5.78[a]–78) **71**	20.5 (< 1.43[a]–352) **84**	–	*TiPP* 2.43 (< 0.81[a]–12.4) **94**

Table 5 (continued)

Author Location *N* (population) Sampling year	TCEP	TCIPP	TDCIPP	TNBP	TEHP	EHDPP	TPHP	TBOEP	Other
United States									
Liu et al. (2016) Indiana 50 adults 2014									
Hair (scalp segment)	240 (60-2740) **68**	450 (100–9840) **88**	360 (70-10490) **90**	–	–	–	220 (70-4710) **98**	–	–
Fingernail	190 (93-1860) **20**	220 (74-2410) **36**	300 (90-1410) **66**	–	–	–	370 (110-59800) **74**	–	–
Toenail	150 (100–150) **8**	230 (90-5150) **32**	230 (75-2300) **50**	–	–	–	1080 (54-232900) **74**	–	–
Liu et al. (2015) Indiana 5 adults Year nr									
Hair (scalp segment)	nr (< 75[a]–1950) **80**	nr (290–1190) **100**	nr (< 75[a]–970) **80**	–	–	–	nr (76–310) **100**	–	–
Fingernail	nr (< 150[a]–< 150) **0**	nr (< 150[a]–<150) **0**	nr (280–630) **100**	–	–	–	nr (< 150[a]–17,500) **100**	–	–

50th percentile (range) % ≥ **limit of detection**

nr not reported

[a]Limit of quantification (LOQ)

[b]Sum of isomers

[c]Average level

et al. 2018). In fact, BBOEP and BBOEHEP were detected in 80% of urine samples from volunteers orally administered a single dose of TBOEP (20 µg/kg b.w.), with comparable median values (0.16 and 0.18 µg/l, respectively) (Völkel et al. 2018). However, the maximum concentration of BBOEHEP was much higher than that of BBOEP (3700 and 69 pmol/kg b.w., respectively) and was reached within 1–2 h. In contrast, BBOEP showed some maxima within 25 h, before a smooth decline.

Several biomonitoring studies with large cohort size provide robust information on general population exposures to PEFRs. They related to a representative sample of the US general population (Ospina et al. 2018), adults in China (Lu et al. 2017) and the United States (Carignan et al. 2018a, b), children in China (Chen et al. 2018) and Germany (Fromme et al. 2014), and pregnant women in the United States (Castorina et al. 2017b; Hoffman et al. 2017a).

No consistent and/or uniform correlation could be established between urinary levels of some PEFR metabolites (mainly diesters) and the concentrations of the corresponding parent compounds in hand wipes or in indoor dust samples from various microenvironments (Carignan et al. 2013; Meeker et al. 2013b; Dodson et al. 2014; Fromme et al. 2014; Cequier et al. 2015; Hoffman et al. 2015b; Hammel et al. 2016; Castorina et al. 2017b; Larsson et al. 2018; Phillips et al. 2018; Tao et al. 2018; Völkel et al. 2018). Associations were generally specific to the PEFR. Some weak or positive correlations were reported, but inconstantly, for the pairs TCEP/BCEP, TDCIPP/BCIPP, TPHP/DPHP, and/or TBOEP/BBOEP. Urinary biomarkers are indicators of integrated personal exposure. Each PEFR may have several different sources and pathways of exposure, and dust sampled from specific indoor microenvironments may not be the sole and/or the primary contributor to the body burden.

Occurrence of PEFRs in other human samples

Most human biomonitoring studies have used urine as biological matrix to evaluate exposure to PEFRs. Less is known about the possibility of using PEFR levels in segments of hair and/or nails as retrospective non-invasive biomarkers for PEFR monitoring. The main PEFRs (unchanged compounds) were detected in most of the hair samples collected in various countries (e.g., TCIPP, TDCIPP, TPHP) (Table 5). Levels measured in hair were highly variable between individuals, with concentrations ranging from ng/g to high concentrations of several µg/g within the study populations (e.g., TDCIPP and TPHP, Kurcharska et al. 2015a; Liu et al. 2016). It was suggested that PEFR levels in the hair are derived from a combination of both external exposure from air and dust and internal exposure. PEFRs in hair reflect long-term exposure while the occurrence of PEFR metabolites in urine most likely corresponds to recent exposure (Kurcharska et al. 2015b; Alves et al. 2017).

A number of studies have reported the presence of PEFRs in other human tissues and body fluids. PEFRs were frequently detected in placenta (Ding et al. 2016; Zhao et al. 2017) and breast milk (Sundkvist et al. 2010; Kim et al. 2014; He et al. 2018a). The median concentration of total PEFRs was around 10–100 ng/g of lipids in breast milk from Sweden and several Asian countries, indicating that substantial exposure occurs at a young age via breastfeeding (Sundkvist et al. 2010; Kim et al. 2014). The parent compounds (Liu et al. 2016; Zhao et al. 2016; Li et al. 2017; Ma et al. 2017; Qiao et al. 2016) and their metabolites (Bui et al. 2017) were found in human serum and blood in a few studies. The metabolism of parent PEFRs tends to occur rapidly and the measurement of metabolites concentrations in urine is generally preferred to the invasive measurement of the non-metabolized chemicals in serum for exposure assessment.

Conclusion

This short review shows that the use of urinary levels of PEFRs metabolites for monitoring internal human exposure to these emerging pollutants is widespread and has gained increasing attention over the past few years. The biomonitoring studies confirm ubiquitous exposure of the general population to PEFRs all over the world, and potentially higher exposures in children and among a number of occupational populations. The levels and compositional patterns of urinary metabolites varied as a function of factors, such as the location and time of sampling. Further information on the toxicokinetics of PEFRs in humans and the continued development and validation of bioanalytical methods will allow refinement of the current biomarkers of exposure to these chemicals. Additional biomonitoring data on PEFRs are still needed to reduce the uncertainty in estimating human exposure, to identify the populations at risk and any possible associations with adverse health effects, to follow exposure trends, and to evaluate governmental prevention strategies and programs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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