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**ABSTRACT**

Indoor dust can contribute substantially to human exposure to known and contaminants of emerging concern (CECs). Novel compounds with high structural variability and different homologues are frequently discovered through screening of the indoor environment, implying that constant monitoring is required. The present study aimed at the identification and semi-quantification of CECs in 46 indoor dust samples collected in Belgium by liquid chromatography high-resolution mass spectrometry. Samples were analyzed applying a targeted and suspect screening approach; the latter based on a suspect list containing > 4000 CECs. This allowed the detection of a total of 55 CECs, 34 and 21 of which were identified with confidence level (CL) 1/2 or CL 3, respectively. Besides numerous known contaminants such as di(2-ethylhexyl) phthalate (DEHP), di(2-ethylhexyl) adipate (DEHA) or tris(2-butoxyethyl) phosphate (TBOEP) which were reported with detection frequencies (DFs) > 90%, several novel CECs were annotated. These included phthalates with differing side chains, such as decyl nonyl and decyl undecyl phthalate detected with DFs > 80% and identified through the observation of characteristic neutral losses. Additionally, two novel organophosphate flame retardants not previously described in indoor dust, i.e. didecyl butoxyethoxyethyl phosphate (DDeBEEP) and bis(butoxyethyl) butyl phosphate (BBEBP), were identified. The implementation of a dedicated workflow provided semi-quantitative concentrations for a set of suspects. Such data obtained for novel phthalates were in the same order of magnitude as the concentrations observed for legacy phthalates indicating their high relevance for human exposure. From the semi-quantitative data, estimated daily intakes and resulting hazard quotients (HQs) were calculated to estimate the exposure and potential health effects. Neither of the obtained HQ values exceeded the risk threshold, indicating no expected adverse health effects.

**KEYWORDS**

Human exposome; contaminants of emerging concern; suspect screening; phthalates; alternative plasticizers; organophosphate flame retardants.

## 1. INTRODUCTION

The indoor environment contributes substantially to human exposure to various environmental contaminants. Thereby, the ingestion and inhalation of, or the dermal contact with indoor dust represent major exposure routes which are especially relevant for toddlers due to crawling behaviour and frequent hand-to-mouth contact (Cui et al., 2023; Dubocq et al., 2021). In recent years, numerous studies have identified various contaminant classes in indoor dust including phthalate and alternative plasticizers, organophosphate flame retardants (PFRs), UV filters, polybrominated diphenyl ethers, polycyclic aromatic hydrocarbons, among others, pointing out the suitability of this matrix to identify indoor contamination (Ao et al., 2018; Christia et al., 2021b; Dvoršćak et al., 2022; Xu and Li, 2021). Several of those can be described as contaminants of emerging concern (CECs), representing contaminants which have recently been reported and for which comprehensive data on their potential toxicity or negative effects on human and environmental health is lacking (Sauvé and Desrosiers, 2014).

While quantitative results obtained through target analysis, commonly applied for contaminant analysis, are important for a thorough exposure assessment(Christia et al., 2021a), these approaches do not allow the detection of contaminants which are not *a priori* targeted. This gap is addressed through the application of suspect screening analysis (SSA) and non-target screening (NTS) approaches which have been widely implemented covering various matrices such as dust, urine, food or soil and most commonly implementing liquid chromatography coupled to high-resolution mass spectrometry (LC-HRMS)(Christia et al., 2021b; Cui et al., 2023; Dubocq et al., 2021). Within SSA, acquired data is matched against a predefined list of suspects ('suspect list') which are assumed to be present in the samples of interest. NTS analyses process data without any *a priori* selections of analytes, prioritizing signals of interest based on different data processing approaches, such as characteristic isotopic and/or fragmentation patterns, statistical comparisons between samples groups, etc(Menger et al., 2020). These approaches support the identification of novel CECs which might be overlooked with traditional targeted methods.

For example, two recent studies using an NTS approach for prioritizing and characterizing compounds based on characteristic fragmentation patterns showed the identification of 20 novel PFRs (Wang et al., 2022; Wang et al., 2020). Other SSA and NTS studies reported additional novel compounds from various classes including plasticizers, pharmaceuticals, and personal care products (PCPs), pointing out the added value of the described approaches and the high variety of CECs present in dust(Christia et al., 2021b; Rostkowski et al., 2019; Zhang et al., 2021).

Recently, the absence of quantitative results within SSA and NTS studies was addressed by semi-quantitative approaches to obtain data for suspect compounds for which reference standards are often

not available. These approaches are based on the selection of calibrators similar in structure and/or retention time (RT) to the suspect compound or the prediction of ionization efficiencies for the latter(Bieber et al., 2023; Malm et al., 2021). Subsequently, the obtained semi-quantified concentrations can be used for further prioritization of the detected compounds, estimation of human exposure and other purposes further improving the usability of obtained results derived from SSA and NTS studies.

Therefore, the present study aimed at combining the added value of SSA and semi-quantification analyzing indoor dust samples collected in Flanders (Belgium) by high resolution mass spectrometry (HRMS). A combination of 1) targeted and suspect screening, 2) implementation of a semi-quantification workflow for a subset of suspect compounds, and 3) the subsequent calculations of estimated daily intakes (EDIs) allowed a comprehensive characterization of a wide range of CECs and an estimation of potential human exposure to the latter easing further compound prioritization.

## 2. MATERIALS AND METHODS

Information on chemicals used in this study can be found in the Supplementary Information (SI, **Table S1 and section SI.2.1**).

### 2.1 Sample collection

A total of 46 indoor dust samples were collected between January and February 2022 at 40 different locations in Flanders, Belgium. The sampled addresses included 24 private homes and 16 public locations (comprising sports halls, university auditoriums, and offices). At three locations, more than one area was sampled leading to a total of 46 samples.

The sample collection protocol was based on a previously described approach(Christia et al., 2021b; Harrad et al., 2008). Briefly, 1 $m^2$ or 4 $m^2$ of carpet or hard flooring, respectively, were vacuumed for 1 min/$m^2$ with a vacuum cleaner equipped with a nylon sock (pore size: 25 µm). To obtain field blank samples, pre-cleaned sodium sulphate was gritted on previously cleaned flooring and collected using the same approach as for the dust samples. In this way, field blank samples were collected at eight locations and used to control possible contamination introduced by sampling or sample preparation. All collected dust samples were transferred to Falcon tubes and stored at room temperature in the dark prior to analysis.

For each sampling site, information about the type (public vs. private) and age of the sampled building, the location (urban vs. rural) and the time passed since the last cleaning was obtained through a questionnaire (**Table S2** provided as Excel).

### 2.2 Sample preparation and instrumental analysis

The sample preparation was based on an in-house developed method (Christia et al., 2021b). In short, 20 mg of dust (< 500 µm) was extracted through sonication with 2.5 mL of a hexane/acetone mixture (1:1; v/v) and 0.5 mL of toluene. After evaporation and reconstitution in 1 mL Hex, extracts were cleaned up and fractionated with SeP-Pak® Vac 3 mL (500 mg) Florisil® solid-phase extraction (SPE) cartridges (Waters; Milford, MA, USA). After elution with 8 mL Hex (fraction A), 10 mL EtOAc (fraction B) and 6 mL (MeOH) (fraction C), fractions B and C were evaporated and reconstituted separately in 100 µL MeOH:H2O (9:1; v/v). Extracts were analysed on an Agilent 6560 ion-mobility quadrupole time-of-flight high resolution mass spectrometer (IM-QTOF-MS) operating in positive polarity coupled to an Agilent Infinity II UHPLC system (Agilent Technologies, Santa Clara, USA). Chromatographic separation was achieved with a Poroshell 120 EC-C18 column (2.1 x 100 mm; 2.7 µm particle size). A detailed description of the sample preparation, instrumental analysis and the included quality control (QC) measures can be found in the SI (**sections SI.2.2 and SI.2.3**).

