Presence of diphenyl phosphate and aryl-phosphate flame retardants in indoor dust from different microenvironments in Spain and the Netherlands and estimation of human exposure

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Abstract

Phosphate flame retardants (PFRs) are ubiquitous chemicals in the indoor environment. Diphenyl phosphate (DPHP) is a major metabolite and a common biomarker of aryl-PFRs. Since it is used as a chemical additive and it is a common impurity of aryl-PFRs as well as a degradation product, its presence in indoor dust as an additional source of exposure should not be easily ruled out. In this study, DPHP (and TPHP) are measured in indoor dust in samples collected in Spain and in the Netherlands (*n*=80). Additionally, the presence of other emerging aryl-PFRs was monitored by target screening. TPHP and DPHP were present in all samples in the ranges 169-142,459 ng/g and 106-79,661 ng/g, respectively. DPHP concentrations were strongly correlated to the TPHP levels ($r=0.90$, $p<0.01$), suggesting that DPHP could be present as degradation product of TPHP or other aryl-PFRs. Estimated exposures for adults and toddlers in Spain to TPHP and DPHP via dust ingestion (country for which the number of samples was higher) were much lower than the estimated reference dose (US EPA) for TPHP. However, other routes of exposure may contribute to the overall internal exposure (diet, dermal contact with dust/consumer products and inhalation of indoor air). The estimated urinary DPHP levels for adults and toddlers in Spain (0.002-0.032 ng/mL) as a result of dust ingestion were low in comparison with the reported levels, indicating a low contribution of this source of contamination to the overall DPHP exposure. Other aryl-PFRs, namely cresyl diphenyl phosphate (CDP), resorcinol bis(diphenyl phosphate) (RDP), 2-ethylhexyl diphenyl phosphate (EDPHP), isodecyl diphenyl phosphate (IDP) and bisphenol A bis(diphenyl phosphate) (BDP), were all detected in indoor dust, however, with lower frequency.

Keywords: Aryl-phosphate flame retardants; Indoor dust; Human exposure; Triphenyl phosphate; Diphenyl phosphate

1. Introduction

Due to their wide use in materials, such as furniture, electronics and textiles, flame retardants (FRs) are widespread in the environment. They are used to prevent ignition and to slow down the spread of an already initiated fire.[1] Concern has been raised considering their migration from materials as it affects the indoor air quality and being inhalation a route for human exposure.[2] The use of PBDEs as flame retardants has been common until they started to be banned or voluntarily phased-out in certain products, such as electrical and electronic equipment or polyurethane foam, due to their known toxicity, persistence and bioaccumulative properties.[3] The European Union has banned the use of pentaBDE and octaBDE in 2004 (Directive 2002/96/EC) and the use of decaBDE in electric and electronic equipment in 2009 (European Court of Justice, 2008). This regulation has led to the introduction of alternatives, such as aryl-phosphate flame retardants (aryl-PFRs), onto the market. Studies have demonstrated an increase in the presence of alternative FRs in indoor dust, for which toxicity is still uncharacterized, in conjunction with the decrease of PBDE.[4-6]

Triphenyl phosphate (TPHP; CAS no. 115-86-6) is an aryl-PFR mainly used as an additive in polymer mixtures used in electronic enclosure applications. The use of TPHP has resulted in environmental contamination due to its migration from materials.[2] TPHP has been reported in indoor dust collected from the floors of residences (<2-1,798,000 ng/g),[4, 8-34] in indoor dust from offices (11-50000 ng/g)[11, 18, 24, 30-34] and in indoor dust from schools and daycare centers (10-90000 ng/g).[11, 21, 24, 26, 30, 33, 35] TPHP has also been reported in dust from cars (<2-170,000 ng/g),[16, 18, 20, 24, 28, 31] and from public microenvironments (PMEs) such as shops, restaurants and supermarkets (14-34200 ng/g).[12, 14, 18, 30, 32] TPHP has also been reported in indoor air (0.19-5.7 ng/m^3),[36, 37] in outdoor air (0.003 ng/m^3),[38] sewage water influent (76-290 ng/L) and effluent (41-130 ng/L) and sewage sludge (52-320 ng/g dw),[39] surface water (<LOD-10.3 ng/L),[40] sediment (5.6-253 ng/g)[41, 42] and in fish (43-230 ng/g lw).[41, 43] Furthermore, TPHP

has been associated with airborne particles over the oceans indicating a potential for long-range atmospheric transport towards the polar regions.[44]

The widespread occurrence of TPHP in the indoor- and outdoor environment has led to concern regarding human health and the environment. The human toxicity of TPHP is considered "low to high" according to a recent alternatives assessment report.[45] Furthermore, PFRs including TPHP may be associated with altered hormone levels and decreased semen quality in men.[46] The aquatic toxicity is considered very high (Fish 96 h EC_{50}=0.4 mg/L, fish 30-day LOEC=0.037 mg/L) and TPHP may cause long-term adverse effects in the aquatic environment.[45] The environmental persistence is considered low, although there is a moderate potential for bioaccumulation.[45]

Human exposure to FRs as well as to other contaminants has been associated with inhalation and ingestion of contaminated indoor dust.[47] High levels of contaminants in indoor dust are posing a risk to human health, particularly vulnerable groups such as toddlers, which are especially exposed to contaminated dust when crawling and playing on the floor as well as when they put items in their mouth.[48]

