Science of the Total Environment 781 (2021) 146667

Contents lists available at ScienceDirect

Science of the Total Environment

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

Targeted and suspect screening of plasticizers in house dust to assess cumulative human exposure risk

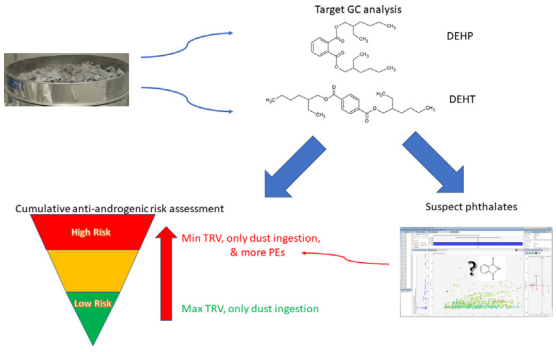
Hale Demirtepe [a,b], Lisa Melymuk [a,*], Garry Codling [a], Ľubica Palkovičová Murínová [c], Denisa Richterová [c], Vladimíra Rašplová [c], Tomáš Trnovec [c], Jana Klánová [a]

[a] RECETOX, Masaryk University, Kamenice 753/5, pavilion D29, 625 00 Brno, Czech Republic
[b] İzmir Institute of Technology, Faculty of Engineering, Department of Environmental Engineering, 35430, Urla, İzmir, Turkey
[c] Department of Environmental Medicine, Faculty of Public Health, Slovak Medical University, Limbová 12, 83303 Bratislava, Slovakia

HIGHLIGHTS

- DEHP & DEHT dominated phthalate & alternative plasticizer dust levels, respectively.
- Acceptable risks estimated for anti-androgenic effects of PEs via dust ingestion.
- Uncertainty in toxicity data and other exposure routes may alter the risk.
- Non-target analysis suggests >50 PEs in dust; many are ignored in risk assessment.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 8 January 2021
Received in revised form 5 March 2021
Accepted 17 March 2021
Available online 23 March 2021

Editor: Jay Gan

Keywords:
Alternative plasticizer
Cumulative risk assessment
Indoor dust
Phthalate ester
Suspect screening

ABSTRACT

Indoor dust is an important exposure route to anthropogenic chemicals used in consumer products. Plasticizers are common product additives and can easily leach out of the product and partition to dust. Investigations of plasticizers typically focus on a subset of phthalate esters (PEs), but there are many more PEs in use, and alternative plasticizers (APs) are seeing greater use after recognition of adverse health effects of PEs. In this study we use full scan high resolution mass spectrometry for targeted and suspect screening of PEs and APs in house dust and to assess the potential risk of human exposure. House dust samples from Eastern Slovakia were investigated and concentrations of $\sum_{12}$PEs and $\sum_{5}$APs ranged 12–2765 μg/g and 45–13,260 μg/g, respectively. APs were at similar levels to PEs, indicating common usage of these compounds in products in homes.

Evaluation of individual compound toxicity combined with human intake via dust ingestion suggested PEs are of lower priority compared to semivolatile organic compounds such as polychlorinated biphenyls due to their lower toxicity. However, cumulative risk assessment (CRA) is a more appropriate evaluation of risk, considering the presences of many PEs in dust and their similar toxic mode of action. CRA based on median toxicity reference values (TRVs) suggested acceptable risks for dust ingestion, however, the wide range of literature-derived TRVs is a large uncertainty, especially for the APs. Use of newer TRVs suggest risk from dust ingestion alone, i.e. not even considering diet, inhalation, and dermal contact. Additionally, screening of full-scan instrumental spectra identified a further 40 suspect PE compounds, suggesting the CRA based on the 12 target PEs underestimates the risk.

* Corresponding author.
E-mail address: lisa.melymuk@recetox.muni.cz (L. Melymuk).

https://doi.org/10.1016/j.scitotenv.2021.146667
0048-9697/

1. Introduction

Due to human and industrial needs, synthetic materials have become ubiquitous in our lives, and most notably plastic products. Global production of plastics reached almost 370 Mtons in 2019 with extensive usage in consumer products (Plastics Europe, 2020). Plastic materials contain a wide range of additives to impart the properties needed in the final products, and this frequently includes plasticizers, forming up to 55% by weight of the material (Narvaez Rincon and Suarez Palacios, 2015). Phthalate esters (PEs) are the most commonly used plasticizers, used to improve flexibility and durability in many consumer products (Kutz, 2017; Stanley et al., 2003). PEs are found in polyvinyl chloride (PVC) products, toys, flooring, carpets, wall coverings, food packaging, medical products, glue and paint (ATSDR, 1997, 2001, 2019; Kutz, 2017; Zhang et al., 2020), as well as cosmetics and insecticides, mainly containing low molecular weight (LMW) PEs such as diethyl phthalate (DEP) and dimethyl phthalate (DMP) (ATSDR, 1995). Many PEs are considered high production volume (HPV) compounds: yearly production and import of bis(2-ethylhexyl)phthalate (DEHP) in the European economic area (EEA) is between 10^4 and 10^5 t, while that of di-*n*-butyl phthalate (DnBP), DEP and DMP is between 10^3 and 10^4 t (ECHA, 2018) (Table S1).

Since plasticizers are applied as additives to a product, they can easily leach out of the product and be emitted to the environment where the products are used or when they are disposed as wastes, hence PEs are broadly detected in the global environment (Net et al., 2015). Due to widespread usage in indoor-related products and physicochemical properties allowing for significant partitioning to particulates, PEs can be found ubiquitously in indoor dust, which is an important human exposure route to PEs, especially to high molecular weight compounds considering their higher abundance in dust than in indoor air (Giovanoulis et al., 2018) and more specifically for infants and toddlers (Wormuth et al., 2006).

Exposure to PEs has been associated with negative effects on reproductive and developmental systems, endocrine disruption (Hauser and Calafat, 2005; Meeker et al., 2009; Swan et al., 2005), allergies and asthma in children (Ait Bamai et al., 2016; Bekö et al., 2015; Bertelsen et al., 2013), obesity and cardiometabolic risk factors in children and adolescents (Amin et al., 2018). Due to the evidence of adverse health effects, especially in children, the use of DEHP, DnBP, butylbenzyl phthalate (BBP), di-isobutyl phthalate (DiBP), di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP) and di-*n*-octyl phthalate (DnOP) has been restricted by the European Commission to not exceed 0.1% by weight of plasticized material in toys and childcare products (REACH, 2018). The same restriction was applied in the USA, but also included di-*n*-pentyl phthalate (DPP), di-*n*-hexyl phthalate (DHP) and dicyclohexyl phthalate (DCHP), but not DIDP and DnOP (CPSC, 2017).

The restrictions on the use of legacy PEs has led to the introduction of alternatives with lower toxic potential. Among these alternative plasticizers (APs), bis(2-ethylhexyl)terephthalate (DEHT) and bis(2-propylheptyl)phthalate (DPHP) have yearly production and import volume up to 10^6 t to the EEA, while acetyl tributyl citrate (ATBC), bis(2-ethylhexyl)adipate (DEHA) and 1,2-*cyclo*hexane dicarboxylic acid diisononyl ester (DINCH) are individually produced and imported in the range from 10^4 to 10^5 t (ECHA, 2018). The larger production volumes for APs compared with legacy PEs suggest similar abundance in indoor environments to the legacy PEs, especially in indoor dust due to their partitioning coefficients similar to PEs (Bui et al., 2016). Therefore, their exposure and potential toxicity should be evaluated carefully. While the APs considered for target analysis in this study have been examined for developmental and reproductive toxicity, there is limited information compared to the PEs. ECHA reports no observed adverse effect levels (NOAELs) based on developmental and reproductive toxicity for DPHP and ATBC and derived no-effect levels (DNEL) based on repeated dose toxicity for all APs, except for DINCH which is based on carcinogenicity (ECHA, 2018). However, despite the perception of lower hazard for the APs, ATBC was found to have endocrine disrupting potential and neurotoxicity (Bui et al., 2016).