### 2.3 Quality control (QC) and data analysis

Prior to any data processing, the mass accuracy of the raw data and stability of the chromatographic conditions were assessed by investigating the signals and RTs obtained for IS in all samples and native compounds included in the QC samples. For these investigations, the 'Find By Formula' algorithm was used (Agilent MassHunter Qualitative Analysis software version B.07.00) applying a mass tolerance of 10 ppm and an overall matching score of at least 70. For the extraction of the IS signals from raw data of the dust samples, both the proton ($[M+H]^+$) and sodium ($[M+Na]^+$) adducts were considered and a peak area consisting of the summed signals of both adducts was reported. For the internal standards (IS) and native compounds included in the QC samples, only the signals obtained for the more abundant of the two mentioned adducts was reported as the selection of the more abundant adduct of each parent compound was relevant for the semi-quantification approach described in **section 2.4**.

After the described QC measures, molecular features were extracted from the raw data using the 'Batch recursive feature extraction' algorithm within the MassHunter Profinder software (version B.08.00;

Agilent Technologies, Santa Clara, USA). Thereby, the minimum peak height was set to 2000 counts. Ions corresponding to $[M+H]^+$ or $[M+Na]^+$ were included. For chromatogram alignment, tolerances were set to 0.20 min and 10 ppm for the retention time and mass tolerance, respectively. All obtained features were imported in the Mass Profiler Professional software (version 15.0, Agilent Technologies) and further filtered using a fold change analysis which only retained features showing at least a 5-fold intensity difference between samples and procedural blanks. Filtered features were matched against a previously developed suspect list using the MassHunter ID Browser (version 10.0). Thereby, a mass tolerance of 7 ppm, an isotope abundance score of 80 and an overall matching score of at least 75 were set. The applied suspect list was based on an in-house suspect list developed within a previous study(Christia et al., 2021b). Additionally, a list of compounds associated with plastic packaging was added to further expand the coverage of the group of plastic related chemicals(Groh et al., 2019). Lastly, a list was included containing new PFRs and triazine UV filters recently discovered in indoor dust and soil samples from South China(Du et al., 2022; Gong et al., 2022; Wang et al., 2020) to potentially confirm the occurrence of these compounds in European dust samples. Ultimately, the final version of the suspect list contained > 4300 entities.

All annotated compounds which fulfilled the matching criteria described above, were manually investigated to confirm compound annotation and avoid the report of false positive detections. Thereby, the mass accuracy, the match between theoretical and experimental isotopic pattern and, if available, the fragmentation spectra were investigated. This aimed at assigning a confidence level (CL) of identification based on the scheme introduced by Schymanski et al.(Schymanski et al., 2014) following considerations described in a previous study. In brief, CL1 was assigned if all experimental data (RT, *m*/*z*, isotopic pattern and fragmentation spectrum) of a feature unequivocally matched data of an available reference standard following the same criteria as mentioned above. CL2A or CL2B were assigned if available experimental fragmentation spectra could be matched with library data (e.g., derived from open-source libraries such as MassBank or mzcloud (date of last access: 01/11/2023)) or provided diagnostic evidence, respectively, and allowed the assignment of a single possible compound structure(Schymanski et al., 2014). As described previously, CL2 was expanded by the addition of CL2C which was assigned if no fragmentation spectrum was available but the remaining data (*m*/*z*, RT and isotopic pattern) unequivocally matched the reference standard (RT difference < 0.2 min, mass error < 7 ppm)(Roggeman et al., 2022). If, based on the available experimental data (incl. a fragmentation spectrum), a tentative candidate could be proposed but no match with a library spectrum was possible and other possible candidates could not be excluded,

CL3 was assigned. Within this study, only compounds which were assigned with CL3 or better in at least one of the investigated samples were reported.

### 2.4 Semi-quantification

A sub-selection of the reference standards included in the QC samples (**Table S1**) were used as calibrators to prepare calibration curves to be used for semi-quantification of the compounds identified through the described SSA approach (**section 2.3**). The calibrator used for semi-quantification of the corresponding suspect was selected aiming to have the highest possible similarity in structure and retention time between calibrator and suspect. The same approach was used to assign an IS to each of the calibrators. For each calibrator, a calibration curve was prepared covering eight calibration points with a concentration range of 0.01 to 2 ng/µL. To each calibration point, the same selection and concentration of IS as used for the dust samples were added. To account for possible matrix effects, the relative peak area (ratio peak areas calibrator/analyte and the IS) was used for semi-quantification of the corresponding suspect in the dust extract. To obtain the peak areas of calibrators and IS, the 'Find By Formula' algorithm with the settings described in section 2.4 was used. Thereby, for each of the calibrators and IS only the more abundant adduct (thus, $[M+H]^+$ or $[M+Na]^+$) was considered as stable ratios of both adducts between calibrants and samples could not be guaranteed.

From the relative areas obtained for each calibration point, the response factor (corresponding to the slope of the calibration curve) was calculated. Through division of the relative area of the suspect of interest ($A_{Susp.}/A_{IS}$) by the response factor ($R_f$) of the assigned calibrant, the concentration of the suspect ($c_{Susp.}$) in the corresponding dust extract was obtained as displayed in the following formula(Malm et al., 2021):

$$c_{Susp.}\,[\mathrm{ng/\mu L}] = \frac{A_{Susp.}/A_{IS}}{R_f}$$

From this data, the concentration in the dust (in µg/g) was calculated. For CECs, very low signal intensities were obtained for the IS in the MeOH fractions obtained through SPE (**section SI.2.2**) which suggested that most of the IS eluted in the previous (EtOAc) fraction. Therefore, semi-quantification of the analytes detected in the MeOH fraction was not possible as no suitable IS was available in that fraction.

### 2.5 Statistical analysis

Semi-quantified concentrations (**section 2.4**) were compared applying a Mann-Whitney U Test between different sample categories after grouping based on housing type (private homes vs. public buildings), location of sample collection (urban vs. rural areas), age of the building (< 20 years vs. > 20 years) and time passed since last cleaning (< 5 days vs. > 5 days). Information for the latter two categories was only available for 32 and 34 of the 46 samples, respectively, so that parts of the dataset were not included in the statistical comparisons for these two categories.

The concentrations were compared only for compounds with a detection frequency (DF) of 50% or higher. As a similar distribution of values cannot be guaranteed in all sample groups, the described testing was based on the comparison of mean n ranks. A difference between groups was considered significant if the obtained (2-tailed) *p*-value was < 0.05. For each sample grouping, the obtained *p*-values, means, 25th, 50th and 75th percentiles are reported. All statistical testing was conducted using the SPSS software (version 28.0.0.0).

