Household Dust as a Repository of Chemical Accumulation: New Insights from a Comprehensive High-Resolution Mass Spectrometric Study
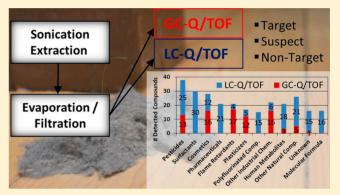
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S Supporting Information

ABSTRACT: Chemical exposure in household dust poses potential risks to human health but has been studied incompletely thus far. Most analytical studies have focused on one or several compound classes, with analysis performed by either liquid or gas chromatography coupled with mass spectrometry (LC-MS or GC-MS). However, a comprehensive investigation of individual dust samples is missing. The present study comprehensively characterizes chemicals in dust by applying a combination of target, suspect, and nontarget screening approaches using both LC and GC with quadrupole time-of-flight (Q/TOF) MS. First, the extraction method was optimized to streamline detection of LC-Q/TOF and GC-Q/TOF amenable compounds and was successfully validated with over 100 target compounds. Nontarget screening with GC-Q/TOF was done by spectral deconvolution followed by a library search. Suspect screening by LC-Q/TOF was carried out with an accurate mass spectral library. Finally, LC-Q/TOF nontarget screening was carried out by extracting molecular features, acquiring tandem mass spectrometric (MS/MS) spectra, and performing compound identification by use of in silico fragmentation software tools. In total, 271 chemicals could be detected in 38 dust samples, 163 of which could be unambiguously confirmed by a reference standard. Many of them, such as the plastic leachable 7,9-di-*tert*-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione (CAS 82304-66-3) and three organofluorine compounds, are of emerging concern and their presence in dust has been underestimated. Advantages and drawbacks of the different approaches and analytical instruments are critically discussed.

■ INTRODUCTION

As people spend a large part of their lives indoors, they are exposed to a plethora of chemicals from indoor sources such as chemicals in household dust.[1] Exposure can occur via inhalation of small dust particles, via dermal uptake, or via ingestion (a route particularly important for infants).[2] House dust is known to be a reservoir for many released compounds and a marker for what is in the air, and exposure can be a potential health risk for humans.[3] Therefore, it is important to investigate and identify chemicals present in household dust. Many studies have shown that house dust is contaminated with a broad range of chemicals such as pesticides, personal care products, plasticizers, flame retardants, and polyfluorinated compounds.[1,4−8] Previous studies have focused on investigating one or several compound classes in a targeted analytical approach. With recent developments in high-resolution mass spectrometry, it is possible not only to look for known compounds (targets) for which authentic standards are available, but also to screen for expected compounds from a database or library (suspects) and even to identify previously unknown compounds (nontargets) through careful examination of the high resolution mass spectra.[9]

While screening methods by liquid chromatography high-resolution mass spectrometry (LC-HRMS) have been applied often for aqueous media,[10−15] nontarget screening studies in other environmental media such as household dust are still rare. So far, the most thorough investigation of nontargets in dust has been done by Rager et al.,[16] who investigated more than 50 dust samples by LC time of-flight (TOF) MS. They linked the proposed formulas to the Distributed Structure-Searchable Toxicity (DSSTox) database of the U.S. Environmental Protection Agency (EPA). However, their identification was based only on molecular formula match, as they did not acquire

tandem mass spectrometric (MS/MS) data. A recent study by Ouyang et al.[17] applied two-dimensional (LC × LC)-TOF MS in order to get a better separation of the nontarget features. However, as they only looked into one dust sample, the generalizability of these results is limited. Other nontarget studies specifically looked at flame retardants or brominated azo dyes in household dust.[18−20] Hilton et al.[21] used two-dimensional (GC × GC)-MS coupled to electron ionization (EI) to investigate nontarget chemicals in dust including phthalates, polycyclic aromatic hydrocarbons, chlorinated compounds, brominated compounds, and nitro compounds.