Evaluation of the risk associated with indoor exposure is crucial, especially considering the range of semi-volatile organic compounds (SVOCs) typically present indoors, with wide variations in concentrations and toxicity. We have previously proposed a framework combining human intake and toxicity reference values (TRVs) to prioritize SVOCs for risk assessment (Demirtepe et al., 2019). The framework, relying on median TRVs reported in literature and by regulatory agencies, enabled a comparative evaluation of risks of individual SVOCs. However, this framework ignores the possibility of mixture effects based on chemicals having similar toxicological endpoints. PEs are known to have common developmental and reproductive health effects (Howdeshell et al., 2008), particularly anti-androgenic effects (Pelletier et al., 2018; Radke et al., 2019). Anti-androgenic effects include decreased fetal testosterone, reduced anogenital distance, reduced reproductive organ weights, retained nipples, decreased sperm production and Leydig cell adenomas (Gray et al., 2000; Kortenkamp and Faust, 2010). Multiple PEs are typically present indoors; therefore cumulative risk assessment (CRA) can more accurately estimate the human exposure risk (Kortenkamp and Faust, 2010; Pelletier et al., 2018).

This study employs ultra-high resolution mass spectrometry coupled with gas chromatography operating in full scan with the aim of (i) identifying the concentrations of target PEs and APs in Slovakian indoor dust, considered representative of European SVOC levels (Demirtepe et al., 2019), and investigating their associations with home characteristics, (ii) assessing human exposure to PEs and APs via dust ingestion, and cumulative anti-androgenic risk of PEs, and (iii) using non-target screening for the evaluation of unquantified/unknown compounds with PE structure.

2. Methods

2.1. Sample collection and preparation

Indoor dust samples from 60 homes in Eastern Slovakia were collected in March–April 2015. Details on sampling location are presented in a previous study (Demirtepe et al., 2019). The dust samples were collected using a household vacuum cleaner with polyester sock inserted in the front of the vacuum tube and vacuuming 1 to 3 m^2 floor surface. The sock was removed from vacuum cleaner, packed in aluminum foil, put into a zip-lock bag, stored in freezer at −18 °C for transport to the laboratory.

The analytical procedure used was published previously (Demirtepe et al., 2019; Jílková et al., 2018; Venier et al., 2016; Vojta et al., 2017; Vykoukalová et al., 2017), and is briefly described here. Dusts were sieved with a 500 μm sieve to remove course particles, and ~ 100 mg were taken for extraction. Dust samples were sonicated three times in 1:1 *v*/v hexane:acetone, and extracts were split 70:30. The 30% aliquot was cleaned and fractionated using activated silica column eluted with DCM (1st fraction), followed by 7:3 v/v acetone:DCM (2nd fraction). The fractionated extracts were exchanged to nonane and stored at −18 °C. Concentrations of polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), polycyclic aromatic hydrocarbons (PAHs), organophosphate esters (OPEs) and halogenated flame retardants (FRs) in these dust samples have been previously reported (Demirtepe et al., 2019). In this study, 55 of the second fraction extracts were available for analysis of plasticizers, i.e. 13 PEs and five APs, listed in Table S1 with CAS numbers and acronyms.

2.2. Instrumental analysis

The extracts were fortified with benzo(*e*)pyrene-d_{12} (Wellington Laboratories Inc., Canada) and PEs and APs were analyzed with a Trace 1300 series gas chromatograph (Thermo Scientific) equipped with 30 m × 0.25 mm × 0.25 μm Rxi5-SIL-MS column coupled to a Q-Exactive GC Orbitrap (Thermo Scientific). The operation was full-scan

(70–1000 amu) in EI mode with a mass resolution of 60,000. Injection was splitless 1 μL at 280 °C. The GC temperature program was 80 °C (3 min hold), then 7 °C min^{-1} to 320 °C (23 min hold). Samples were quantified based on a 15-point internal calibration curve, with R^2 greater than 0.99 for all compounds. Mass accuracy was <2 ppm and the instrument was checked for drift in mass every 12 h during instrumental run. The calibration range covered 4 orders of magnitude in order to include the concentration range expected for some PEs.

2.3. QA/QC

These extracts were not initially extracted for PEs; therefore, the potential for elevated blank contamination was high, especially with the ubiquitous contamination in a typical laboratory. However, field blanks (4 vacuum socks) were treated as per the samples. Method detection limits (MDLs) were calculated as the average of the field blank samples plus three times the standard deviation of the blanks (ng/sample). MDLs were converted to μg/g dust by dividing by a nominal sample amount of 0.1 g. The instrument detection limits (IDLs) were derived from the lowest concentration of the analyte detected in the calibration curve. The IDL was used as the MDL for compounds that were not detected in the blanks (Table S2). For compounds having >50% detection frequency, average blank contamination corresponded to 1.2 ± 0.5% of mean concentration of each analyte. The average of the blanks was subtracted from sample values that were > MDL, and values <MDL were recorded as such. Additionally, indicative method quantification limits (MQLs) were calculated as the average of the field blank samples plus ten times the standard deviation of the blanks. Blank levels, MDLs and MQLs are reported in Table S2.

The 1st fraction extracts were also checked for PEs & APs, but the target peak areas were lower than 1% of that in 2nd fraction, hence they were not included in further analysis. DiBP contamination in the calibration curve was high and calibration for this compound cannot be accurately performed; thus, it is not discussed further in this study.

We analyzed NIST standard reference material (SRM) 2585 for PEs & APs and compared the measured concentrations with previously reported values in seven studies since SRM 2585 is not certified for plasticizers (Table S3). PEs were within the range of SRM values previously reported, although we measured consistently lower DEHP concentration than previous studies except for one (Christia et al., 2019). For APs, only two studies have reported SRM concentrations of DEHT, and one study ATBC and DEHA. Our values for DEHA and DEHT were consistent with those of Kademoglou et al. (2018) and Christia et al. (2019), but for ATBC were significantly greater than those of Christia et al. (Table S3). The SRM samples were spiked with recovery standards before extraction and the average recoveries were 95.2%, 80.2% and 81.7% ($n = 3$) for DMP-d4, DnBP-d4, and DEHP-d4, respectively.

2.4. Data analysis

Statistical analyses were conducted using IBM SPSS 25. For statistical analysis, values below detection were substituted by $\sqrt{2}/2 \cdot$MDL. Shapiro-Wilk normality test showed non-normal distribution for indoor dust data ($p < 0.001$) hence non-parametric tests, i.e. Spearman correlation (r_s) and Mann Whitney *U* test, were applied. Analysis of variance (ANOVA) was conducted after log-transforming the data. $p < 0.05$ was considered the threshold for statistical significance.

2.4.1. Cumulative risk assessment

Human intake of PEs and APs via dust ingestion was calculated using the daily exposure dose (DED) formula and exposure parameters given in the SI based on the US EPA Exposure Factors Handbook (U.S. EPA, 2011). Intakes were calculated for median and high (95th percentile) intake scenarios for a child aged between six and eleven, as dust was collected from children's bedrooms, and for an adult male. For compounds whose median is <MDL, we used substituted values as defined above for median scenario. Toxicity reference values (TRVs), defined as the maximum dose of a compound that a person can be exposed daily without a health risk, were collected as non-carcinogenic oral doses from literature and regulatory sources (Table S4). Then, for cumulative risk assessment of PEs, relative potency factors (RPFs) and reference doses (RfD) were compiled from literature for individual PEs (Table 1). Since DEHP is the common compound for studies presenting RPFs, it was selected as the index compound and median of its TRVs was used as RfD_{DEHP} in cumulative hazard quotient (HQ) calculation, given below (Pelletier et al., 2018):

$$Cumulative\ HQ = \frac{\sum_{i=1}^{n} DED_i \times RPF_i}{RfD_{DEHP}} \quad (1)$$

where *DED* and *RfD* were given in μg/kg/d, and *RPF* was unitless.

2.4.2. Screening for suspect PEs

Full scan MS spectra of indoor dust samples, standard mixtures and blanks were transferred to MS-DIAL software for deconvolution, alignment and peak identification (Tsugawa et al., 2015). The details of MS-DIAL settings and parameters are provided in the SI.