### 2.6 Exposure assessment

Based on the semi-quantitative concentrations measured as described in section 2.5, the exposure based on the inadvertent ingestion of dust was estimated. For this assessment, the sample dataset was divided in “homes” and “public spaces” to better represent the different exposure scenarios. EDI (mg/kg body weight /day) was calculated following the general approach described, e.g., by Harrad et al.(Harrad et al., 2008) and recently used by McGrath et al.(McGrath et al., 2022):

$$\text{EDI} = \frac{\text{Concentration } \left[\frac{\text{mg}}{\text{g}}\right] \times \text{Ingestion [g/day]} \times \text{Fraction}}{\text{Body weight [kg]}}$$

where concentration refers to concentrations of semi-quantified compounds (mg/g dust). It should be noted that the concentration of samples was assigned as 0 if the compound was not detected. Ingestion refers to dust ingestion rates of 20 and 60 mg/day and of 50 and 100 mg/day for adults and toddlers in the $50^{th}$ and $95^{th}$ percentile exposure scenarios, respectively, fraction refers to the time fraction spent at home (0.69 for adults and 0.91 for toddlers) or in public spaces (0.18 for adults)(Klepeis et al., 2001; Poma et al., 2020), and body weight refers to a fixed average body mass of 70 kg for adults and 12 kg for toddlers. Bioaccessibility was assumed to be 100% for each compound, to provide a conservative estimate of internal exposure(Christia et al., 2021a).

The potential risk of non-carcinogenic effects (Hazard Quotient, HQ) per individual compound was then calculated by dividing the EDI by the relative oral reference dose factor (*RfD*, mg/kg bw/d), if available.

When the *RfD* was not available, such as the case for most semi-quantified compounds, the reference dose value of the calibrant used for semi-quantification was chosen as the most suitable proxy. HQ values equal to or greater than 1 indicate a potential exposure risk for the target population.

## 3. RESULTS AND DISCUSSION

### 3.1 Quality control and quality assurance results

Prior to any data processing and analysis, the QC results were investigated by assessing the peak areas obtained for the native compounds and IS in the QC samples and for the IS in the dust samples. These results are summarized in **Tables S3** (QC samples) and **S4** (dust samples), whereby in both cases a distinction was made between the EtOAc and MeOH fractions.

Except for 2,2-bis(chloromethyl)-1,3-propanediyl bis(bis(2-chloroethyl) phosphate) (V6; belonging to the class of PFRs), all native QC compounds and IS were detected with a DF of 100% in the EtOAc fractions of the QC samples meeting the data extraction criteria listed in **section 2.3**. This indicates the suitability of the sample preparation approach for the included compound classes and the utilization of the same data processing settings for the dust samples. For both fractions, all observed average absolute mass errors (AMEs) and relative standard deviations (RSDs) of RTs were below 7 ppm and 0.4%, respectively, showing satisfying mass accuracy and chromatographic stability of the method. In the MeOH fraction of the QC samples, 45% (14 out of 31) of the native QC compounds were detectable with DFs ranging between 33 and 100% indicating that suspect analytes from similar compound classes as the QC compounds were more likely to be detected in the EtOAc fraction. Additionally, some QC compounds were detected in both fractions indicating an incomplete elution with EtOAc. However, in all these cases, the signal observed in the MeOH fraction was at least one order of magnitude lower compared to the EtOAc fraction, confirming that the latter fraction is expected to contain compounds structurally similar to the set of QC analytes.

In the EtOAc fraction of the dust samples (**Table S4**), all six IS were detected with DFs of 100% and stable RTs (RSDs < 0.2%) indicating no major analyte losses during sample preparation. Similar to the results obtained for the native QC compounds in the MeOH fractions, only one of the IS showed a DF of 100% within that fraction, suggesting that most IS eluted in the EtOAc fraction. Given the suspect screening approach of the study, which aimed at covering a broad range of potential analytes rather than ensuring optimal conditions for a limited number of compounds, a complete separation of all compounds between

the two fractions was outside the scope of the study and the presented QC results were considered acceptable.

### 3.2 Suspect screening results – identified compounds

Based on the workflow described in section 2.4, a total of 55 compounds were identified (total of both, EtOAc and MeOH fractions), whereby only compounds identified with CL3 or better are reported here. CL1 or 2 were assigned if compounds could unequivocally be confirmed by matching all identifiers (*m*/*z*, RT, isotopic pattern, and fragmentation spectrum) to one of the QC standards (**Table S1**) or if the obtained fragmentation spectrum could be matched with library data allowing to assign only one possible candidate. Subsequently, based on the list of compounds assigned with CL2 or 3, 11 reference standards were purchased after the suspect screening analysis to confirm the most relevant suspects. Consequently, for eight compounds which were initially identified at CL2 or CL3, this allowed the assignment of CL1. For one compound, comparison with a reference standard improved the assigned CL from 3 to 2C resulting in the final summaries of identified compounds listed in **Tables 1** (CL1 and CL2, n = 34) and **S5** (CL3, n = 21). For only one compound, the comparison with the reference standard led to the identification of a false positive showing the reliability of the applied identification workflow. To each of the identified compounds, a compound class was assigned allowing the identification of the major contaminant classes as shown in **Figure 1**.

Most identified compounds belonged to the PFRs, with 13 compounds assigned with CL1 or 2, and 3 compounds assigned with CL3. In total, ten PFRs were unequivocally confirmed with a reference standard by matching all identifiers and thus resulting in CL1. Except for tris(1,3-dichloro-2-propyl)phosphate, all PFRs identified with CL1 showed DFs > 80%. Three PFRs, [4-[2-(4-diphenoxy-phosphoryloxyphenyl)-propan-2-yl]phenyl] diphenyl phosphate, diphenylcresyl phosphate and tributyl phosphate, were detected with a DF of 84.8%, 89.1% and 52.2%, respectively, and were assigned with CL2C as no fragmentation spectra could be obtained. These findings of known PFRs in indoor dust at high DFs confirm their ubiquitous occurrence in the indoor environment which was reported and quantified in numerous previous studies from Europe, the US and Asian countries(Esplugas et al., 2022; Hoang et al., 2023; Lee et al., 2020; Tang et al., 2020; Xu et al., 2016; Zhou et al., 2017).

Besides these well studied PFRs, three novel compounds were identified. As first, bis(2,4-di-tert-butylphenyl)pentaerythritol diphosphate (BDTPDP) was detected with CL2 and a DF of 89.1%. This novel PFR was first reported by Liu and Mabury(Liu and Mabury, 2019) in indoor dust from Toronto (Canada), who suggested that its occurrence in indoor dust originates from the oxidation of the antioxidant (AOX)

bis(2,4-di-tert-butylphenyl) pentaerythritol diphosphite (AO626). This finding identified organophosphate antioxidants as a potential source of PFR contamination in dust. Wang et al.(Wang et al., 2020) confirmed the occurrence of BDTPDP in dust collected from North China and provided a reference MS/MS spectrum for this compound which was matched with the data obtained in this study, allowing the assignment of CL2 and confirming the occurrence of this novel PFR also in European indoor environments.