As a major metabolite of aryl-PFRs, DPHP has been used as a biomarker for assessing exposure to TPHP in indoor dust and has been widely reported in urine in the range <0.13-727 ng/mL.[25, 49-54] However, the urinary levels of DPHP are not correlated to TPHP concentrations in indoor dust (r_S=0.04,[50] ; r_S=0.15,[25]) indicating other exposure routes. A possible additional source could be the direct exposure to DPHP itself as it is used in other applications (e.g. DPHP is used as a catalyst in polymerization processeses[55,56] and as an additive in paints and coatings according to PubChem database) or direct exposure to DPHP via indoor dust ingestion as it may be present as an impurity and/or as a degradation product as a result of spontaneous or microbial hydrolysis of TPHP and/or of other aryl-PFRs. Furthermore, DPHP has been reported to be a metabolite of some other aryl-PFRs, such as 2-

ethylhexyl diphenyl phosphate (EDPHP),[57,58] resorcinol bis(diphenyl phosphate) (RDP)[59] and *tert*-Butylphenyl diphenyl phosphate (BPDP).[60] There is almost no data available about the presence of DPHP in the indoor environment, to the best of our knowledge only one study has reported levels of DPHP (75-190 ng/g) in 4 dust samples collected in Australia.[53]

In the present study, TPHP and DPHP levels were studied in indoor dust samples collected from households, offices, cars and public microenvironments in the Netherlands in June 2016 (n=23) and in Spain in March and April 2017 (n=57). The levels of TPHP and DPHP were compared between different microenvironments and between the two countries and the correlation between TPHP and DPHP levels was investigated. Human exposure to TPHP and DPHP via indoor dust ingestion was estimated using different exposure scenarios. It should be taken into account that this is only one of the major identified exposure routes to flame retardants, which include also the diet, dermal contact with dust/consumer products and inhalation of indoor air.

Furthermore, to gain knowledge about the presence of other aryl-PFRs in indoor dust, which could contribute to the formation of DPHP, the presence of other emerging aryl-PFRs were screened, namely cresyl diphenyl phosphate (CDP), RDP, EDPHP, isodecyl diphenyl phosphate (IDP) and bisphenol A bis(diphenyl phosphate) (BDP) by injection of authentic standards.

2. Materials and methods

2.1. Chemicals and reagents

Acetonitrile and methanol were acquired from VWR chemicals (Llinars del Vallès, Barcelona, Spain). Ammonium acetate was obtained from Sigma Aldrich (Zwijndrecht, the Netherlands). Ultra-high-quality water was obtained from a Milli-Q water purification system (Millipore, Madrid, Spain). Standard reference material (SRM) 2585 (organic contaminants

in house dust) was provided by the National Institute of Standards and Technology (NIST). TPHP, DPHP, TPHP-d_{15} and DPHP-d_{10} were obtained from Sigma Aldrich (Zwijndrecht, the Netherlands). Cresyl diphenyl phosphate (CDP), isodecyl diphenyl phosphate (IDP), 2-ethylhexyl diphenyl phosphate (EDPHP), resorcinol bis(diphenyl phosphate) (RDP) and bisphenol A bis(diphenyl phosphate) (BDP) analytical standards were obtained from AccuStandard (New Haven, CT).

2.2. Sample collection

Sampling was performed using a filter (40 μm) mounted in a nozzle adapted to a vacuum cleaner and samples were not further sieved. Dust samples were collected from residences in the Netherlands in June 2016 from floors (*n*=12) and from the surface of electrical equipment (*n*=11) and in Spain in March and April 2017 from the floors of living rooms (*n*=9), bedrooms (*n*=9), offices (*n*=4), surfaces of electrical equipment (*n*=13), cars (*n*=15) and public microenvironments (PMEs) (*n*=7) (two electronic shops, two clothing shops, one sport clothing shop, one decoration shop and one cafeteria). Due to the limited amount of dust on top of electrical equipment, these samples were of approximately 20-50 mg.

2.3. Sample treatment and method validation

Approximately 50 mg dust (except for dust on top of electronic equipment, 20-50 mg) were accurately weighed in 15 mL glass tubes and spiked with IS (TPHP-d_{15} and DPHP-d_{10}, 0.1 μg each) prior to extraction. Salting-out extraction with acetonitrile was performed with 3 M aqueous ammonium acetate (NH_4Ac):acetonitrile (1:1 v/v) by vortex for 2 min followed by centrifugation at 3000 rpm for 5 min. After phase-separation, the acetonitrile layer was collected and transferred to a glass tube. The extraction was repeated 2 times and the acetonitrile layers (~ 6 mL) were combined and evaporated to approximately 1.5 mL (N_2, 50°C). Sample clean-up was performed with dispersive SPE (75 mg $MgSO_4$, 25 mg PSA, 25

mg C_{18}, 25 mg GCB) by vortex for 2 min followed by ultracentrifugation at 10 000 rpm for 5 min. The extract was then evaporated to near dryness (N_2, 50°C) and reconstituted in 200 μL MilliQ water:acetonitrile (1:1 v/v) by vortex for 30 s followed by ultracentrifugation at 10,000 rpm for 5 min. Extracts were transferred to LC vials and aliquots of 5 μL were injected into the LC-MS/MS system.

Procedural blanks were included in each set of experiments and used for data treatment to correct for possible blank contamination. Blank values for DPHP and TPHP (average, n=10) were of 10±2 ng/g for TPHP and 5±1 ng/g for DPHP (detectable but far below the estimated method LOQ).

The analytical performance of the method was evaluated for extraction recovery (%), clean-up recoveries (%), matrix effects (%), and reproducibility (RSD%) by using the indoor dust reference material SRM 2585 (50 mg).

2.4. Apparatus and sample analysis

For separation, an Agilent Technologies 1200 LC system was used with a Phenomenex Luna® C_{18} column (2.0 mm i.d., 100 mm length, 3.0 μm particle size). The mobile phase consisted of 5 mM aqueous ammonium acetate (A) and methanol (B) at a flow rate of 0.25 mL/min. The gradient was as follows: initial 20% B, increased to 95% in 7.5 min and hold for 3 min and finally re-conditioning for 7 min. The MS/MS system was an Agilent Technologies 6420 Triple Quadrupole mass spectrometer equipped with LC-electrospray ionization (ESI) source. The source parameters were set as following: Gas temperature, 320°C; gas flow, 12.0 L/min; nebulizer, 50 psi; capillary voltage, +/-4000 V; MS1 heater, 100°C; MS2 heater, 100°C. The MRM transitions for target masses are given in Table S-1. TPHP, BADP, RDP, IDP, EDPHP and CDP were analyzed in positive ionization mode and DPHP was analyzed in both negative and positive ionization mode.