Data from MS-DIAL were processed using Python Pandas software. A total of 5412 features were found in samples, standards, and blanks, though some features are likely to be the same compound separated by retention time drift. To remove contaminant features found in the laboratory blanks, the MDL (mean plus 3 times the standard deviation) of nonane instrumental blanks ($n = 5$) was applied to all samples. Features below the MDL were excluded from further study. Each feature detected by MS-DIAL included a comprehensive list of ions; this was reduced to include just those within 10% of the most abundant ion and then the top 10 of these were retained for preliminary investigation. Where two ions were detected with less than 0.0005 amu mass difference, the most abundant was retained in any feature.

The primary structure of PEs is the 1,2-benzenedicarboxylic acid with multiple possible alkyl side chains (Fig. S1A). Therefore, the mass 149.0226 (+/− 0.0003 amu), due to protonated phthalic anhydride structure (Fig. S1B), is a characteristic feature and often the most abundant, with the exception of dimethyl phthalates and the

Table 1
Cumulative hazard quotients calculated with various RPFs. RPFs in bold indicates the reference compound used by the corresponding study.

References	RPF					ΣHQ			
						Child		Adult	
	DEHP	BBP	DEP	DnBP	DPP	median	high	median	high
Benson (2009)	**1.00**	0.21		0.64	1.26	1.1×10^{-2}	0.64×10^{-1}	1.73×10^{-3}	1.00×10^{-2}
German Federal Environment Agency (2011)	1.00	1.00	0	1.00	3.00	1.1×10^{-2}	0.70×10^{-1}	1.79×10^{-3}	1.10×10^{-2}
Hannas et al. (2011)	0.11				**1.00**	1.2×10^{-3}	0.62×10^{-2}	1.82×10^{-4}	0.97×10^{-3}
Fournier et al. (2016)[a]	**1.00**	0.088	21			1.2×10^{-2}	0.75×10^{-1}	1.81×10^{-3}	1.17×10^{-2}
Howdeshell et al. (2008)	**1.00**	0.83		0.96	2.93	1.1×10^{-2}	0.69×10^{-1}	1.78×10^{-3}	1.08×10^{-2}
Gray et al. (2000)	**1.00**	1.00	0	0.5		1.1×10^{-2}	0.64×10^{-1}	1.73×10^{-3}	1.00×10^{-2}
Varshavsky et al. (2016)	0.61	0.26	0.024	**1.00**		0.73×10^{-2}	0.47×10^{-1}	1.14×10^{-3}	0.73×10^{-2}

[a] Calculated with DEHP as reference since cypermethrin was used as reference in Fournier et al. (2016).

diphenyl-isophthalates. For dimethyl phthalates, two CH_3 groups are on the alkyl side chain, and the diphenyl *iso*phthalates have two benzene rings, giving characteristic fragments of 163.0382 and 225.0552, respectively. After filtering the ion list for these masses and eliminating the features corresponding to the targeted PEs, the remaining features were considered "suspect PEs".

3. Results and discussion

3.1. Targeted PEs and APs in indoor dust

Nine out of 12 PEs and three out of five APs had >50% detection frequency in dust samples from Slovakian homes. The median concentration of $\sum_{12}$PEs was 376 μg/g, with the greatest contribution from DEHP (80%), followed by DnBP and DnOP. $\sum_5$APs had a median concentration of 200 μg/g. DEHT was the dominant AP, with a mean contribution of 37%. The median concentrations of DEHT, ATBC and DEHA were higher than that of six frequently detected PEs, indicating abundant use of APs in homes. Descriptive statistics for PEs and APs are presented in Table 2.

When compared to the SVOCs identified in our previous study (Demirtepe et al., 2019), the median concentrations of $\sum_{12}$PEs (376 μg/g) and $\sum_5$APs (200 μg/g) were an order of magnitude greater than that of $\sum_{14}$OPEs (12.4 μg/g) and two orders of magnitude greater than that of $\sum_{27}$PAHs (2.0 μg/g). This was consistent with previous publications where PEs were identified at one to two orders of magnitude greater concentration than OPEs (Bergh et al., 2011; He et al., 2016; Luongo and Östman, 2016; Yang et al., 2020, 2019).

The median PE concentrations in indoor dust in this study were comparable to the concentrations reported in existing publications on PEs in house dust (Table S5). In most studies DEHP was the most frequently detected compound (>70% of samples) and found at the highest concentration. DEHP concentrations from literature are compared in Fig. 1 grouped by continent and in Fig. S2 by country. In Europe, the median concentration across all studies investigated here was 270 μg/g, with the lowest median observed in Belgium (62 μg/g) and the greatest in Bulgaria (1050 μg/g). The European median for DEHP is similar to the median in this study (319 μg/g), and within the range for other regions (137 μg/g for North America, $n_{NAmer} = 6$ and 435.5 μg/g for Asia, $n_{Asia} = 14$; Table S5). Thailand, with the second highest median concentration of 1739.3 μg/g (Promtes et al., 2019), has to date no DEHP restrictions (Sedtasiriphokin et al., 2017) though a new toy safety proposal on DEHP has been proposed in 2020.

Table 2
Descriptive statistics for PEs and APs for Slovakian homes ($n = 55$, μg/g).

	Median	Geomean	Mean	SD	Min	Max	% Frequency
Phthalate esters (PEs)							
DEEP	<MDL	0.012	0.027	0.064	<MDL	0.43	31
DEHP	319	245	470	524	<MDL	2615	98
DMEP	<MDL	0.057	0.072	0.066	<MDL	0.36	18
BBP	2.94	2.81	9.14	16.7	<MDL	87.9	93
DCHP	0.98	1.01	2.34	3.74	0.038	19.4	100
DEP	1.42	1.53	7.36	27.3	<MDL	201	80
DHP	0.19	0.23	0.85	2.20	<MDL	12.3	95
DMP	0.071	0.11	0.37	0.82	<MDL	5.44	96
DnBP	24.3	24.6	78.7	196	<MDL	1160	84
DnOP	13.2	12.6	20.2	20.3	<MDL	119	95
DNP	0.94	0.79	1.52	1.82	<MDL	8.16	96
DPP	<MDL	<MDL	0.039	0.11	<MDL	0.64	36
Total $\sum_{12}$PEs	376	309	590	655	11.8	2765	
Alternative plasticizers (APs)							
ATBC	13.4	14.1	41.5	65.8	<MDL	307	96
DEHA	7.50	6.91	21.2	48.6	<MDL	274	93
DEHT	71.3	66.0	186	629	<MDL	4713	95
DPHP	<MDL	33.2	49.5	64.8	<MDL	382	38
DINCH	<MDL	45.7	300	1770	<MDL	13,200	33
Total $\sum_5$APs	200	227	597	1870	45.4	13,260	

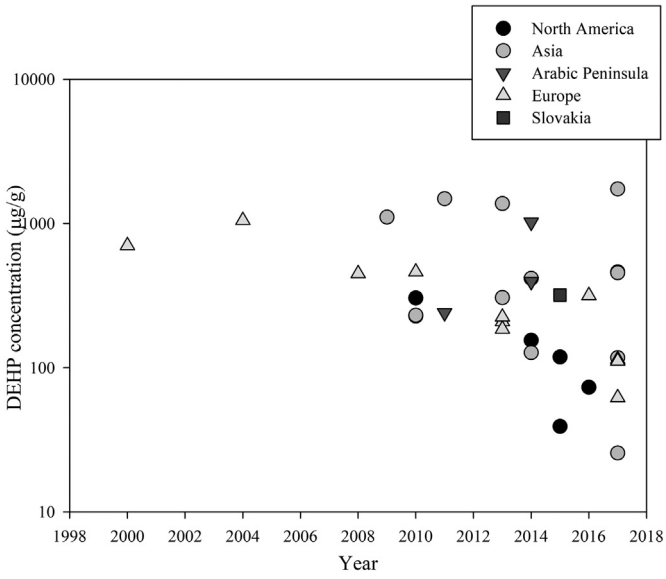


Fig. 1. Median DEHP concentrations in indoor dust samples from various continents with respect to sampling year. The studies reporting these levels are listed in Table S5.