Furthermore, two novel PFRs were identified for the first time in indoor dust. These included didecyl butoxyethoxyethyl phosphate (DDeBEEP) and bis(butoxyethyl) butyl phosphate (BBEBP) which were detected with DFs of 4.4% and 45.7%, respectively. The fragmentation spectra obtained for DDeBEEP (**Figure S1**) partially matched spectra reported by Wang et al.(Wang et al., 2022) for compounds carrying a butoxyethoxyethyl moiety. Additionally, neutral losses corresponding to the loss of one and two hydrocarbon side chains with ten carbons were observed. Lastly, a fragment confirming the presence of a phosphate group was observed ($[H_4PO_4]^+$; theoretical *m/z* 98.9842). Based on the available data, it could not be unequivocally determined whether the hydrocarbon side chains are branched or linear. This, combined with the absence of reference spectra, led to the assignment of DDeBEEP at CL3 (**Table S5**).

The fragmentation spectrum obtained for BBEBP (**Figure S2**) partially matched with the reference spectrum obtained for tris(2-butoxyethyl) phosphate (TBOEP) confirming both the presence of a phosphate group and at least one butoxyethyl moiety. Again, observed neutral losses indicated the presence of a butyl and two butoxyethoxy substituents leading to the proposal of the structure indicated in **Figure S2** at CL3.

The second largest group of identified compounds were plastic additives, including phthalates (PHs) and alternative plasticizers (APs). Three and six phthalates were assigned with CL1 and CL3, respectively. Di(2-ethylhexyl), diisodecyl and diisononyl phthalate (DEHP, DIDP and DINP) were all assigned with CL1 through matching with a reference standard and were all detected with a DF > 90%. These results are in line with previous studies which identified these phthalates as the major phthalate homologues worldwide(Bu et al., 2020; Zhu et al., 2023). Likewise for the novel PFRs, the described suspect screening approach allowed the identification of the novel phthalate homologue decyl nonyl phthalate (DeNoP) detected with a DF of 93.5%. **Figure S3** shows an example of a fragmentation spectrum obtained for DeNoP in one dust samples. The different and partially uneven numbered substituents were proposed based on the observation of neutral losses corresponding to hydrocarbon side chains with nine and ten carbon atoms. Thereby, the observed wide peak (**Figure S3**) suggested the coelution of numerous isomers indicating branched side chains. The phthalate backbone was confirmed through the characteristic fragment for phthalate esters

with a (theoretical) *m*/*z* value of 149.0233(Jeilani et al., 2011). A reference standard was purchased whereby decyl nonyl phthalate was available with linear side chains (CAS 96507-76-5). Between the linear reference standard and the (assumably) branched decyl nonyl phathalate (DeNoPH) observed in the samples, a RT difference of 1.05 min was observed which is assumed to be caused by the very slow increase in the percentage of the stronger (organic) eluent within the applied gradient (**section 2.3**) allowing a separation between branched and linear compounds. Nevertheless, clear similarities were observed between the fragmentation spectra obtained in the dust samples and the reference standards (**Figures S3/S4**).

A previous study reported compounds with the same molecular formula as DeNoPH ($C_{27}H_{44}O_4$) in indoor dust samples to which phthalate esters were assigned(Christia et al., 2021b). However, no further experimental evidence was provided hampering a more confident compound identification. The results presented here allow a more in-depth characterization of a potentially novel and highly abundant phthalate (**section 3.4**). Following a similar approach as described for DeNoP, two more phthalates with different and partially uneven numbered substituents were identified. These included decyl undecyl (DeUnPH) and undecyl dodecyl phthalate (UnDoPH), detected with DFs of 82.6% and 4.3%, respectively, at CL3. Similar to DeNoPH, the lengths of the side chains were confirmed through the observation of corresponding neutral losses in both cases (**Figures S5/S6**) while the phthalate backbone was confirmed through the characteristic fragment with *m*/*z* 149.0233.

Apart from the described phthalate plasticizers, three known alternative plasticizers, (DEHA, acetyltributyl citrate and tris(2-ethylhexyl) trimellitate) were detected with CL1 and a DF of 100% indicating the simultaneous occurrence of legacy phthalate and alternative plastic additives. Three additional adipate homologues were identified at CL3 (Table S5). Thereby, an adipate backbone was assigned based on the observation of characteristic fragments which matched the reference spectrum obtained for DEHA included in the QC samples. The assigned possible side chains should be interpreted cautiously as they could not unequivocally be confirmed through the available fragmentation data.

After a first data analysis cycle, a sub selection of compounds identified at CL3 was made for which reference standards were purchased to increase identification confidence and provide an alternative approach for semi-quantification (**section 3.4**). This allowed to assign eight additional compounds with CL1 (marked with an * in **Table 1**). For example, these included the three biocides, diethyltoluamide (DEET), carbendazim and propiconazole, all of which were detected with DFs > 60% and have already been described in previous indoor dust studies (Béranger et al., 2019; Ouyang et al., 2017; Rostkowski et al.,

2019). Furthermore, three UV filters have been assigned with CL1/2C, some of which have also been introduced in previous studies on indoor dust(Carpinteiro et al., 2010). Similarly, a recent study characterized the worldwide occurrence of 1,3-diphenylguanidine and 1,3-di-o-tolylguanidine in indoor dust based on a sample set collected in 11 countries(Li and Kannan, 2023). Both compounds were also detected in the present study, covering an additional geographical location as the abovementioned study did not include samples from Belgium and the only European datapoints derived from Greece and Romania. These findings confirm the occurrence of the mentioned compound classes in the indoor environment and provide an extra datapoint for the estimation of the geographical range of their occurrence.

Further, three antistatic agents were detected (N,N-bis(2-hydroxyethyl)-dodecanamide (CL2), N,N-bis(2-hydroxyethyl) oleamide and N-(2-hydroxyethyl) octadecanamide (both CL3) all of which carried at least one hydroxyethyl moiety (confirmed through the observation of both a characteristic neutral loss and fragment). These compounds thus only differed by the length of and presence of double bonds in the conjugated fatty acid chain. Even though the applied identification workflow cannot unequivocally exclude the presence of branched side chains or determine the position of the double bond assumed in some of the reported compounds, these results confirm high structural variabilities in classes of CECs. Additionally, one of the assigned antistatics (N,N-bis(2-hydroxyethyl)oleamide) is a potential source for the detected oleamide (CL3; DF 21.8%) which might be formed as a degradation product.

Lastly, two synthetic antioxidants (AOX) were identified at CL1 through matching with reference standards. These included N,N'-hexamethylene bis (3,5-di-t-butyl-4-hydroxy-hydrocinnam-amide) (AO 1098), which was detected with a total DF of 28.2%. The observed DF is in agreement with a previous report of AO 1098 in indoor dust samples collected in Toronto, Canada (DF = 33%) (Liu and Mabury, 2020). The other AOX was N-1,3-dimethylbutyl-N-phenyl-p-phenylenediamine (6PPD) showing a total DF of 63.1%. Again, this is in line with a previous study which reported 6PPD in South-Chinese houses near an E-waste dismantling site (DF = 56%)(Huang et al., 2021). In this Chinese location, the main transformation product of 6PPD, 6PPD-Quinone, was detected in 6 of the 18 houses, which was not confirmed in the presented study.