Quantification of TPHP and DPHP in indoor dust

Quantification of TPHP and DPHP in indoor dust was performed using the *quantitative analysis MassHunter workstation* software from Agilent Technologies and using their respective deuterated internal standards. The method was evaluated based on extraction efficiency, clean-up losses, matrix effects and reproducibility.

For TPHP and DPHP, the instrument linear range was 0.005-5 µg/mL and 0.005-10 µg/mL, respectively. The instrument LOD and LOQ (TPHP and DPHP) were 0.1 ng/mL and 5 ng/mL, respectively. Method LOD and LOQ were calculated based on a signal-to-noise ratio higher than 3 and 10, respectively, considering sample amount, final extract volume, and total recovery. The estimated method LOD and LOQ for TPHP were 1.54 ng/g and 73.96 ng/g, respectively. For DPHP, the estimated method LOD and LOQ were 0.38 ng/g and 19.23 ng/g, respectively.

Statistics

One-way ANOVA was employed to investigate if the TPHP and DPHP concentrations were significantly different in dust collected in Spain and in the Netherlands as well as in dust collected from different microenvironments. Pearson correlation was performed in order to investigate the correlation between TPHP and DPHP in indoor dust (data was normally distributed, after logarithmic transformation, Kolmogorov-Smirnov normality test). For the statistical calculations, the microenvironments were divided into four groups: floor dust (bedrooms, living rooms and offices), dust collected from the surface of electronic equipment, car dust and dust from the floors of public microenvironments.

Screening of aryl-phosphate flame retardants

Target screening of aryl-PFRs was performed using the *quantitative analysis MassHunter workstation* software from Agilent Technologies, namely CDP, RDP, EDPHP, IDP and BDP.

The main ion $[M+H]^+$ as well as two abundant fragment ions for each target compound were selected. Criteria used for positives were signal-to-noise ratio above 3 and qualifier ratio within 80-120% range of the ratio observed from injected authentic standards.

Instrumental LODs of these compounds were calculated from the analysis of authentic standards (0.0001-10 ng/mL) and considering peak areas of S/N≥3. Method LODs were estimated from instrumental LODs taking into account the concentration factor of the method (sample size of 50 mg and final extract volume of 200 μL) and considering 100% total recovery and were 8 ng/g for RDP, 20 ng/g for EDPHP and IDP and 40 ng/g for CDP and BDP.

3. Results and discussion

3.1. Method optimization and validation

The method for quantification of TPHP and DPHP in indoor dust was evaluated based on extraction recovery (%), clean-up recoveries (%), matrix effects (%), and reproducibility (RSD%) by using the indoor dust reference material SRM 2585 (50 mg). Since the material already contained TPHP and DPHP at relatively high concentrations, the deuterated internal standards (IS) were employed for recovery optimization. The reference material was spiked in triplicates with 0.1 μg IS (TPHP-d_{15} and DPHP-d_{10}). The spiking was done before extraction, before clean-up or at the final reconstitution step in order to assess the extraction efficiency, clean-up losses, matrix effects and total recoveries. When spiked before extraction, the SRM was left stand for 2 h to allow the solvent to evaporate in order to mimic as much as possible the interaction of the compound with the dust matrix.

The extraction of TPHP and DPHP from spiked SRM was performed by salting-out extraction with acetonitrile and 3 M aqueous NH_4Ac as described in section 2.3. A two-phase system was used to reduce co-extraction of unwanted matrix components and thus to achieve

cleaner extracts. After extraction, due to the complexity of the dust matrix, a clean-up step with QuEChERS (75 mg $MgSO_4$, 25 mg PSA, 25 mg C_{18}, 25 mg GCB) was assessed. For TPHP, signal suppression due to matrix was significant and the signal improved from 13±2% to 29±5% when clean-up was utilized following the salting-out extraction with acetonitrile and 3 M aqueous NH_4Ac. For DPHP, the matrix effects were lower when analyzed in the negative ionization mode (87±2%) compared to the positive ionization mode (62±1%) so that negative ionization was selected for further experiments. The extraction recoveries for TPHP and DPHP were 92±19% and 79±3%, respectively and the clean-up recoveries were 91±6% and 100±7% for TPHP and DPHP, respectively. Total recoveries (extraction + clean-up + matrix effects) for TPHP and DPHP based on triplicate spiking experiments were 24±5% and 69±2%, respectively, and losses are expected to be well compensated by their deuterated IS.

Although concentrations of aryl-PFRs are not certified in SRM 2585, TPHP has been reported by other authors ranging 980±60[31] to 1110±48.[61] The observed average concentration of TPHP and DPHP in SRM 2585 (n=3) were 1075±151 ng/g and 4967±129 ng/g, respectively, which for TPHP is in accordance with previously reported concentrations. In this sense, despite the low total recoveries of TPHP (mainly due to matrix effects), the method worked properly for the quantitation of TPHP and matrix effects were compensated by the deuterated internal standard. Matrix effects did not change drastically between samples. The total recovery in the real dust samples were 28±12% (mean 25%) for TPHP and 101±21% (mean 101%) for DPHP, respectively.