An important observation was that DEHP concentrations reported in indoor dust show a significant decrease over time ($n = 33$, $r_s = -0.44$, $p < 0.05$) (Fig. 1). The regulatory agencies in the EU and US prohibited DEHP use in children's products in 2005 and listed it in the candidate list for substance of very high concern in 2008 (CPSC, 2017; ECHA, 2020). More recent DEHP concentrations reported in dust from Europe and North America are generally lower than those in Asia, and the decrease in reported dust concentrations of DEHP is much stronger when considering only European and North American records ($n = 17$, $r_s = -0.88$, $p < 0.001$; Fig. S3). This suggests that stocks and indoor uses of DEHP are being rapidly removed from indoor environments and that restrictions in use can be effective in reducing DEHP exposure. Nevertheless, a more in-depth literature survey would be required to make a definite conclusion on trends observed.

So far, few studies have identified APs in house dust, although we found AP concentrations to be comparable to PEs (Table S5). Median indoor DEHT, ATBC and DEHA concentrations from Slovakia were greater than those from Norway (Kademoglou et al., 2018), Ireland, Belgium and Netherlands, except for DEHT from Ireland (Christia et al., 2019). Median DEHT concentrations from Slovakia were also higher than that from Germany (Nagorka et al., 2011), and within the range of the studies reporting DEHT in USA (Hammel et al., 2019; Shin et al., 2020). DEHA and ATBC concentrations from the US (Subedi et al., 2017) were higher than those from Slovakia, while DEHA levels from Japan (Kishi et al., 2018) and Qatar (Nayef et al., 2019) were similar to that from Slovakia. Finally, median ATBC concentration from Slovakia was higher than that from China (Tang et al., 2020) and the US (Shin et al., 2020).

3.2. Possible sources of PEs and APs

Spearman's Rank correlations between PEs and APs suggested similar indoor sources (Table S6). For example, strong correlations were observed between DEHP, DnOP and DEHA, all of which are known to be used in wires and cables (ATSDR, 1997, 2019; Lowell Center for Sustainable Production, 2011) and DEHP and DnBP, which are commonly used in furniture (Lowell Center for Sustainable Production, 2011). We also explored the correlations between PEs, APs and OPEs measured in our previous study (Demirtepe et al., 2019). We found weak significant correlations for some compounds, such as tri-n-butyl phosphate correlated with DEP ($r_s = 0.28$, $p < 0.05$) and DMP ($r_s = 0.40$, $p < 0.01$) which have common uses as plasticizers in cellulose lacquers, plastics, and vinyl resins (Lyche, 2017; PubChem, 2020).

A questionnaire provided ancillary information on characteristics of the Slovakian homes. We hypothesized that presence of PVC flooring would result in higher PE concentrations in dust, as has been previously noted (Bornehag et al., 2005). However, no significant difference in individual PEs and total PE concentrations was found between homes with ($n = 17$) and without ($n = 33$) PVC flooring. A possible reason can be that the contribution of PVC flooring to PEs found in the dust may be limited compared to other PE sources in homes, such as furniture, carpets, wires and cables, packaging materials, etc. (ATSDR, 2019, 2001; Lowell Center for Sustainable Production, 2011). On the other hand, we found that DnBP, DnOP, DEHP, ∑PEs, ATBC and DEHT had significantly greater concentrations in homes with carpeting ($n = 8$) than homes without carpeting ($n = 42$) (Mann-Whitney U test, $p < 0.05$); these compounds are used in carpets (ATSDR, 2001, 1997; US EPA, 2019), which may be acting as a source to indoor dust. Lastly, we explored the correlations with building age. Only DMP ($r_s = 0.44$, $p < 0.05$) and DEP ($r_s = 0.35$, $p < 0.05$) correlated with building age, having greater concentrations in older homes. Additionally, DMP concentrations were significantly higher in homes more than 45 years old than homes less than 45 years old (one-way ANOVA, $F = 2.96$, $p < 0.05$), which we attribute to past use of DMP as a solvent in insecticides (Lyche, 2017).

3.3. Exposure and toxicity assessment of PEs and APs

PEs are known or suspected to have a range of health effects including altered immune system, developmental and reproductive effects, endocrine disruption, liver and kidney toxicity (ATSDR, 2019; Mitro et al., 2016), among which developmental and reproductive effects have been the most studied on laboratory animals and also in humans (Johnson et al., 2012; Kay et al., 2014; Wang et al., 2019). On the other hand, the toxicological information for APs is relatively scarce. Studies have examined their developmental and reproductive toxicity potentials and carcinogenicity, and APs have DNELs (ECHA, 2018). We first estimated exposure to PEs and APs and compared them with respect to their individual toxicity; we then evaluated the mixture effects of PEs via a cumulative risk assessment (CRA).

The available toxicity reference values (TRVs) for PEs and APs are given in Table S4. Comparison of median TRVs for PEs revealed the highest toxicity for DEHP, followed by DnOP, DnBP, DCHP, BBP, DEP, DMP, while APs have higher TRVs than PEs except for DEP and DMP (Table S4). DEHP has a large range of TRVs reported, which might be due to different endpoints used, e.g. ATSDR provided an MRL of 0.1 μg/kg/d for a developmental endpoint and IRIS provided RfD of 20 μg/kg/d for increase in liver weight. Additionally, structure-activity relationship (SAR) studies showed that straight-chain PEs with four to seven carbons have higher potency for developmental and reproductive toxicity, and branching of the side chain and unsaturation of the side chain increases the potency, while cyclic side chain does not (Li et al., 2019). Accordingly, DHP, DPP, DnBP should have higher toxic potency among the straight chain PEs, while DiBP and DEHP should have higher potency among branched chain PEs (Li et al., 2019). BBP, having a mixed carbon chain in the structure, is equipotent to DnBP and DEHP (Howdeshell et al., 2008). On the other hand, DnOP does not have developmental and reproductive toxicity at the highest doses tested (Li et al., 2019), although has the second lowest median TRV. Hence, usage of multiple endpoints in different toxicity assessments creates uncertainty in evaluating human risk.

In our previous study, we used TRVs derived from literature and regulatory sources to evaluate relative toxicities of SVOCs and merged this information with indoor exposure estimates for prioritization of compound risks (Demirtepe et al., 2019). Using this previously developed framework, we added PEs and APs into the evaluation from Demirtepe et al. (2019) (Fig. 2) to compare exposure and toxicity of PEs and APs to other SVOCs via dust ingestion. The estimated intakes for median and high intake scenarios and for a child and an adult male are provided in Table S7 for individual compounds. The human intake via dust ingestion for a child ranged between <0.01 ng/kg/d for DPP and 211 ng/kg/d for DEHP according to the median intake scenario. DEHP had a two order of magnitude higher intake than tris(2-butoxyethyl) phosphate, which had the highest intake via dust ingestion (1.62 ng/kg/d) among previously reported SVOCs from these same samples (which included OPEs, PCBs, PAHs, OCPs and halogenated FRs) (Demirtepe et al., 2019). PEs and APs have higher TRVs (indicating lower toxicity) than PCBs,