### 3.3 Semi-quantification results

Suspect compounds identified with the SSA in the EtOAc fraction were semi-quantified using the available reference standards listed in **Table S1**. As described in **section 2.5**, the semi-quantification was based on

the response factors obtained from the relative areas between calibrators and assigned IS. Thereby, the same IS and (most abundant) adduct were considered for both, quantified suspect and corresponding calibrator. This resulted in the minimum, maximum and median concentrations listed in **Table S6** whereby the latter was calculated applying the lower bound approach, thus assigning a concentration of zero for samples in which a compound was not detected. **Figure 2** shows the boxplots summarizing the semi-quantified concentrations for the PHs and PFRs. All other compounds are summarized in **Figure S7**. In both cases, the boxplots include all compounds with a DF ≥ 45% and exclude datapoints corresponding to non-detects. For the interpretation of these semi-quantitative data, a few limitations have to be considered as discussed in a previous study using a similar approach (Belova et al., 2023). Firstly, the unavailability of a structurally similar IS and calibrators for all classes of suspects introduces a bias, especially if the intrinsic responses between calibrator and suspect show a big difference. Additionally, even though a maximum similarity in RT of IS and calibrant/suspect was sought after, a difference in RT and the fact that the calibration curves were prepared in solvent, do not allow an optimal compensation for possible matrix effects. Lastly, an extrapolation of the calibration curve was necessary to cover the high phthalate concentration observed in some samples (**Figure 2**). Nevertheless, the reported semi-quantitative data can serve as a tool for a general estimation of dust concentrations, prioritization of compounds for future (targeted) studies and estimation of human exposure (**section 3.6**).

The median and maximum concentrations observed for phthalates ranged between n.d. — 73 µg/g and 31 — 646 µg/g, respectively, and showed a generally higher concentration range than observed for PFRs (**Figure 2**). Interestingly, high concentrations of one particular phthalate in a sample were often accompanied by at least one other phthalate showing high concentrations in the same sample. For example, the sample with the overall maximum concentration of DINP (437 µg/g) also showed the overall maximum concentration of DeNoP (646 µg/g) and the third highest concentrations of DIDP (67 µg/g) and DEHP (96.8 µg/g). This indicates a potential exposure to a mixture of these compounds. Also, the semi-quantified concentrations obtained for the newly identified phthalates with differing substituents such as DeNoP were in the same order of magnitude as the values observed for the legacy phthalates such as DINP and DEHP. This points out the relevance of the newly identified phthalates and suggests that targeted methods in which these phthalates are not included, may underestimate phthalate concentrations and consequently the human exposure to these compounds.

Median and maximum concentrations observed for PFRs ranged between n.d. - 2 µg/g and 1 - 51 µg/g, respectively. Similar to the observations described for phthalates, several samples showed a simultaneous

occurrence of various PFRs at higher concentrations. Again, the newly identified PFRs (BDTPDP and BBEBP) showed concentrations comparable to the data obtained for some of the targeted PFR homologues.

In the EtOAc fraction, five compounds were confirmed after purchase of reference standards (**Table 1**). Therefore, for these compounds, two different quantification approaches using two different calibrators were possible. On the one hand, these compounds were quantified using the calibrators derived from the reference standards included in the QC samples (**Table S6**). On the other hand, calibration curves of the newly purchased standards were prepared in the same calibration ranges. For both approaches, the same IS was used. This allowed to estimate the influence of using a structurally less similar calibrator for quantification and compare these concentrations with the results obtained using a reference standard of the corresponding compound as calibrator. **Table S7** summarizes the minimum, maximum and median concentrations obtained using the two approaches. As described in **section 2.4**, the suspect's concentration is derived by the division of the suspect's (relative) signal through the response factor of the used calibrator. Therefore, the differences in quantified concentrations observed for the two approaches are proportional to the differences in the response factors of the two possible calibrants. Thereby, the response factors differed by a factor of up to 9 between the two approaches, resulting in proportional differences in semi-quantified concentrations. This indicates the high importance of similar response factors between suspect and calibrator in case no reference standard is available. Thereby, an optimal selection of calibrator can be addressed by simulative tools predicting response factors for identified suspect facilitating the selection of suitable calibrators(Malm et al., 2021).

### 3.4 Statistical comparison

Obtained semi-quantified concentrations were compared between sample groups whereby latter were based on the type of sampled housing, the housing location, the age of the building and the time passed since the last cleaning. The obtained *p*-values and means are summarized in **Tables S8 to S11** whereby the most significant differences were observed between public buildings and homes. Out of 26 compounds for which data were compared, 16 showed significantly higher ($p < 0.05$) concentrations in public buildings compared to homes. These included, among others, all phthalates with a DF > 50% except for DEHP. Propiconazole was the only compound showing significantly higher concentrations in homes. These results suggest a generally higher CEC contamination in public spaces which might be caused by a higher number and variety of contamination sources. For several contaminants, significant differences were observed between rural and urban locations whereby the latter showed significantly higher

concentrations in all cases. For the remaining groupings (age and time passed since the last cleaning) the number of significant differences was low, not allowing the characterization of a clear trend in the quantified concentrations.

### 3.5 Risk assessment based on semi-quantified concentrations

The EDIs and HQs calculated from the semi-quantified concentrations are summarized in **Table S12**. Thereby, the HQs calcucated for semi-quantified suspect compounds should be interpreted with care since for those no *RfD* values were available and the *RfD* value of the calibrant used for semi-quantification was applied as indicated in **Table S12**. **Figure 3** summarises the data obtained for PFRs for datapoints representing samples collected in private homes considering the 95$^{th}$ percentile exposure scenario. The remaining datasets are summarized in **Figures S8-S18**. In all Figures, only *RfD* values which can directly be assigned to the semi-quantified compound are shown thus excluding reference values for suspect compounds for which no *RfD* value was available and estimations based on the *RfD* values of the calibrant had to be made.

Overall, EDIs of PFRs ranged from 1.1E-09 to 1.2E-05 mg/kg bw/day, with corresponding HQs between 2.2E-08 and 9.2 E-04. The EDIs (mg/kg bw/day) of PFRs (TBOEP, TPHP, TEHP, TCIPP, and TCEP) that can be compared with other studies from different regions and/or countries in Europe ranged from 2.0E-08 to 5.7E-05 for adults and from 1.1E-07 to 5.0E-05 for children, respectively. This indicated that EDIs of the selected PFRs in Flemish dust were within comparable ranges as reported for other European countries(Dou and Wang, 2023). However, compared to EDIs of children from studies in China and other Asian regions(Dou and Wang, 2023), median EDIs of TEHP and TCIPP in Flemish residential dust (7.80E-08 and 2.38E-07 mg/kg bw/day, respectively) are still within the range of 4.0E-08 to 2.1E-06 and 4.0E-08 to 7.8E-06 mg/kg bw/day, respectively. Thereby, the EDIs used for these comparisons were based on slightly different body weights used for the calculations (32/80 kg and 29/63 kg for children/adults from Western and Asian countries, respectively).

Of the newly identified PFRs, semi-quantified concentrations were only available for BDTPDP and BBEBP allowing the calculation of their EDIs, which resulted in comparable values as for the legacy PFR compounds. This highlights the potential for human exposure to these compounds and the need for further monitoring in the environment and humans.