3.2 TPHP and DPHP concentrations in indoor dust

TPHP and DPHP were detected at high concentrations in all samples analyzed from the Netherlands and from Spain (Table 1). The highest concentrations of both TPHP and DPHP were observed in dust samples collected from the seats and dashboards of cars (142,459 ng/g and 79,661 ng/g for TPHP and DPHP, respectively) followed by dust collected from on top

of electronic equipment (45,330 ng/g and 21,899 ng/g for TPHP and DPHP, respectively). To the best of our knowledge, only one study has reported DPHP in indoor dust in the range 75-190 ng/g.[53] In general, TPHP levels were higher than the DPHP levels, commonly 2-3 times higher, in some cases up to 90 times higher. However, in some samples (*n*=14) the concentration of DPHP was up to 2-10 times higher than that of TPHP. These samples were collected in different microenvironments and in both Spain and the Netherlands. This is also the case of the reference material 2585 employed for the optimization and validation of the method, which showed a DPHP concentration about five times higher than that of TPHP. This could be due to the presence of DPHP coming from the degradation of aryl-PFRs other than TPHP or from other sources of contamination, such as consumer products containing DPHP as an additive (e.g. paint or coatings).

The high concentrations of TPHP and DPHP found on top of electronic equipment in comparison to concentrations observed in dust collected from the floor in the same room (Figure S-1) suggest that electronic equipment is a relevant source of TPHP and DPHP in the indoor environment. Differences in contamination patterns between floor dust and dust from elevated surfaces (electronics) should be also considered as a plausible cause. However, no correlation was observed between the concentrations found in floor dust and in dust collected from the surface of electronic equipment (TPHP, r=0.18; DPHP, r=0.04).

One-way ANOVA revealed that there was not a statistically significant difference between TPHP and DPHP levels in dust collected in Spain and in the Netherlands (TPHP, p=0.94, DPHP, p=0.62). The microenvironments were divided into four groups: floor dust (bedrooms, living rooms and offices), dust collected on top of electronic equipment, car dust and dust collected from the floors of public microenvironments. Among these groups, no statistically significant difference in TPHP and DPHP levels were revealed except between car dust and floor dust. The concentrations of TPHP and DPHP in car dust were significantly higher than

in floor dust ($p<0.05$), which could be explained by high amounts of flame retardants being used in the manufacturing of car seats and dashboards and/or less frequently cleaning of cars in comparison to houses. Regarding the ratio of the median values of TPHP and DPHP (Table 1), measured ranges were in the same order of magnitude (0.9-4.5 in Spain and 1.9-3.8 in the Netherlands).

Table 1. TPHP and DPHP detection frequency (DF) and concentrations (ng/g) in indoor dust from different microenvironments in Spain and the Netherlands.

		DF (%)	Mean ± SD	Median	Min	Max	[a]TPHPmedian/ DPHPmedian
TPHP (Spain)	Living rooms (*n*=9)	100	3161 ± 6051	944	265	18912	4,5
	Bedrooms (*n*=9)	100	674 ± 297	734	211	1094	3,7
	Offices (*n*=4)	100	760 ± 413	637	412	1353	0,9
	On top of electronics (*n*=13)	100	5900 ± 7105	2416	1270	26210	1,4
	Cars (*n*=15)	100	18305 ± 36362	4441	762	142459	1,9
	Public microenvironments (*n*=7)	100	665 ± 281	687	169	1004	1,9
DPHP (Spain)	Living rooms (*n*=9)	100	241 ± 127	211	111	461	
	Bedrooms (*n*=9)	100	314 ± 284	197	106	1031	
	Offices (*n*=4)	100	771 ± 354	712	408	1251	
	On top of electronics (*n*=13)	100	3211 ± 5780	1753	299	21899	
	Cars (*n*=15)	100	8294 ± 19897	2311	923	79661	
	Public microenvironments (*n*=7)	100	371 ± 103	357	263	556	
TPHP (The Netherlands)	Homes and offices (*n*=12)	100	3073 ± 3789	1438	172	12853	1,9
	On top of electronics (*n*=11)	100	10353 ± 12688	9786	285	45330	3,8
DPHP (The Netherlands)	Homes and offices (*n*=12)	100	1199 ± 1227	742	151	4189	
	On top of electronics (*n*=11)	100	2781 ± 2102	2581	218	6588	

[a]Ratio of the median values of TPHP and DPHP in each microenvironment

The TPHP concentrations in indoor dust from homes in Spain and in the Netherlands are in line with those previously reported in Europe (Figure 1, Table S-2).[8, 12, 15, 21, 24, 30, 31, 34] The same accounts for TPHP concentrations in dust collected from on top of electronic equipment as well as from floors of offices and public microenvironments (Figure 1, Table S-2).[11, 12, 20, 24, 30, 31, 34, 62] The median TPHP concentration observed in car dust (4,441 ng/g) was however somewhat higher than reported before (135-3,700 ng/g). Reported TPHP concentrations in house dust as well as in dust from other microenvironments span over a wide concentration

range (<2-1,798,000 ng/g) with the highest concentration reported being observed in house dust from the U.S.[9] The lowest concentration was observed in house dust from Pakistan[14, 16] and in car dust from Kuwait.[16] This high variation in TPHP concentrations, spanning several orders of magnitude, may be explained by different fire-safety regulations in different countries as well as different regulations regarding the production and use of PBDEs. Variability between measurements due to the analytical challenges related to the analysis of aryl-PFRs should be also taken into account.[63]

