Environment International 119 (2018) 438–446

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Associations between allergic symptoms and phosphate flame retardants in dust and their urinary metabolites among school children

Atsuko Araki[a], Michiel Bastiaensen[b], Yu Ait Bamai[a], Nele Van den Eede[b], Toshio Kawai[c], Tazuru Tsuboi[c], Rahel Mesfin Ketema[a,d], Adrian Covaci[b], Reiko Kishi[a,*]

[a] Hokkaido University Center for Environmental and Health Sciences, Kita 12, Nishi 7, Kita-ku, Sapporo 060-0812, Japan
[b] Toxicological Center, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium
[c] Osaka Occupational Health Service Center, Japan Industrial Safety and Health Association, 2-3-8, Tosabori, Nishi-ku, Osaka 550-0001, Japan
[d] Hokkaido University, Graduate School of Health Sciences, Kita 12, Nishi 5, Kita-ku, Sapporo 060-0812, Japan

ARTICLE INFO

Handling Editor: Heather Stapleton

Keywords:
Phosphate flame retardants
Allergies
House dust
Urine
Metabolites
Children

ABSTRACT

Background: Phosphate flame retardants (PFRs) are ubiquitously detected in indoor environments. Despite increasing health concerns pertaining to PFR exposure, few epidemiological studies have examined PFR exposure and its effect on children's allergies.

Objectives: To investigate the association between PFRs in house dust, their metabolites in urine, and symptoms of wheeze and allergies among school-aged children.

Methods: A total of 128 elementary school-aged children were enrolled. House dust samples were collected from upper-surface objects. Urine samples were collected from the first morning void. Levels of 11 PFRs in dust and 14 PFR metabolites in urine were measured. Parent-reported symptoms of wheeze, rhinoconjunctivitis, and eczema were evaluated using the International Study of Asthma and Allergies in Childhood questionnaire. The odds ratios (ORs) of the Ln transformed PFR concentrations and categorical values were calculated using a logistic regression model adjusted for sex, grade, dampness index, annual house income, and creatinine level (for PFR metabolites only).

Results: The prevalence rates of wheeze, rhinoconjunctivitis, and eczema were 22.7%, 36.7%, and 28.1%, respectively. A significant association between tris(1,3-dichloroisopropyl) phosphate (TDCIPP) in dust and eczema was observed: OR (95% confidence interval), 1.44 (1.13–1.82) (> limit of detection (LOD) vs < LOD). The ORs for rhinoconjunctivitis (OR = 5.01 [1.53–16.5]) and for at least one symptom of allergy (OR = 3.87 [1.22–12.3]) in the 4th quartile of Σtris(2-chloro-isopropyl) phosphate (TCIPP) metabolites was significantly higher than those in the 1st quartile, with significant *p*-values for trend (P_{trend}) (0.013 and 0.024, respectively). A high OR of 2.86 (1.04–7.85) (> LOD vs < LOD) was found for hydroxy tris(2-butoxyethyl) phosphate (TBOEP)-OH and eczema. OR of the 3rd tertile of bis (1,3-dichloro-2-propyl) phosphate (BDCIPP) was higher than the 1st tertile as a reference for at least one symptom (OR = 3.91 [1.25–12.3]), with a significant P_{trend} = 0.020.

Conclusions: We found that TDCIPP in house dust, and metabolites of TDCIPP, TBOEP and TCIPP were associated with children's allergic symptoms. Despite some limitations of this study, these results indicate that children's exposure to PFR may impact their allergic symptoms.

1. Introduction

Organophosphate triesters are a class of chemicals predominantly used as additives in flame retardants and plasticizers. After the manufacturer's voluntary phase-out of the use of polybrominated diphenyl esters and polybrominated biphenyls, the use of phosphorus flame retardants (PFRs) as alternative flame retardant additives is on the rise (Kajiwara et al., 2011; Le Cann et al., 2011; Bergman et al., 2012). Polyurethane foam, thermoplastics, resins, polyvinylchloride, synthetic rubbers, and textiles are some of the major products that contain tri-*n*-butyl phosphate (TNBP), tris (2-chloroethyl) phosphate (TCEP), tris(2-chloro-isopropyl) phosphate (TCIPP), tris (1,3-dichloro-2-propyl) phosphate (TDCIPP), and triphenyl phosphate (TPHP) (Stapleton et al., 2009; Van den Eede et al., 2011). TNBP, TPHP, and tricresyl phosphate (TMPP) are also used as lubricants, and tris (2-butoxyethyl) phosphate (TBOEP) is often used in floor covering and as a plasticizer in floor

* Corresponding author.
E-mail address: rkishi@med.hokudai.ac.jp (R. Kishi).

https://doi.org/10.1016/j.envint.2018.07.018
Received 26 April 2018; Received in revised form 9 July 2018; Accepted 11 July 2018

finish products and polish (Kajiwara et al., 2011). Since PFRs have been used in many housing materials and consumer products, their presence in indoor dust has been widely studied (Garcia et al., 2007; Stapleton et al., 2009; Bergh et al., 2011; Ali et al., 2012a; Ali et al., 2012b; Dirtu et al., 2012; Dodson et al., 2012; Araki et al., 2014; Tajima et al., 2014).