The EDIs calculated for plasticizers ranged from 2.14E-07 to 3.74E-04 mg/kg bw/day, with corresponding HQs between 9.53E-07 and 8.10E-03. As expected, the highest EDI and relative HQ values were calculated

for the legacy phthalate DEHP, corresponding to the toddler exposure in the 50th and 95th percentile scenario. The EDIs (mg/kg bw/day) for DEHP in Flemish dust were lower for both adults and toddlers when comparing with EDIs from various studies from Asia (3.08E-03 and 6.37E-03 mg/kg bw/day), North America (2.65E-03 and 5.84E-03 mg/kg bw/day) and Europe (2.43E-03 and 6.74E-03 mg/kg bw/day)(Hammel et al., 2019; Qu et al., 2022). The EDIs from alternative plasticizers DEHA and ATBC in Flanders showed lower results for both the 50th and 95th percentile scenario in toddlers and adults compared to a recent study from the USA (4.33E-07 and 3.48E-08 mg/kg bw/day, 1.13E-06 and 8.99E-08 mg/kg bw/day for DEHA and ATBC, respectively)(Subedi et al., 2017).

Interestingly, the risk assessment of the two newly identified phthalates (i.e. decyl nonyl phthalate and decyl undecyl phthalate) showed EDI and HQ values in the same order of magnitude as DEHP (up to 9.77E-05 mg/kg bw/day and 4.89E-03, respectively). This highlights the relevance of such novel findings and calls for further (bio)monitoring investigation of these compounds. Finally, the EDIs of the other selected compounds were calculated with up to 1.29E-05 mg/kg bw/day, with a corresponding max HQ of 6.47E-04 for triethylene glycol bis(2-ethylhexanoate).

The above-mentioned results suggest that the exposure of the target population to individual CECs is lower than the risk threshold and should thus not suffer adverse health effects through dust ingestion. However, EDI calculated from dust ingestion covers only one exposure pathway and the available RfDs are based on the current toxicological evidence. Further research to identify relevant human exposure biomarkers to assess internal exposure levels of newly identified phthalates is needed.

## 4. CONCLUSIONS

This study investigated the occurrence of known contaminants and CECs in 46 indoor dust samples collected in Belgium. The application of a combined targeted and suspect screening approach allowed the identification of 55 contaminants, 34 of which were assigned with a high confidence level (1 or 2). Besides the detection of a set of known and well-studied compounds such as DEHP, DEHA or TBOEP, the applied workflow lead to the identification of a set of novel phthalates. In contrast to known and well-studied PHs, these novel compounds contained side chains with differing chain lengths, e.g. decyl nonyl or decyl undecyl phthalates, both of which were detected with a DF > 80%. Additionally, two novel PFRs, not previously described in dust, were reported: DDeBEEP and BBEBP, showing a DF of 4.4% and 45.7%,

respectively. These findings demonstrate the high structural variability in the classes of PHs and PFRs, pointing out the need for potential reevaluation of compounds included in targeted quantitative methods. For a sub-selection of the identified compounds, semi-quantitative data was acquired, showing similar concentration ranges for the novel compounds as for the traditional PHs and PFRs, while also allowing the calculation of EDIs. Through the comparison of these EDIs with available *RfDs*, HQs were obtained, which indicated no potential health risks. However, the presented approach accounts solely for the exposure through dust ingestion and does not consider other exposure routes or mixture effects through the combined exposure to various contaminants.

In conclusion, this study clearly highlights the added value of suspect screening approaches and the need for implementation of such approaches in biomonitoring studies.

## 5. ACKNOWLEDGMENTS

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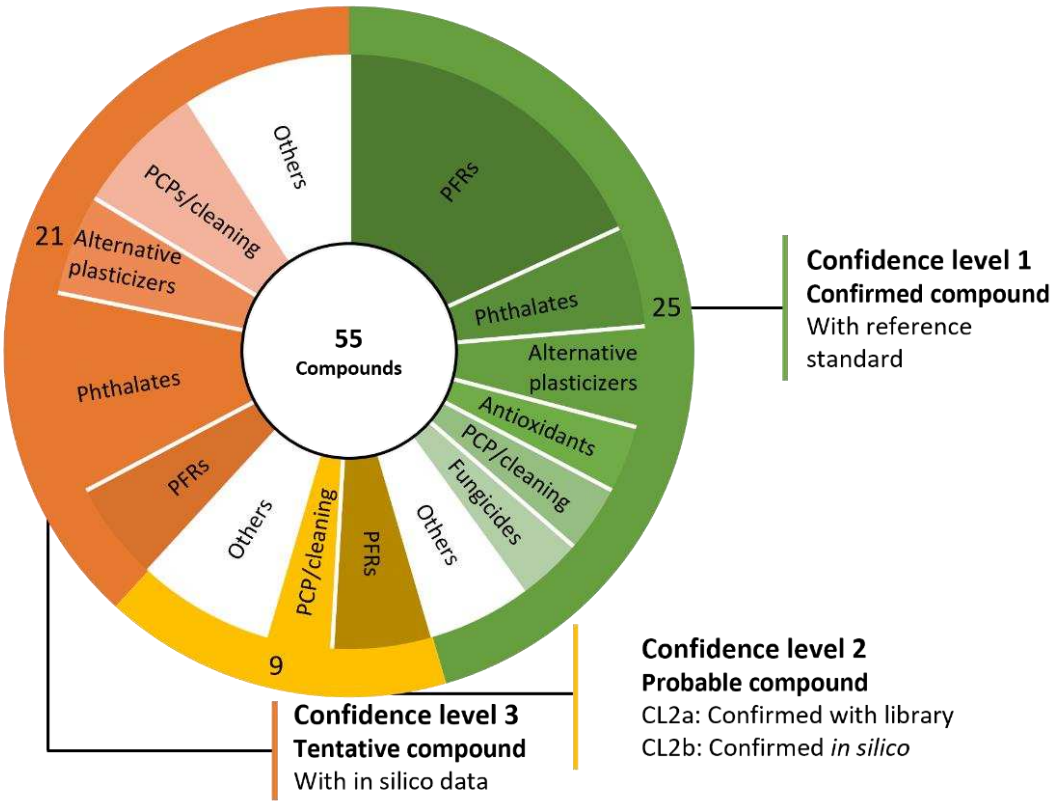


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526 Figure 1: Compounds detected in the dust with confidence level 1-3 and the subcategories they belong
527 to. With PFR: phosphate flame retardant; PCP: personal care products.