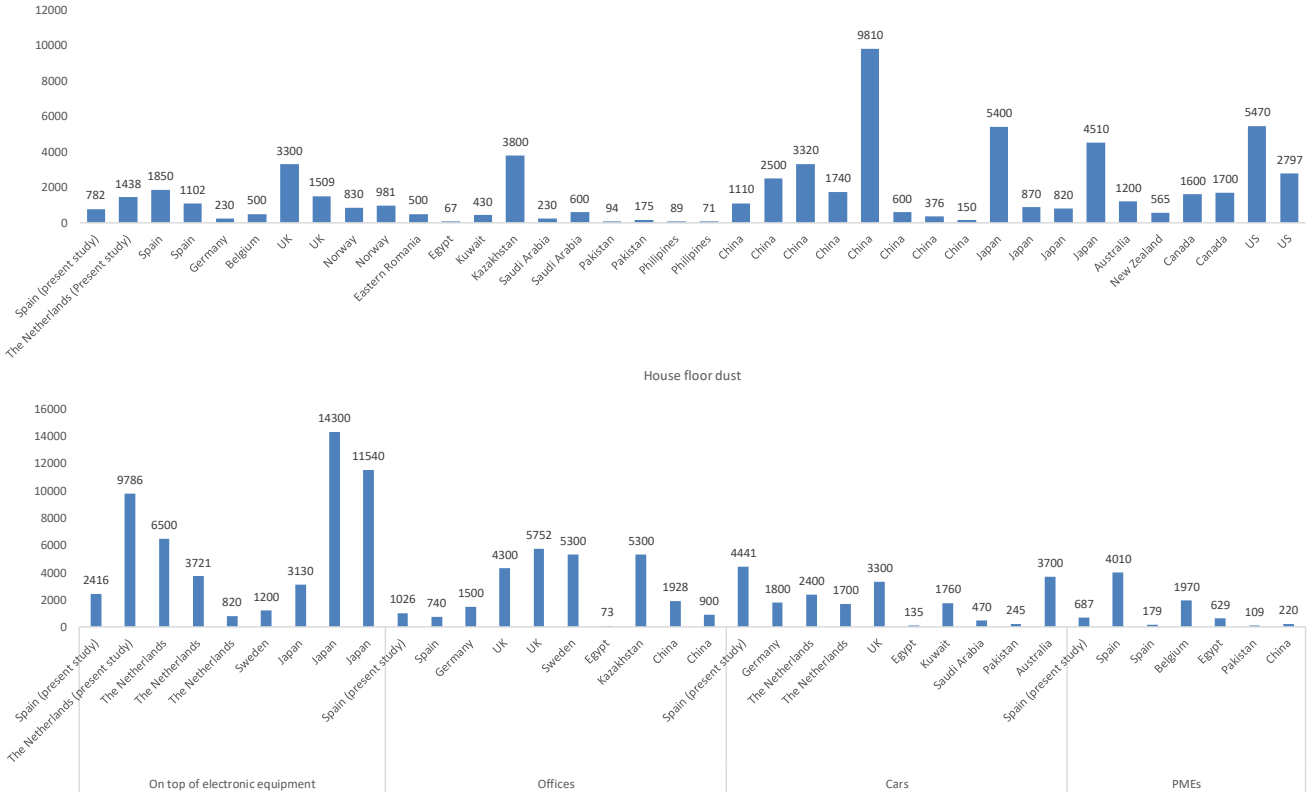


Figure 1. Reported median concentrations TPHP (ng/g) in indoor dust from houses (top) and from the surface of electronic equipment, offices, cars and public microenvironments (bottom) in this study and in other countries.

2.4. 3.3. Correlation between TPHP and DPHP in indoor dust

Pearson correlation was performed to investigate the correlation between TPHP and DPHP concentrations in indoor dust. Taking into account all the samples collected from the

297 Netherlands and Spain (*n*=80), we observed a strong and statistically significant positive
298 correlation between the concentration of TPHP and DPHP in indoor dust (r=0.90, p<0.01)
299 (Figure 2).

300 Pearson correlation was also performed for individual microenvironments (Figure S-2).
301 Statistically significant positive correlations were observed in dust collected from floors of
302 houses and offices (r=0.46, p<0.05) (Figure S-2 A), on top of electronic equipment (r=0.60,
303 p<0.01) (Figure S-2 B) and cars (r=0.99, p<0.01) (Figure S-2 C). Positive correlation was
304 also observed in dust collected from public microenvironments (r=0.69) (Figure S-2 D),
305 however, not statistically significant (p=0.12). These findings suggest that the presence of
306 DPHP in indoor dust may be related to the presence of TPHP as an impurity and/or as *ong*
307 *diet, indoor dust inhalation and dermal contact with contaminated dust or products, being*
308 *the latter the more recently discussed in the literatu*a degradation product. However, it cannot
309 be ruled out that the presence of DPHP in indoor dust might also be a result of degradation of
310 other aryl-PFRs or to its use as product additive. Chemical hydrolysis, photodegradation or
311 biodegradation may play a role with different magnitude in each microenvironment. The ratio
312 of TPHP to DPHP in the different microenvironments were in the range 0.09-89.68. One-way
313 ANOVA revealed that there were no statistically significant difference in the TPHP-DPHP
314 ratio between the different microenvironments (p=0.82) or between dust collected in Spain
315 and in the Netherlands (p=0.54).