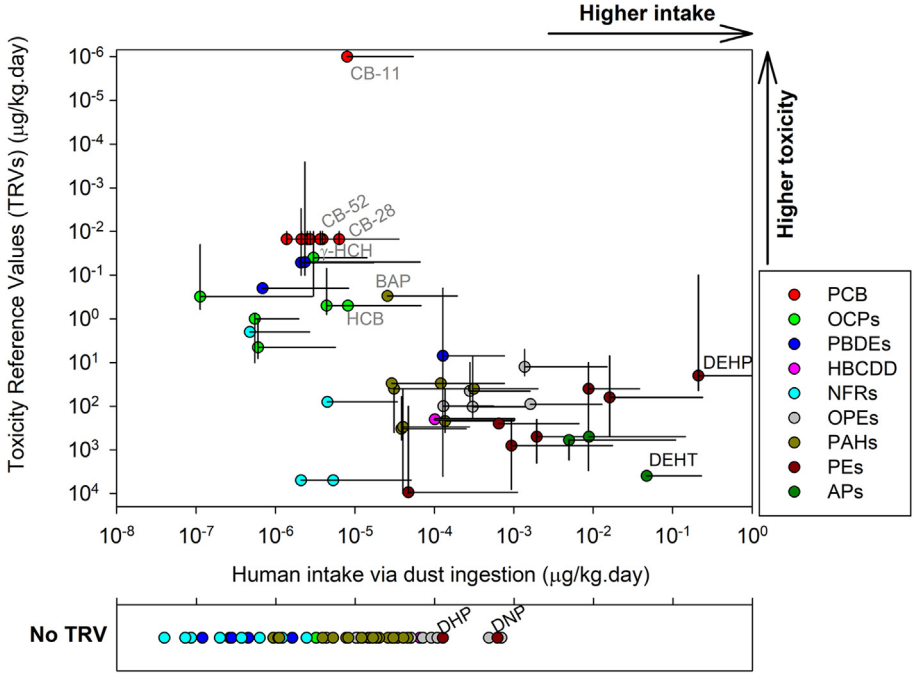


Fig. 2. Human intake via dust ingestion vs toxicity reference values of indoor SVOCs, PEs and APs. Vertical lines represent the range of TRVs reported in the literature, horizontal lines represent the high intake scenario, and points represent median exposure scenario and median TRVs. The box below the graph shows compounds with no available TRVs. Modified from Demirtepe et al. (2019).

OCPs and PBDEs, but similar TRVs to many PAHs, OPEs and NFRs (Fig. 2). Hence, although PEs and APs had the highest human intake among SVOCs, this assessment did not place them among the high priority compounds for indoor risk assessment, although, as with the OPEs, the uncertainty regarding the TRVs combined with their high exposures suggests potential for concern.

Moreover, co-occurrence of PEs in the indoor environment leads to human exposure to multiple PEs with possible common health effects. Several PEs affect the reproductive development of fetal male rat via a common mode of toxicity (Howdeshell et al., 2008), and studies on the mixture effects of PEs showed that the effect was best predicted by dose addition (Hannas et al., 2011; Howdeshell et al., 2008). Hence, CRA was employed to understand the risks associated with the total PE contamination of indoor dust. We focused on additive anti-androgenic effects, and calculated the cumulative hazard quotients (ΣHQ) given in Eq. (1) by using the Tier 2 approach presented by Pelletier et al. (2018).

ΣHQs were calculated for a child and an adult male for median and high intake scenarios using the RPFs available for five PEs (Table 1). ΣHQs were < 1 for each set of RPFs for a child and an adult male for both scenarios. ΣHQ values calculated by using RPFs from different studies given in Table 1 were on the same order of magnitude, except for Hannas et al. (2011) in which only two RPFs were available for PEs. Percent contribution of PEs to ΣHQs was highest for DEHP, i.e. more than 89% for all set of RPFs, followed by DnBP (Fig. 3). This was expected since DEHP is the dominant PE and has higher RPF than other PEs. Overall, the CRA identified no unacceptable risks for children and male adults regarding anti-androgenic effects due to indoor exposure via dust ingestion.

Some uncertainties and limitations are associated with use of the CRA. First, the CRA results represented only indoor dust ingestion exposure pathway, while dermal contact with dust and inhalation of indoor air might also contribute to total human exposure to PEs. Additionally, other SVOCs having anti-androgenic effects, such as p,p'-DDE, BDE-99 (Kortenkamp and Faust, 2010), and benzo(*a*)pyrene (Fournier et al., 2016) were identified in the same dust samples but were not included in this CRA since the first two have no RPFs available. Yet these compounds should also contribute to the ΣHQs. Another important contribution might come from DiBP, which has RPFs ranging 0.15–1.00 (Benson, 2009; German Federal Environment Agency, 2011; Hannas et al., 2011; Howdeshell et al., 2008). However, DiBP was not quantified in this study due to high background contamination.

Second, the RPFs derived from different studies may be incomparable since the experimental parameters and uncertainty factors used to derive reference and benchmark doses might be different (Benson, 2009; Fournier et al., 2016). Subsequently, the differences in specific endpoints such as the decrease in fetal testosterone vs. reduced reproductive organ weights might create uncertainty in comparability of data. However, the variation in RPFs did not lead to large variations among calculated HQs since daily exposure dose to DEHP was one to four orders of magnitude higher than other PEs, i.e. HQs were dominated by DEHP intake. It is also important to note that the median of available TRVs for DEHP was used as RfD_{DEHP} in the calculation of HQs (Eq. (1)). If we had used the minimum of reported TRVs, which is 0.1 μg/kg/d, and is also the most recent reported value (ATSDR, 2019), we would have obtained HQs > 1. Therefore, uncertainty in the TRVs is an important factor impacting HQ calculation and the CRA. Data available for many compounds were inconsistent, e.g. DEP was found 21 times more potent than DEHP according to Fournier et al. (2016) but zero potent according to most of the studies in Table 1. Positive correlations were found between DEP exposure and effects in human studies, but no associations were found in most of the animal studies, which might be explained by co-exposure to other PEs in human studies (NRC, 2008).

This highlights the importance of placing indoor exposure measurements into context by acknowledging the differing toxicities and toxic endpoints of individual compounds, at minimum through a combined assessment of exposures and TRVs (e.g., Fig. 2), but ideally incorporating the importance of mixture effects through use of HQs or a similar technique. Yet in all aspects, the biggest limitation at present remains the quality and comparability of TRVs, which are lacking for many compounds, or, when present, often have order-of-magnitude ranges, leading to similar uncertainty in the risk evaluations for which they are used.

3.4. Screening for other suspect PEs

Approximately 40 PEs are considered important for monitoring due to their use and HPV (Staples, 2003), however fewer are regularly monitored. This may be due to the limitations on standard mixtures, instrumental detection and sample contamination such as observed for DiBP in this study. All sample data in this study was collected on a GC-Orbitrap operating in full scan, allowing for screening of other PEs not included in the target analysis. MS-DIAL software was used to identify peaks, deconvolute and group the samples providing the opportunity to assess the number of peaks which are suspect PEs according to common PE feature masses. In total 5411 features were identified by MS-DIAL. After removing features reflecting background contamination, and selecting only the 10 most abundant ions, the features were filtered for target feature masses (149.0226, 163.0382 and 225.0552, +/− 0.0003 amu), which resulted in 63 features. Of the three masses, only the 149.0226 mass had any detectable peaks. Removing those features with low frequency of detection, i.e. < 10% of samples, 48 suspect compounds remained. Based on ion masses and retention times, seven of

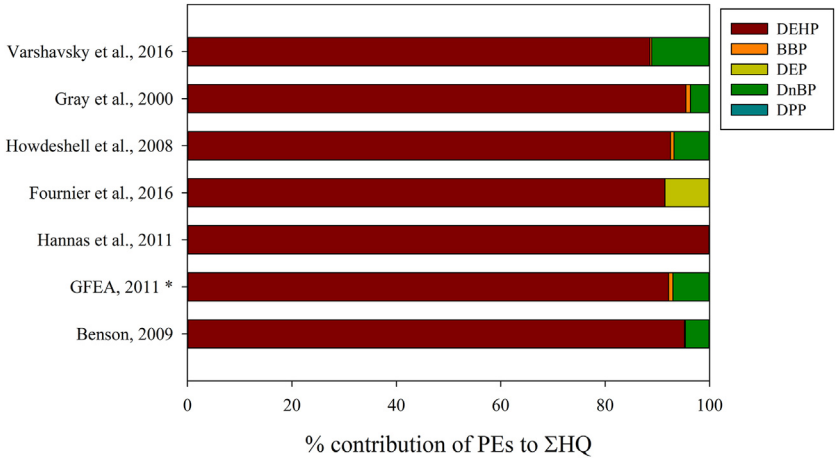


Fig. 3. Percent contribution of PEs to ΣHQs calculated by using RPFs from studies given in the y-axis. * GFEA refers to German Federal Environment Agency.

these were found to correspond to the target PEs already included in the study, leaving 41 suspect PEs with the protonated phthalic anhydride structure.