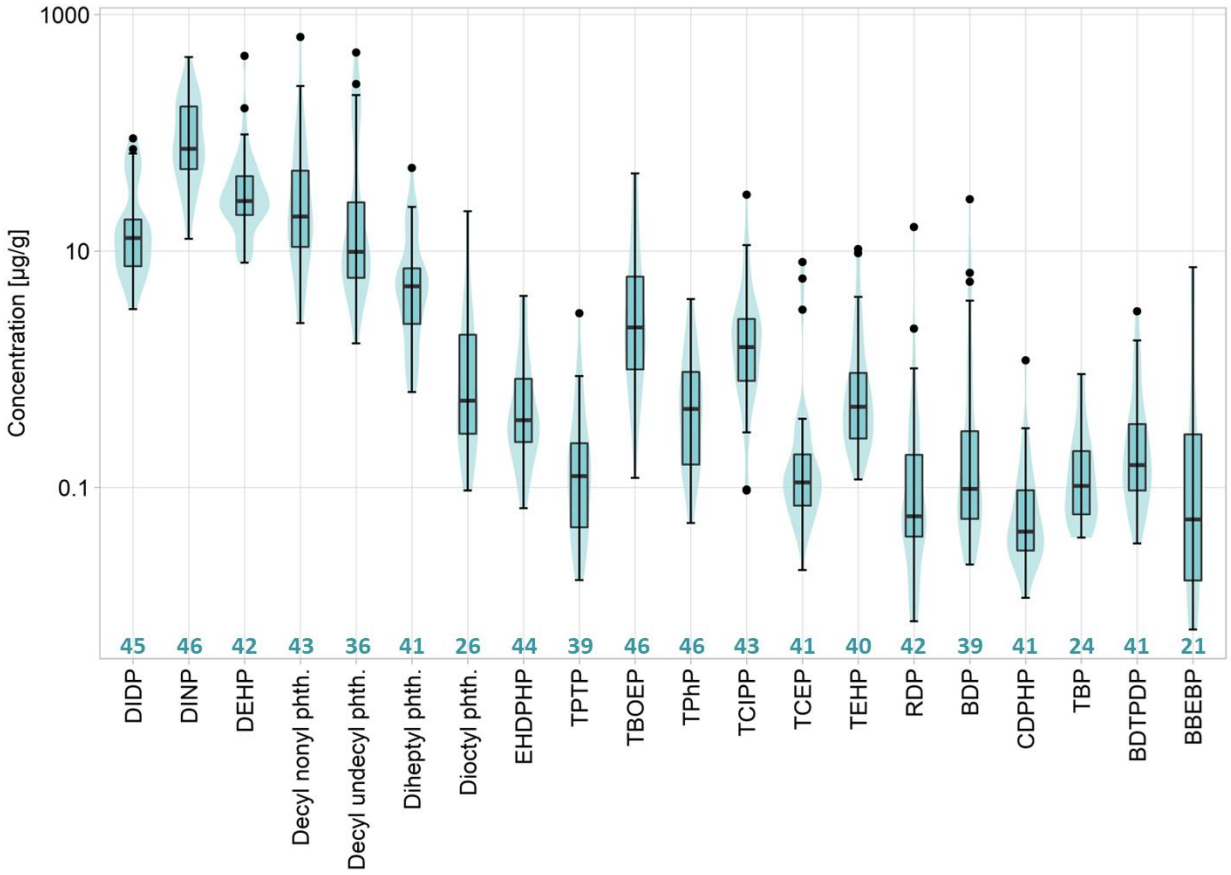


Figure 21: Violin plots and boxplots representing the semi-quantified concentrations obtained for phthalates and organophosphate flame retardants detected with a detection frequency ≥ 50%. The presented plots only include datapoints for which a concentration was obtained, thus excluding non-detects. Therefore, for each boxplot/compound the underlying number of datapoints (n) is indicated below the plot. The full names corresponding to each of the abbreviations can be found in Table 1 and Table S5.

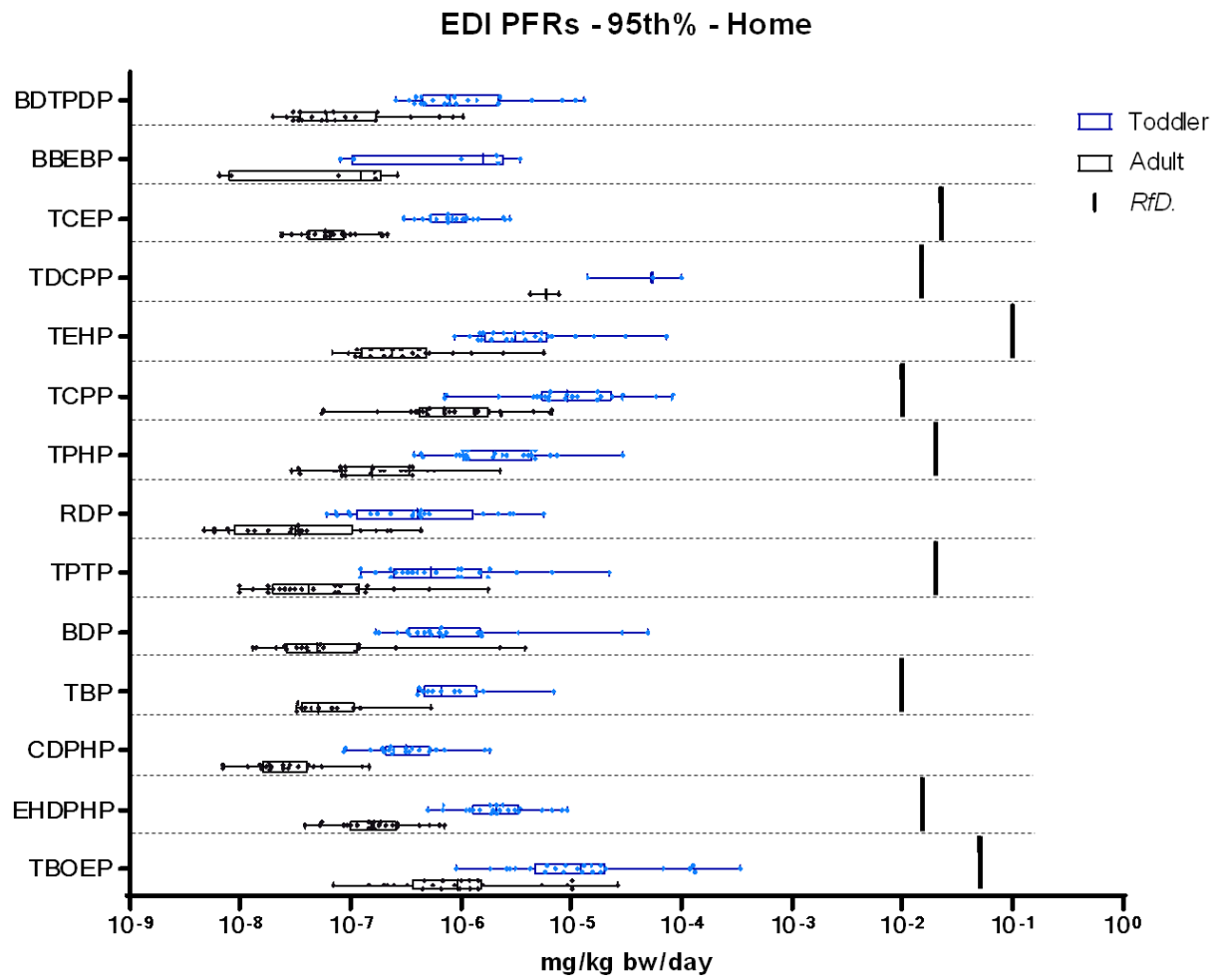


Figure 32: Boxplots of Estimated Daily Intakes (EDIs) obtained from the semi-quantified concentrations of organophosphate flame retardants (PFRs) for samples collected in private homes. For the calculation of EDIs, the 95$^{th}$ percentile exposure scenario was considered. Obtained EDIs were compared with reference dose values (*RfD*) indicated with a black line and obtained for the corresponding compound from the literature sources listed in **Table S12**. If no *RfD* is indicated, no datapoint for the corresponding semi-quantified compound was available.