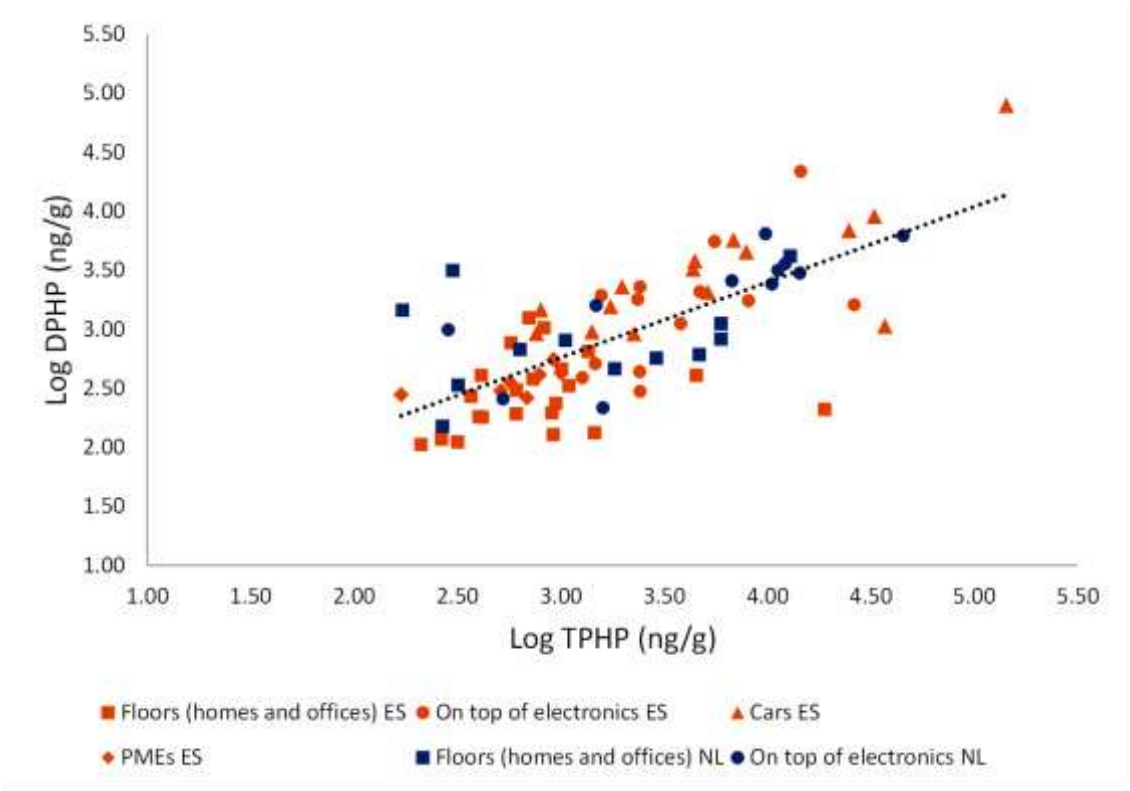


Figure 2. Pearson correlation between TPHP and DPHP concentration in different microenvironments in indoor dust from Spain (ES) and the Netherlands (NL), r=0.90, p<0.01.

3.4. Human exposure to TPHP and DPHP via indoor dust ingestion

Human exposure scenarios to TPHP and DPHP via dust ingestion in Spain were estimated using a method based on that described by Abdallah and Covaci.[18] Briefly, average and high dust ingestion rates (95th percentile) for adults (2.6 mg/day and 8.6 mg/day, respectively) and toddlers (41 mg/day and 140 mg/day, respectively)[64] were used to calculate an average and a worst-case scenario exposure to TPHP and DPHP via indoor dust. Estimated exposure scenarios were calculated based on median and maximum concentrations in indoor dust in homes (bedrooms and living rooms), offices, cars and public

microenvironments (different stores and one cafeteria) in Spain, taking into account the time spent in each environment according to the typical human activity patterns described by Abdallah and Covaci[18] (i.e. for adults 63.8% home, 22.3% office, 5.1% Public microenvironments, 4.1% car and 4.7% outdoors, and for toddlers 86.1% home, 5.1% Public microenvironments, 4.1% car and 4.7% outdoors). Occupational exposure of drivers (e.g. taxi drivers and truck drivers) were estimated by using the concentrations in cars as representative concentrations for the working environment (i.e. time fraction spent in car was 26.4%).

The estimated exposure to TPHP and DPHP for different exposure scenarios including workers (offices), drivers, non-workers and stay-home toddlers are illustrated in Figure 3. The estimated daily exposure based on average dust ingestion rates and median concentrations are in line with those reported elsewhere which are in the range 0.9-58.5 ng/day, 7.0-30.2 ng/day and 3-75.4 ng/day for adult workers, non-workers and stay-home toddlers, respectively (Table S-3).[12, 13, 15, 17, 18, 32-34]

For adults, the calculated worst-case scenario exposure estimates are in line with those reported elsewhere (based on high dust ingestion rate and 95th percentile or maximum concentration) which are in the range 13.0-953.2 ng/day and 70.0-506.1 ng/day for workers and non-workers, respectively (Table S-3).[12, 13, 15, 17, 18, 32-34] However, the worst-case scenario estimated daily exposure to TPHP via dust ingestion for stay-home toddlers was 3104.5 ng/day, a value that is higher than those reported in previous studies (Table S-3). Despite the high estimated daily exposure for toddlers, all calculated exposure estimates for different scenarios are far below the reference dose of 164,500 ng/day (adults) and 28,905 ng/day (toddlers) calculated from the lowest reported chronic NOAEL, 23.5 mg/kg/day[65] divided by a safety factor of 10,000 and assuming body weights of 70 kg and 12.3 kg for adults and toddlers, respectively according to US EPA.[66] To the best of our knowledge, this is the first

study to report estimated daily exposure scenarios to DPHP via indoor dust ingestion. It is worth mentioning that this is only one of identified the major routes of human exposure to flame retardants, among diet, indoor air inhalation and dermal contact with contaminated dust or products, being the latter the more recently discussed in the literature.