A list of 65 candidate PEs (Table S8) was generated from literature including the compounds detected by target analysis ($n = 13$ target compounds; Table S1). Many more PEs have been published but were excluded if no published retention time index (RTI) or retention time (RT) were available and if no GC spectra had been published. From the list of PEs, 54 had published n-alkane scale RTIs and for the majority also multiple published RTs were available. Additionally, the methods using a similar GC column of the current study (30 m with 5% diphenyl) were given priority. For the remaining compounds, a linear regression analysis between the RT of corresponding compounds in our target method and the method in the literature was used to estimate an RTI value and RT. For most of the remaining compounds more than two published RTs were used in estimation of RTI.

Using the estimated RT, 12 additional PEs were tentatively identified (1,2-benzenedicarboxylic acid monopentyl ester (MPeP), 2-{[(4-methylpentyl)oxy]carbonyl}benzoate, bis(2-ethylhexyl) *iso*phthalate, bis(4-methyl-2-pentyl) phthalate isomer (BMPP), butyl *cyclo*hexyl phthalate, diallyl phthalate (DAP), di-*n*-heptyl phthalate, di-isoheptyl phthalate, di-isononyl phthalate (DINP), hexyl decyl phthalate, monomethyl phthalate (MMP), octyl hydrogen phthalate (MnOP)). As many PEs have the same masses (149, 150, 105 and 104), confirmation ions may be of relatively low intensity compared to the primary ion, and many of the protonated phthalic anhydride masses detected were within 10–20s of each other, a more in-depth study would be needed to confirm identification.

Among the tentatively identified PEs, a few are particularly notable. For example, DINP is produced and imported annually between 10^5 and 10^6 t in EEA (ECHA, 2018) and is restricted for certain uses (REACH, 2018). Additionally, DINP is an endocrine disrupting chemical at high doses, although it has a lower toxic potential than others such as DPP and DEHP (Hannas et al., 2011). Di-*n*-heptyl phthalate and di-isoheptyl phthalate have lower production volumes, but a higher toxic potential than some of our target PEs. SAR studies found that di-*n*-heptyl phthalate and di-isoheptyl phthalate have higher potency for developmental toxicity and testosterone production in fetal testis (Li et al., 2019). These compounds may be of concern if they have high human intake via dust ingestion, and if they were included in overall assessments of PE mixture toxicity, the mixture toxicity would be higher. Although we have estimated a low risk based on the set of target analytes in our study, the presence of more than 40 suspect PEs suggests an underestimation of both human exposure to PEs and the associated PE mixture toxicity. This suggests for a more complete evaluation of PE exposure and toxicity, PEs with HPV and higher toxicity potential should be prioritized in lists of targeted analysis for indoor dust and other environmental matrices.

4. Conclusion

This study reports the results of targeted (12 PEs and five APs) and suspect screening of plasticizers in indoor residential dust. Dust concentrations of APs were comparable to, or in some homes even higher than, the concentrations of PEs. While we found no association of plasticizer concentrations in dust with presence of PVC flooring, homes with carpeting had higher concentrations of PEs and APs than homes without, suggesting carpeting as an important source of plasticizers in dust. We also found significant correlations between DMP and DEP and building age, which might be due to past use of these LMW PEs as insecticides in older homes.

We evaluated the risk of indoor plasticizer exposure via dust ingestion by combining toxicity and human intake estimates. DEHP was found to have the highest human intake but a lower toxicity compared to other SVOCs, e.g. PCBs and OCPs. However, a cumulative anti-androgenic risk assessment is more meaningful since mixture effects can prevail when multiple PEs with a common mode of toxicity occur. CRA estimated acceptable risks for children and male adults, however the wide range of reported TRVs is a large source of uncertainty and the biggest limitation in risk evaluation and can directly change whether the CRA crosses the hazard threshold. Furthermore, inclusion of other exposure routes, especially dietary intake, would lead to higher hazard quotients associated with PE intake. Lastly, more than 40 suspect PEs were identified through suspect screening, suggesting higher mixture toxicity if a larger set of PEs is considered. All PEs with high production volumes and high toxicity potential are recommended to be quantified in indoor studies, together with APs which have comparable indoor levels to PEs.

Funding

This research was supported by Czech Science Foundation [GAČR 19-20479S], RECETOX Research Infrastructure [LM2018121], Slovak Ministry of Health [2012/47-SZU-11], and Center of Excellence of Environmental Health, [ITMS No. 26240120033], funded by ESIF.

CRediT authorship contribution statement

Hale Demirtepe: Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Lisa Melymuk:** Writing – review & editing, Supervision. **Garry Codling:** Methodology, Writing – review & editing. **Ľubica Palkovičová Murínová:** Supervision, Funding acquisition, Writing – review & editing. **Denisa Richterová:** Investigation, Resources, Writing – review & editing. **Vladimíra Rašplová:** Investigation, Resources, Writing – review & editing. **Tomáš Trnovec:** Conceptualization, Supervision, Funding acquisition. **Jana Klánová:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2021.146667.

References

Ait Bamai, Y., Araki, A., Kawai, T., Tsuboi, T., Saito, I., Yoshioka, E., Cong, S., Kishi, R., 2016. Exposure to phthalates in house dust and associated allergies in children aged 6–12 years. Environ. Int. 96, 16–23. https://doi.org/10.1016/j.envint.2016.08.025.

Amin, M.M., Ebrahimpour, K., Parastar, S., Shoshtari-Yeganeh, B., Hashemi, M., Mansourian, M., Poursafa, P., Fallah, Z., Rafiei, N., Kelishadi, R., 2018. Association of urinary concentrations of phthalate metabolites with cardiometabolic risk factors and obesity in children and adolescents. Chemosphere 211, 547–556. https://doi.org/10.1016/j.chemosphere.2018.07.172.

ATSDR, 1995. Toxicological Profile for Diethyl Phthalate. Atlanta, Georgia.

ATSDR, 1997. Toxicological Profile for Di-n-Octylphthalate. Atlanta, Georgia.

ATSDR, 2001. Toxicological Profile for Di-n-Butyl Phthalate. Atlanta, Georgia.

Agency for Toxic Substances and Disease Registry (ATSDR), 2019. Toxicological profile for Di(2-ethylhexyl)phthalate (DEHP). U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.

Bekö, G., Callesen, M., Weschler, C.J., Toftum, J., Langer, S., Sigsgaard, T., Høst, A., Kold Jensen, T., Clausen, G., 2015. Phthalate exposure through different pathways and allergic sensitization in preschool children with asthma, allergic rhinoconjunctivitis and atopic dermatitis. Environ. Res. 137, 432–439. https://doi.org/10.1016/j.envres.2015.01.012.

Benson, R., 2009. Hazard to the developing male reproductive system from cumulative exposure to phthalate esters-dibutyl phthalate, diisobutyl phthalate, butylbenzyl phthalate, diethylhexyl phthalate, dipentyl phthalate, and diisononyl phthalate. Regul. Toxicol. Pharmacol. 53, 90–101. https://doi.org/10.1016/j.yrtph.2008.11.005.

Bergh, C., Torgrip, R., Emenius, G., Östman, C., 2011. Organophosphate and phthalate esters in air and settled dust - a multi-location indoor study. Indoor Air 21, 67–76. https://doi.org/10.1111/j.1600-0668.2010.00684.x.

Bertelsen, R.J., LØdrup Carlsen, K.C., Calafat, A.M., Hoppin, J.A., Håland, G., Mowinckel, P., Carlsen, K.H., LØvik, M., 2013. Urinary biomarkers for phthalates associated with asthma in Norwegian children. Environ. Health Perspect. 121, 251–256. https://doi.org/10.1289/ehp.1205256.

Bornehag, C.G., Lundgren, B., Weschler, C.J., Sigsgaard, T., Hagerhed-Engman, L., Sundell, J., 2005. Phthalates in indoor dust and their association with building characteristics. Environ. Health Perspect. 113, 1399–1404. https://doi.org/10.1289/ehp.7809.