However, few reports have described the associations between PFRs exposure and human health. Three studies have indicated adverse associations of reproductive function and PFR exposure, with PFR being associated with lower levels of free thyroxine and prolactin levels, the reduced quality of semen and embryos, and the lower success of several in vitro fertilization outcomes, such as successful fertilization, implantation clinical pregnancy, and live birth (Meeker and Stapleton, 2010; Carignan et al., 2017; Carignan et al., 2018). One birth cohort study found that maternal PFR exposure resulted in decreased intelligence quotient scores and working memory among children (Castorina et al., 2017). One case-control study found that the occurrence and severity of papillary thyroid cancer was associated with a higher exposure to TCEP (Hoffman et al., 2017). Our previous cross-sectional study examined the associations between PFR levels in house dust and inhabitants' prevalence of sick building syndrome (Kanazawa et al., 2010), as well as asthma and allergies (Araki et al., 2014). We found that the prevalence of atopic dermatitis was higher when the concentrations of TCIPP and TDCIPP were higher, and the prevalence of asthma and allergic rhinitis was higher when the concentration of TNBP was higher. However, the concentration of PFRs in house dust does not exactly reflect individual exposure levels. Moreover, no study to date has focused on children, who are considered to be more vulnerable to the development of allergic symptoms via exposure to household dust, despite living in the same environment as adults (Ait Bamai et al., 2014b).

Recently, the biomonitoring of PFR has been established, and the metabolites of the abundant PFRs in indoor dust, such as TDCIPP, TCIPP, TCEP, TPHP, TBOEP, and TNBP, were quantified as a measure of the internal exposure of individuals (Van den Eede et al., 2013; Van den Eede et al., 2015). This study aimed to investigate the association between the PFRs in house dust and their metabolites in urine, and the prevalence of allergies in children. We hypothesized that increasing levels of TDCIPP and TCIPP in dust and their metabolites in urine are associated with an increasing risk of developing allergic symptoms.

2. Methods

2.1. Study participants

This study was conducted with elementary school-aged children (n = 128) using a questionnaire and a home visit for environmental measurements, in October and November of 2009 and 2010. Details on participant selection have been reported previously (Ukawa et al., 2013; Ait Bamai et al., 2014a; Tajima et al., 2014). Briefly, an initial cross-sectional study was conducted in Sapporo city in 2008. The questionnaire was distributed to 6393 school children from 12 public elementary schools with an additional query of whether they were interested in participating in a home survey. Of the 4408 students who responded to the questionnaire, 951 (from 832 families) agreed to a home visit for the conduction of environmental measurements in the following calendar years. In 2009 and 2010, 681 families with children who were still attending the same elementary school as in 2008 were contacted for a home visit. Through this selection procedure, we identified a total of 128 families (18.8%) that agreed to the home visit, and we successfully adjusted a schedule for the same.

2.2. Questionnaire

When investigators visited each house for environmental measurements in 2009 or 2010, self-administered questionnaires were distributed at the 1st visit, and investigators collected the responses 2 days later, during the 2nd visit. The questionnaire included questions on children's sex, school grade, duration spent at home, duration of sleep, and parental history of allergies. Parents also filled in data pertaining to the type of dwelling, building structure, building age, renovations, floor and wall materials used, the presence of an indoor smoker at home, the presence of pets, and dampness-related signs of mold growth, moldy odor, condensation, water leakage, and high humidity levels in the bathroom.

To define children's allergies, the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was used (Beasley, 1998). We classified participants as having wheeze when their parents answered "Yes" to the question: "Has your child had wheezing or whistling in the chest in the last 12 months?" Allergic rhinoconjunctivitis was defined by the following questions: (a) "Has your child had a problem with sneezing, or a runny/blocked nose in the absence of a cold or flu in the last 12 months?", and (b) "Has this nose problem been accompanied by itchy, watery eyes?". Eczema was defined by the following questions: (a) "Has your child had an itchy rash that has appeared and disappeared for at least 6 months?"; (b) "Have the aforementioned itchy rashes appeared at any time during the last 12 months?"; and (c) "Have the aforementioned itchy rashes affected one or several of the following areas: the folds of the elbows, the back of knees, the front of the ankles, the underside of the buttocks, or the areas around the neck, ears, or eyes?" When a child was defined as having wheeze, eczema and/or allergic rhinoconjunctivitis, the response was" Yes" for at least one of the before mentioned symptoms.

Table 1
Characteristics of the participants.

		Total (n = 128)	
		n	%
Sex	Boys	68	53.1
	Girls	60	46.9
Grade	2	14	10.9
	3	35	27.3
	4	27	21.1
	5	24	18.8
	6	28	21.9
Parental history of allergy	No	29	22.7
	Mother only	48	37.5
	Father only	15	11.7
	Both	36	28.1
Annual household income	< 3 million	6	4.7
(Japanese yens/year)	3–5 million	25	19.5
	5–8 million	50	39.1
	> 8 million	28	21.9
	Missing	19	14.8
Wheeze	Yes	29	22.7
Rhinoconjunctivitis	Yes	47	36.7
Eczema	Yes	36	28.1
At least one of the above symptoms	Yes	72	56.3
		Mean/ median	SD (or IQR)
Height (cm)	Mean ± SD	137.2	± 10.8
Weight (kg)	Mean ± SD	32.1	± 8.3
Body mass index (kg/m^2)	Mean ± SD	16.8	± 2.5
Duration spend at home (hour)	Median, IQR	15	(15–16)
Duration of sleep (hour)	Median, IQR	9.5	(9.0–9.8)
Birth weight (g)	Mean ± SD	3098.5	± 419.4
Breast milk (month)	Median, IQR	10	(3 − 13)

IQR, inter quartile, range; SD, standard deviation.

2.3. PFR measurements in settled home dust

Details on dust collection and PFR analysis through gas chromatography/mass spectrometry (GC/MS), together with quality control and quality assurance, have been reported elsewhere (Ait Bamai et al., 2014a; Tajima et al., 2014). Briefly, dust samples were collected from