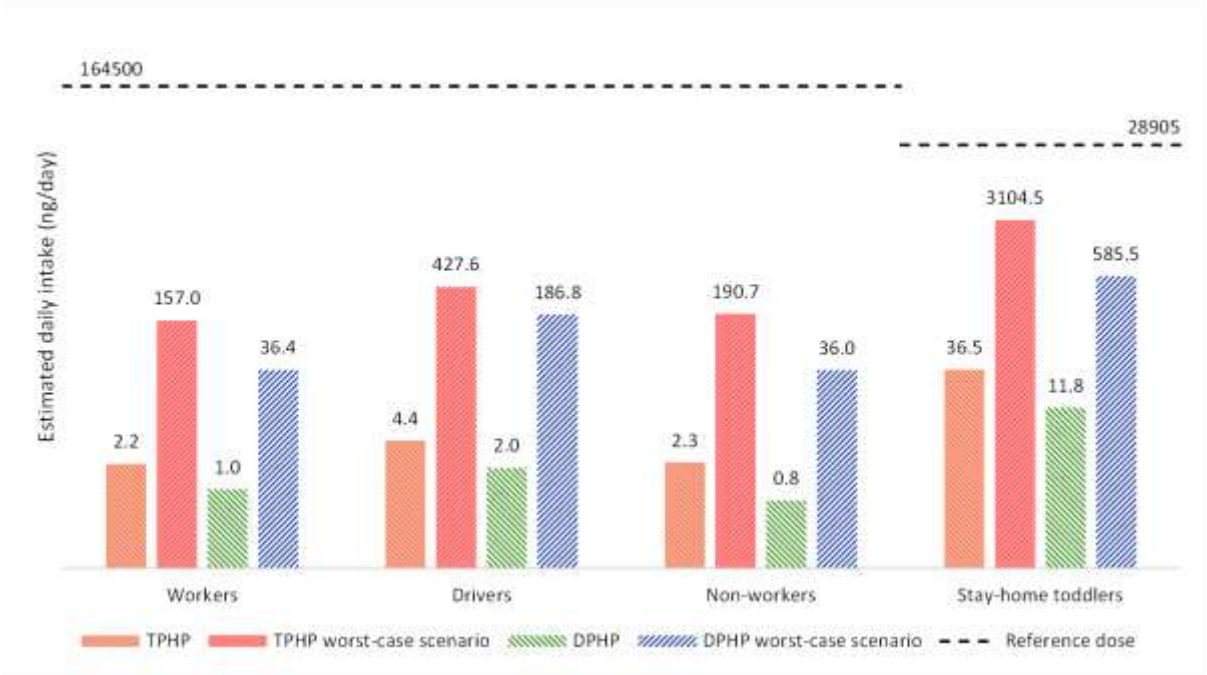


Figure 3. Estimated daily intake (ng/day) for different exposure scenarios in Spain. TPHP and DPHP exposure scenarios are estimated based on average dust ingestion rates and median concentrations measured in indoor dust. Worst-case scenarios are estimated based on high dust ingestion rates and maximum concentrations observed in indoor dust. Reference doses for adults and toddlers are calculated from the lowest reported chronic NOAEL, 23.5 mg/kg/day[65] divided by a safety factor of 10,000 and assuming body weights of 70 kg and 12.3 kg for adults and toddlers, respectively.

3.5 Estimated urinary levels of DPHP via indoor dust ingestion

Estimated urinary levels of DPHP as a result of exposure to TPHP and DPHP via indoor dust were calculated based on the median and maximum levels of TPHP and DPHP in indoor dust in Spain (country for which the sample size was higher and more diverse in terms of microenvironments). The time fractions spent in each microenvironment were also taken into

account according to the typical human activity patterns described in the previous section. A method based on that described by Van den Eede et al.[53] was employed. Briefly, an average and a high dust ingestion rate (95th percentile) for adults (2.6 mg/day and 8.6 mg/day) and toddlers (41 mg/day and 140 mg/day)[64] were assumed. Other assumptions were the complete absorption of TPHP and DPHP after dust ingestion as well as the complete excretion of DPHP in urine and that DPHP is absorbed and excreted unchanged.[67] The assumption that TPHP is metabolized into DPHP by liver enzymes at a rate of 20% was also included.[68] Based on these assumptions and assuming a mean urinary output of 800 mL/day for adults and 600 mL/day for children, estimated DPHP urinary levels (ng/mL) were calculated for different exposure scenarios in Spain including workers (offices), drivers, non-workers and stay-home toddlers.

The estimated urinary DPHP levels as a result of exposure to TPHP and DPHP via indoor dust ingestion (based on average dust ingestion rates and median concentrations) were 0.002 ng/mL, 0.004 ng/mL, 0.002 ng/mL and 0.032 ng/mL for adult workers, drivers, non-workers, and stay-home toddlers, respectively (Table 2). These estimated urinary DPHP levels as a result of exposure to TPHP and DPHP via indoor dust ingestion are not high enough to explain the high DPHP urinary levels reported in the literature ranging <0.13-727 ng/mL.[25, 49-54]

The worst-case scenario urinary DPHP levels estimated for the different exposure scenarios (based on high dust ingestion rate and maximum concentration in dust) were 0.085 ng/mL, 0.34 ng/mL, 0.094 ng/mL, and 2.011 ng/mL for workers (offices), drivers, non-workers and stay-home toddlers, respectively (Table 2). The estimated urinary DPHP level in toddlers is 40 times higher than the worst-case scenario previously reported (0.05 ng/mL).[53] Furthermore, the estimated worst-case scenario urinary levels of DPHP are in the same range

as the lower urinary DPHP concentrations reported previously (<0.13 ng/mL),[54] however, still inadequate to explain the high DPHP levels reported in urine.[25, 49-54]

Van den Eede et al.[69] showed that serum enzymes are involved in the transformation of TPHP into DPHP and that the amount TPHP that reaches the liver after intake may be strongly reduced. Therefore, the metabolic transformation rate of TPHP into DPHP (by serum and liver enzymes) could be higher than 20% resulting in an underestimation of urinary DPHP levels. The same study also investigated the hydrolysis products of EDPHP by serum enzymes and results suggest an additional production of DPHP from EDPHP, however, at a much lower rate than for TPHP.

It should be noted that the TPHP and DPHP concentrations in indoor dust vary over several orders of magnitude between different environments and that the estimated urinary DPHP levels cannot be compared directly to reported urinary levels elsewhere without a large degree of uncertainty. Furthermore, it should be taken into account that higher urinary levels could be reached via dust ingestion since the excretion of DPHP would reach a peak only at a certain time after ingestion depending on the kinetics of DPHP excretion via urine. Additionally other exposure routes than dust ingestion should be considered since according to recent studies dermal contact with contaminated dust seems to be a major exposure route for aryl-PFRs and concentrations of TPHP in handwipes were associated with concentrations of urine metabolites.[70,71]

Table 2. Estimated urinary DPHP concentration (ng/mL) for different exposure scenarios in Spain.