Bui, T.T., Giovanoulis, G., Cousins, A.P., Magnér, J., Cousins, I.T., de Wit, C.A., 2016. Human exposure, hazard and risk of alternative plasticizers to phthalate esters. Sci. Total Environ. 541, 451–467. https://doi.org/10.1016/j.scitotenv.2015.09.036.

Christia, C., Poma, G., Harrad, S., de Wit, C.A., Sjostrom, Y., Leonards, P., Lamoree, M., Covaci, A., 2019. Occurrence of legacy and alternative plasticizers in indoor dust from various EU countries and implications for human exposure via dust ingestion and dermal absorption. Environ. Res. 171, 204–212. https://doi.org/10.1016/j.envres.2018.11.034.

CPSC, 2017. 16 CFR Part 1307 Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates.

Demirtepe, H., Melymuk, L., Diamond, M.L., Bajard, L., Vojta, Š., Prokeš, R., Sáňka, O., Klánová, J., Palkovičová Murínová, Ľ., Richterová, D., Rašplová, V., Trnovec, T., 2019. Linking past uses of legacy SVOCs with today's indoor levels and human exposure. Environ. Int. 127, 653–663. https://doi.org/10.1016/j.envint.2019.04.001.

ECHA, 2018. European Chemicals Agency - Information on Chemicals [WWW Document]. URL https://echa.europa.eu/brief-profile/-/briefprofile/100.043.099 (accessed 9.8.18).

ECHA, 2020. Candidate List of Substances of Very High Concern for Authorisation [WWW Document]. URL https://echa.europa.eu/candidate-list-table (accessed 6.1.20).

Fournier, K., Tebby, C., Zeman, F., Glorennec, P., Zmirou-Navier, D., Bonvallot, N., 2016. Multiple exposures to indoor contaminants: derivation of benchmark doses and relative potency factors based on male reprotoxic effects. Regul. Toxicol. Pharmacol. 74, 23–30. https://doi.org/10.1016/j.yrtph.2015.11.017.

German Federal Environment Agency, 2011. Substance Monograph: Phthalates – New and Updated Reference Values for Monoesters and Oxidised Metabolites in Urine of Adults and Children.

Giovanoulis, G., Bui, T., Xu, F., Papadopoulou, E., Padilla-Sanchez, J.A., Covaci, A., Haug, L.S., Cousins, A.P., Magnér, J., Cousins, I.T., de Wit, C.A., 2018. Multi-pathway human exposure assessment of phthalate esters and DINCH. Environ. Int. 112, 115–126. https://doi.org/10.1016/j.envint.2017.12.016.

Gray, L.E., Ostby, J., Furr, J., Price, M., Veeramachaneni, D.N.R., Parks, L., 2000. Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. Toxicol. Sci. 58, 350–365. https://doi.org/10.1093/toxsci/58.2.350.

Hammel, S.C., Levasseur, J.L., Hoffman, K., Phillips, A.L., Lorenzo, A.M., Calafat, A.M., Webster, T.F., Stapleton, H.M., 2019. Children's exposure to phthalates and non-phthalate plasticizers in the home: the TESIE study. Environ. Int. 132, 105061. https://doi.org/10.1016/j.envint.2019.105061.

Hannas, B.R., Lambright, C.S., Furr, J., Howdeshell, K.L., Wilson, V.S., Gray, L.E., 2011. Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate, and diisononyl phthalate. Toxicol. Sci. 123, 206–216. https://doi.org/10.1093/toxsci/kfr146.

Hauser, R., Calafat, A.M., 2005. Phthalates and human health. Occup. Environ. Med. 62, 806–818. https://doi.org/10.1136/oem.2004.017590.

He, R., Li, Y., Xiang, P., Li, C., Zhou, C., Zhang, S., Cui, X., Ma, L.Q., 2016. Organophosphorus flame retardants and phthalate esters in indoor dust from different microenvironments: bioaccessibility and risk assessment. Chemosphere 150, 528–535. https://doi.org/10.1016/j.chemosphere.2015.10.087.

Howdeshell, K.I., Wilson, V.S., Furr, J., Lambright, C.R., Rider, C.V., Blystone, C.R., Hotchkiss, A.K., Gray, L.E., 2008. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicol. Sci. 105, 153–165. https://doi.org/10.1093/toxsci/kfn077.

Jílková, S., Melymuk, L., Vojta, Š., Vykoukalová, M., Bohlin-Nizzetto, P., Klánová, J., 2018. Small scale spatial variability of flame retardants in indoor dust and implications for dust sampling. Chemosph. 206, 132–141. https://doi.org/10.1016/j.chemosphere.2018.04.146.

Johnson, K.J., Heger, N.E., Boekelheide, K., 2012. Of mice and men (and rats): phthalate-induced fetal testis endocrine disruption is species-dependent. Toxicol. Sci. 129, 235–248. https://doi.org/10.1093/toxsci/kfs206.

Kademoglou, K., Giovanoulis, G., Palm-Cousins, A., Padilla-Sanchez, J.A., Magnér, J., De Wit, C.A., Collins, C.D., 2018. In vitro inhalation bioaccessibility of phthalate esters and alternative plasticizers present in indoor dust using artificial lung fluids. Environ. Sci. Technol. Lett. 5, 329–334. https://doi.org/10.1021/acs.estlett.8b00113.

Kay, V.R., Bloom, M.S., Foster, W.G., 2014. Reproductive and developmental effects of phthalate diesters in males. Crit. Rev. Toxicol. 44, 467–498. https://doi.org/10.3109/10408444.2013.875983.

Kishi, R., Ketema, R.M., Ait Bamai, Y., Araki, A., Kawai, T., Tsuboi, T., Saito, I., Yoshioka, E., Saito, T., 2018. Indoor environmental pollutants and their association with sick house syndrome among adults and children in elementary school. Build. Environ. 136, 293–301. https://doi.org/10.1016/j.buildenv.2018.03.056.

Kortenkamp, A., Faust, M., 2010. Combined exposures to anti-androgenic chemicals: steps towards cumulative risk assessment. Int. J. Androl. 33, 463–472. https://doi.org/10.1111/j.1365-2605.2009.01047.x.

Kutz, M., 2017. Applied Plastics Engineering Handbook. Elsevier, Second Edi. ed.

Li, X., Mo, J., Zhu, Q., Ni, C., Wang, Y., Li, H., Lin, Z. kun, Ge, R.S., 2019. The structure–activity relationship (SAR) for phthalate-mediated developmental and reproductive toxicity in males. Chemosphere 223, 504–513. doi:https://doi.org/10.1016/j.chemosphere.2019.02.090.

Lowell Center for Sustainable Production, 2011. Phthalates and their Alternatives: Health and Environmental Concerns (Lowell).

Luongo, G., Östman, C., 2016. Organophosphate and phthalate esters in settled dust from apartment buildings in Stockholm. Indoor Air 26, 414–425. https://doi.org/10.1111/ina.12217.

Lyche, J.L., 2017. Phthalates. In: Gupta, R. (Ed.), Reproductive and Developmental Toxicology. Academic Press.

Meeker, J.D., Calafat, A.M., Hauser, R., 2009. Urinary metabolites of di(2-ethylhexyl) phthalate are associated with decreased steroid hormone levels in adult men. J. Androl. 30, 287–297. https://doi.org/10.2164/jandrol.108.006403.

Mitro, S.D., Dodson, R.E., Singla, V., Adamkiewicz, G., Elmi, A.F., Tilly, M.K., Zota, A.R., 2016. Consumer product chemicals in indoor dust: a quantitative meta-analysis of U.S. Studies. Environ. Sci. Technol. 50, 10661–10672. https://doi.org/10.1021/acs.est.6b02023.

Nagorka, R., Conrad, A., Scheller, C., Süßenbach, B., Moriske, H.J., 2011. Diisononyl 1,2-cyclohexanedicarboxylic acid (DINCH) and Di(2-ethylhexyl) terephthalate (DEHT) in indoor dust samples: concentration and analytical problems. Int. J. Hyg. Environ. Health 214, 26–35. https://doi.org/10.1016/j.ijheh.2010.08.005.