Table 1: Compounds identified with confidence level (CL) 1 and 2 in at least one of the indoor dust samples. CL2C represents a sub-division of the initial scheme of levels of identification confidence(Schymanski et al., 2014) which is explained in **section 2.3**. For each compound the detection frequency (DF) at a certain CL, the total DF and the fraction in which the compound was detected, is indicated. With PHs: phthalates, APs: alternative plasticizers, PFRs: organophosphate flame retardant, AOX: synthetic antioxidants, PCPs: Personal care products, CPs: Cleaning products.

| Name | Formula | DF (CL) [%] | DF total [%] | Class | Fraction |
|---|---|---|---|---|---|
| Diisodecyl phthalate (DIDP) | $C_{28}H_{26}O_4$ | 97.8 (1) | 97.8 | PHs | EtOAc |
| Diethylhexyl phthalate (DEHP) | $C_{24}H_{38}O_4$ | 91.3 (1) | 91.3 | PHs | EtOAc |

| | | | | | |
|---|---|---|---|---|---|
| Diisononylphthalate (DINP) | $C_{26}H_{42}O_4$ | 100 (1) | 100 | PHs | EtOAc |
| Diethylhexyl adipate (DEHA) | $C_{22}H_{42}O_4$ | 95.7 (1)<br>4.3 (2C) | 100 | Adipates (APs) | EtOAc |
| Acetyltributyl citrate (ATBC) | $C_{20}H_{34}O_8$ | 100 (1) | 100 | Citrates (APs) | EtOAc |
| Tris(2-ethylhexyl) trimellitate (TOTM) | $C_{33}H_{54}O_6$ | 2.2 (1)<br>97.8 (2C) | 100 | Trimellitates (APs) | EtOAc |
| 2-Ethylhexyl diphenyl phosphate (EHDPHP) | $C_{20}H_{27}O_4P$ | 84.8 (1)<br>10.9 (2C) | 95.7 | PFRs | EtOAc |
| Tri-p-tolyl phosphate (TPTP) | $C_{21}H_{21}O_4P$ | 63.0 (1)<br>21.7 (2C) | 84.8 | PFRs | EtOAc |
| Tris(2-butoxyethyl) phosphate (TBOEP) | $C_{18}H_{39}O_7P$ | 87.0 (1)<br>13.0 (2C) | 100 | PFRs | EtOAc |
| Triphenyl phosphate (TPHP) | $C_{18}H_{15}O_4P$ | 87.0 (1)<br>13.0 (2C) | 100 | PFRs | EtOAc |
| Tris(1-chloro-2-propyl) phosphate (TCIPP) | $C_9H_{18}Cl_3O_4P$ | 65.2 (1)<br>28.3 (2C) | 93.5 | PFRs | EtOAc |
| Tris(1,3-dichloro-2-Propyl)phosphate (TDCIPP) | $C_9H_{15}Cl_6O_4P$ | 2.2 (1)<br>10.9 (2C) | 13.1 | PFRs | EtOAc |
| Tris(2-chloroethyl) phosphate (TCEP) | $C_6H_{12}Cl_3O_4P$ | 8.7 (1)<br>80.4 (2C) | 89.1 | PFRs | EtOAc |
| Tris(2-ethylhexyl) phosphate (TEHP) | $C_{24}H_{51}O_4P$ | 17.4 (1)<br>69.6 (2C) | 87.0 | PFRs | EtOAc |
| Resorcinol bis(diphenyl phosphate) (RDP) | $C_{30}H_{24}O_8P_2$ | 2.2 (1)<br>89.1 (2C) | 91.3 | PFRs | EtOAc |
| Bisphenol A bis(diphenyl phosphate) (BDP) | $C_{39}H_{34}O_8P_2$ | 10.9 (1)<br>73.9 (2C) | 84.8 | PFRs | EtOAc |
| Diphenylcresyl phosphate (CDPHP) | $C_{19}H_{17}O_4P$ | 89.1 (2C) | 89.1 | PFRs | EtOAc |
| Tributylphosphate (TBP) | $C_{12}H_{27}O_4P$ | 52.2 (2C) | 52.2 | PFRs | EtOAc |
| Bis(2,4-di-tert-butylphenyl)penta-erythritol diphosphate (BDTPDP) | $C_{33}H_{50}O_8P_2$ | 23.9 (2)<br>65.2 (4) | 89.1 | PFRs | EtOAc |
| N,N'-hexamethylene bis (3,5-di-t-butyl-4-hydroxy-hydrocinnam-amide) (AO1098) | $C_{40}H_{64}N_2O_4$ | 2.2 (1)<br>26.0 (2C) | 28.2 | AOX | MeOH |
| N-1,3-dimethylbutyl-N-phenyl-p-phenylenediamine (6PPD)* | $C_{18}H_{24}N_2$ | 45.7 (1)<br>17.4 (2C) | 63.1 | AOX | EtOAc |
| N-(2-ethoxyphenyl)-N-(2-ethylphenyl) Oxamide* | $C_{18}H_{20}N_2O_3$ | 10.9 (1)<br>21.7 (2C) | 32.6 | UV filters | EtOAc |

| | | | | | |
|---|---|---|---|---|---|
| Bemotrizinol* | $C_{38}H_{49}N_3O_5$ | 4.3 (1)<br>6.6 (2C) | 10.9 | UV filters | MeOH |
| Octabenzone* | $C_{21}H_{26}O_3$ | 4.3 (1)<br>45.7 (2C) | 50.0 | PCPs/<br>CPs | MeOH |
| Diethyltoluamide (DEET)* | $C_{12}H_{17}NO$ | 23.9 (1)<br>54.3 (2C) | 78.2 | PCPs/biocide | MeOH |
| Bumetrizole[1] | $C_{17}H_{18}ClN_3O$ | 34.8 (2C) | 34.8 | UV filters | EtOAc |
| Carbendazim* | $C_9H_9N_3O_2$ | 10.9 (1)<br>54.3 (2C) | 65.2 | Fungicides | MeOH |
| Propiconazole* | $C_{15}H_{17}Cl_2N_3O_2$ | 10.9 (1)<br>65.2 (2C) | 76.1 | Fungicides | EtOAc |
| Triphenylphosphine oxide* | $C_{18}H_{15}OP$ | 37.0 (1)<br>58.7 (2C) | 95.7 | Other | MeOH |
| Paracetamol | $C_8H_9NO_2$ | 10.9 (2A) | 10.9 | Pharmaceutic als | EtOAc |
| N,N-bis(2-hydroxyethyl)-dodecanamide | $C_{16}H_{33}NO_3$ | 82.6 (2A)<br>15.2 (4) | 97.8 | PCPs/<br>cleaning products | MeOH |
| 1,3-diphenylguanidine | $C_{13}H_{13}N_3$ | 80.4 (2A)<br>17.4 (4) | 97.8 | Other | MeOH |
| 1,3-di-o-tolylguanidine | $C_{15}H_{17}N_3$ | 2.2 (2A)<br>30.4 (4) | 32.6 | Other | MeOH |
| Triethylene glycol bis(2-ethylhexanoate) | $C_{22}H_{42}O_6$ | 71.7 (2A)<br>23.9 (4) | 95.6 | Other | EtOAc |

*Compound confirmed with reference standard acquired after the first analysis cycle. Full match with reference standard allowing the assignment of CL1.

[1]As no fragmentation spectra to be matched with purchased reference standard were available in samples, CL 2C was assigned.

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