	Average ingestion rate		High ingestion rate	
	Median	**Maximum**	**Median**	**Maximum**
Workers	0.002	0.026	0.006	0.085
Drivers	0.004	0.103	0.012	0.340
Non-workers	0.002	0.028	0.005	0.093
Stay-home toddlers	0.032	0.589	0.109	2.011

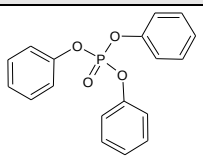
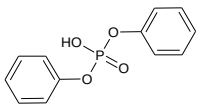
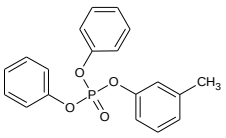
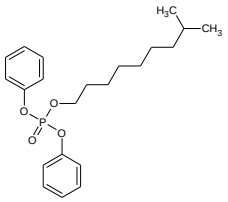
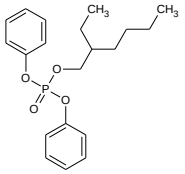
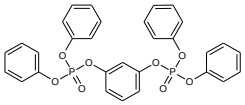
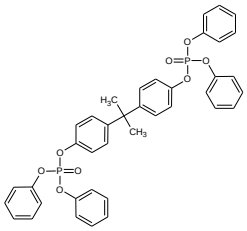
3.6. Screening of aryl-PFRs in indoor dust

TPHP and DPHP were detected in all samples analyzed from Spain (*n*=57) and the Netherlands (*n*=23). Other aryl-PFRs, namely CDP, RDP, EDPHP, IDP and BDP were all detected in indoor dust, however, with lower frequency (Table 3).

EDPHP was the most frequently detected aryl-PFR after TPHP and DPHP with a detection frequency of 64.9% and 65.2% in Spain and the Netherlands, respectively, followed by IDP (50.9% and 43.5%), BDP (33.3% and 34.8%), CDP (3.5% and 8.7%) and RDP (0% and 4.3%). Due to strong matrix effects and the lack of suitable internal standards for these compounds they were not quantified. Detection frequencies of all aryl-PFRs included in the present study were similar in samples collected from Spain and the Netherlands (Table S-4).

We should point out that not all possible aryl-PFRs were screened in this study, for example isopropylated and tert-butylated triarylphosphate isomers (ITP and TBPP) were not included, and they could also be related to DPHP.

Table 3. Compound name, CAS, molecular structure, chemical formula, monoisotopic mass and detection frequency (%) of TPHP, DPHP, CDP, IDP, EDPHP, RDP, and BDP in indoor dust from Spain and the Netherlands.

Compound CAS	Molecular structure	Chemical formula	Monoisotopic mass (g/mol)	Detection frequency (%)	
				Spain (*n*=57)	The Netherlands (*n*=23)
Triphenyl phosphate (TPHP) 115-86-6		$C_{18}H_{15}O_4P$	326.070801	100	100
Diphenyl phosphate (DPHP) 838-85-7		$C_{12}H_{10}O_4P$	250.039490	100	100
Cresyl diphenyl phosphate (CDP) 26444-49-5		$C_{19}H_{17}O_4P$	340.086456	3.5	8.7
Isodecyl diphenyl phosphate (IDP) 29761-21-5		$C_{22}H_{31}O_4P$	390.195984	50.9	43.5
2-Ethylhexyl diphenyl phosphate (EDPHP) 1241-94-7		$C_{20}H_{27}O_4P$	362.164703	64.9	65.2
Resorcinol bis(diphenyl phosphate) (RDP) 57583-54-7		$C_{30}H_{24}O_8P_2$	574.094666	0	4.3
Bisphenol A bis(diphenyl phosphate) (BDP) 5945-33-5		$C_{39}H_{34}O_8P_2$	692.172913	33.3	34.8

4. Conclusions

TPHP and DPHP were present at high concentrations with 100% detection frequency in all samples analyzed from Spain and the Netherlands. The highest maximum concentrations of

448 TPHP and DPHP were observed in dust collected from the seats and dashboards of cars
449 (142,459 ng/g and 79,661 ng/g for TPHP and DPHP, respectively), followed by dust
450 collected from the surface of electronic equipment (45,330 ng/g and 21,899 ng/g for TPHP
451 and DPHP, respectively). This suggests a high use of TPHP in the manufacturing of car
452 interiors and electronic equipment that are important contamination sources of this
453 compound. The lowest concentrations of TPHP (169 ng/g) and DPHP (106 ng/g) were
454 observed in floor dust collected from public microenvironments and bedrooms, respectively.

455 TPHP concentrations in house dust in Spain and the Netherlands are in line with those
456 reported in other European countries. The strong correlation between TPHP and DPHP levels
457 ($r=0.90$, $p<0.01$) suggests that TPHP could be a source for DPHP in indoor dust, probably as
458 a result of degradation. However, other possible sources for DPHP in indoor dust cannot be
459 ruled out since DPHP has been suggested to be an impurity, degradation product and
460 metabolite of some aryl-PFRs and it is used as a product additive. Indeed, other aryl-PFRs
461 were present in dust samples, namely CDP, IDP, EDPHP, RDP and BDP although less
462 frequently detected.

463 The estimated average daily exposure to TPHP and DPHP in Spain is highest for toddlers
464 (36.5 ng/g and 11.8 for TPHP and DPHP, respectively) followed by drivers (4.4 ng/g and 2.0
465 for TPHP and DPHP, respectively), which are both far below the reference dose for TPHP of
466 164,500 ng/day (adults) and 28,905 ng/day (toddlers). The estimated average urinary DPHP
467 concentrations as a result of exposure to TPHP and DPHP via indoor dust ingestion are far
468 below and insufficient to explain the high DPHP levels reported in urine. Only in the
469 estimated worst-case scenario, urinary DPHP concentrations are in the same range as the
470 lower reported DPHP levels. Other sources of TPHP exposure and/or the presence of other
471 aryl-PFRs that are degraded and/or metabolised into DPHP may be relevant sources to
472 explain the high concentrations of DPHP reported in urine.

Conflict of interest

The authors declare no conflicts of interest.

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