Narvaez Rincon, P.C., Suarez Palacios, O.Y., 2015. Plasticizers. In: Palsule, S. (Ed.), Encyclopedia of Polymers and Composites. Springer, Berlin Heidelberg, pp. 1–13 https://doi.org/10.1007/978-3-642-37179-0_73-1.

Nayef, N., Qasmi, A., Al-thaiban, H., Helaleh, M.I.H., 2019. Indoor phthalates from household dust in Qatar : implications for non-dietary human exposure. Environ. Sci. Pollut. Res. 26, 421–430. https://doi.org/10.1007/s11356-018-3604-8.

Net, S., Sempéré, R., Delmont, A., Paluselli, A., Ouddane, B., 2015. Occurrence, fate, behavior and ecotoxicological state of phthalates in different environmental matrices. Environ. Sci. Technol. 49, 4019–4035. https://doi.org/10.1021/es505233b.

NRC, 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. National Academies Press, Washington, DC.

Pelletier, M., Glorennec, P., Mandin, C., Le Bot, B., Ramalho, O., Mercier, F., Bonvallot, N., 2018. Chemical-by-chemical and cumulative risk assessment of residential indoor exposure to semivolatile organic compounds in France. Environ. Int. 117, 22–32. https://doi.org/10.1016/j.envint.2018.04.024.

Plastics Europe, 2020. Plastics - the facts 2020.

Promtes, K., Kaewboonchoo, O., Kawai, T., Miyashita, K., Panyapinyopol, B., Kwonpongsagoon, S., Takemura, S., 2019. Human exposure to phthalates from house dust in Bangkok. Thailand. J. Environ. Sci. Heal. - Part A Toxic/Hazardous Subst. Environ. Eng. 54, 1269–1276. https://doi.org/10.1080/10934529.2019.1637207.

PubChem, 2020. U.S. National Library of Medicine National Center for Biotechnology Information [WWW Document]. URL https://pubchem.ncbi.nlm.nih.gov/ (accessed 1.31.20).

Radke, E.G., Glenn, B.S., Braun, J.M., Cooper, G.S., 2019. Phthalate exposure and female reproductive and developmental outcomes: a systematic review of the human epidemiological evidence. Environ. Int. 130, 104580. https://doi.org/10.1016/j.envint.2019.02.003.

REACH, 2018. Commission Regulation (EU) 2018/2005 of 17 December 2018 Amending Annex XVII to Regulation (EC) no 1907/2006 of the European Parliament and of the Council Concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as Regar.

Sedtasiriphokin, N., Supornsilchai, V., Jantarat, C., Nosoongnoen, W., 2017. Phthalate exposure in Thai children and adolescents. Asian Biomed. 11, 343–352. https://doi.org/10.1515/abm-2018-0006.

Shin, H.M., Moschet, C., Young, T.M., Bennett, D.H., 2020. Measured concentrations of consumer product chemicals in California house dust: implications for sources, exposure, and toxicity potential. Indoor Air 30, 60–75. https://doi.org/10.1111/ina.12607.

Stanley, M.K., Robillard, K.A., Staples, C.A., 2003. Introduction. In: Staples, C.A. (Ed.), Phthalate Esters - Handbook of Environmental Chemistry. Springer, Berlin Heidelberg, pp. 1–7.

Staples, C.A., 2003. Phthalate esters. Handbook of Environmental Chemistry. Springer. https://doi.org/10.1007/b11460.

Subedi, B., Sullivan, K.D., Dhungana, B., 2017. Phthalate and non-phthalate plasticizers in indoor dust from childcare facilities, salons, and homes across the USA. Environ. Pollut. 230, 701–708. https://doi.org/10.1016/j.envpol.2017.07.028.

Swan, S.H., Main, K.M., Liu, F., Stewart, S.L., Kruse, R.L., Calafat, A.M., Mao, C.S., Redmon, J.B., Ternand, C.L., Sullivan, S., Teague, J.L., The Study for Future Families Research Team, 2005. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ. Health Perspect. 113, 1056–1061. https://doi.org/10.1289/ehp.8100.

Tang, B., Christia, C., Malarvannan, G., Liu, Y.E., Luo, X.J., Covaci, A., Mai, B.X., Poma, G., 2020. Legacy and emerging organophosphorus flame retardants and plasticizers in indoor microenvironments from Guangzhou, South China. Environ. Int. 143, 105972. https://doi.org/10.1016/j.envint.2020.105972.

Tsugawa, H., Cajka, T., Kind, T., Ma, Y., Higgins, B., Ikeda, K., Kanazawa, M., VanderGheynst, J., Fiehn, O., Arita, M., 2015. MS-DIAL: data independent MS/MS deconvolution for comprehensive metabolome analysis. Nat. Methods 12, 523–526. https://doi.org/10.1038/nmeth.3393.

U.S. EPA, 2011. Exposure Factors Handbook 2011 Edition (Final Report). Washington, DC.

US EPA, 2019. Proposed Designation of Di-Ethylhexyl Phthalate (DEHP) (1,2-Benzene- Dicarboxylic Acid, 1,2-Bis (2-Ethylhexyl) Ester) (CASRN 117-81-7) as a High-Priority Substance for Risk Evaluation.

Varshavsky, J.R., Zota, A.R., Woodruff, T.J., 2016. A novel method for calculating potency-weighted cumulative phthalates exposure with implications for identifying racial/ethnic disparities among U.S. reproductive-aged women in NHANES 2001-2012. Environ. Sci. Technol. 50, 10616–10624. https://doi.org/10.1021/acs.est.6b00522.

Venier, M., Audy, O., Vojta, Š., Bečanová, J., Romanak, K., Melymuk, L., Krátká, M., Kukučka, P., Okeme, J., Saini, A., Diamond, M.L., Klánová, J., 2016. Brominated flame retardants

in the indoor environment - comparative study of indoor contamination from three countries. Environ. Int. 94, 150–160. https://doi.org/10.1016/j.envint.2016.04.029.
Vojta, Š., Melymuk, L., Klánová, J., 2017. Changes in flame retardant and legacy contaminant concentrations in indoor air during building construction, furnishing, and use. Environ. Sci. Technol. 51, 11891–11899. https://doi.org/10.1021/acs.est.7b03245.
Vykoukalová, M., Venier, M., Vojta, Š., Melymuk, L., Bečanová, J., Romanak, K., Prokeš, R., Okeme, J.O., Saini, A., Diamond, M.L., Klánová, J., 2017. Organophosphate esters flame retardants in the indoor environment. Environ. Int. 106, 97–104. https://doi.org/10.1016/j.envint.2017.05.020.
Wang, Y., Ni, C., Li, X., Lin, Z., Zhu, Q., Li, L., Ge, R.S., 2019. Phthalate-induced fetal leydig cell dysfunction mediates male reproductive tract anomalies. Front. Pharmacol. 10, 1–11. https://doi.org/10.3389/fphar.2019.01309.
Wormuth, M., Scheringer, M., Vollenweider, M., Hungerbühler, K., 2006. What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? Risk Anal. 26, 803–824. https://doi.org/10.1111/j.1539-6924.2006.00770.x.
Yang, C., Harris, S.A., Jantunen, L.M., Siddique, S., Kubwabo, C., Tsirlin, D., Latifovic, L., Fraser, B., St-Jean, M., De La Campa, R., You, H., Kulka, R., Diamond, M.L., 2019. Are cell phones an indicator of personal exposure to organophosphate flame retardants and plasticizers? Environ. Int. 122, 104–116. https://doi.org/10.1016/j.envint.2018.10.021.
Yang, C., Harris, S.A., Jantunen, L.M., Kvasnicka, J., Nguyen, L.V., Diamond, M.L., 2020. Phthalates: relationships between air, dust, electronic devices, and hands with implications for exposure. Environ. Sci. Technol. https://doi.org/10.1021/acs.est.0c00229.
Zhang, Qinghao, Sun, Y., Zhang, Qingnan, Hou, J., Wang, P., Kong, X., Sundell, J., 2020. Phthalate exposure in Chinese homes and its association with household consumer products. Sci. Total Environ. 719, 136965. https://doi.org/10.1016/j.scitotenv.2020.136965.