Upon taking a closer look at the chemicals previously detected in dust and the analytical methods with which the chemicals were analyzed, it becomes clear that dust contains chemicals with diverse physicochemical properties and structures. Chemicals range from very polar and nonvolatile surfactants to nonpolar and semivolatile brominated flame retardants. This is also reflected in the number of analytical studies that have investigated chemicals in dust; roughly the same number of methods are based on LC-MS compared to GC-MS. To date there is no study that comprehensively investigated chemicals by both platforms (LC-MS and GC-MS) at the same time. Hence, a complete picture of the chemical fingerprint in household dust is missing, as is a comparison of the strengths and weaknesses of the two analytical approaches.

This research gap is addressed in the present study, which uses a target, suspect, and nontarget screening workflow for polar to semipolar chemicals analyzed by LC-HRMS as well as a target and nontarget screening method for nonpolar chemicals analyzed by GC-HRMS. A total of 38 household dust samples were collected in California, and the findings of the detected chemicals are discussed. The differences between the nontarget screening approaches on both platforms (LC-HRMS and GC-HRMS) are critically discussed, and the complementary roles of the two platforms are acknowledged. Knowledge of the comprehensive chemical fingerprint in dust is the basis for further investigations of chemicals that may be the cause for negative health outcomes.

■ MATERIALS AND METHODS

Dust Sampling and Extraction. Dust samples from 38 households in the areas of Sacramento and Fresno, CA, were collected from the main living area with the high-volume small surface sampler (HVS3) using a standard protocol[22] and stored in a poly(tetrafluoroethylene) (PTFE) container at −20 °C until extraction. Dust samples were sieved (106 μm) and 100 mg aliquots were sonication-extracted with hexane/acetone (3:1 v/v) and acetone (100%). The extract was evaporated, filtered, and split into GC and LC fractions, which were run on the corresponding instruments (see section S2.1 in Supporting Information for details).

Targeted Chemical List Selection. A total of 76 chemicals to be analyzed by GC-Q/TOF and 56 chemicals to be analyzed by LC-Q/TOF were selected for this study (Tables S1.1 and S5.1). The selection comprised one or multiple indicator compounds from substance classes identified previously[1,4,6,23−26] or compounds present in consumer products listed in the Consumer Product Chemical Profiles (CPCP) database.[27] The target list consisted of pentabromodiphenyl ether (BDE), organophosphate flame retardants (OP-FR), phenols, polycyclic aromatic hydrocarbons (PAH), phthalates, UV filters, components of fragrances, pesticides,

plasticizers, parabens, biocides, polyfluorinated compounds, surfactants, and skin oils.

GC-Q/TOF and LC-Q/TOF Analysis. Analysis on the GC-Q/TOF was carried out on an Agilent 7890B gas chromatograph with a HP-5MS (30 m × 0.25 mm, 0.25 μm) column coupled to an Agilent Q/TOF 7200B instrument running in electron ionization (EI) mode. A 78 min run time with a linear temperature gradient from 35 to 325 °C was chosen to separate all 76 target chemicals and all major peaks in the analysis of a dust extract. Details of the analytical settings are found in Table S2.2.

The analytical method for the LC-Q/TOF was taken from Moschet et al.[28] for water extracts. In brief, a C18 column (2.5 × 100 mm, 1.8 μm, Zorbax Eclipse Plus, Agilent Technologies, Inc.) was used for separation with the following mobile phases: for positive ionization mode, (A) ultrapure water plus 0.1% formic acid and (B) acetonitrile plus 0.1% formic acid; for negative ionization mode, (A) ultrapure water plus 1 mM ammonium fluoride and (B) acetonitrile. Ammonium fluoride in ultrapure water was chosen in negative mode because it had >10× higher sensitivity for phenolic compounds such as bisphenol A compared to other buffers tested. The injection volume was 10 μL. An Agilent 6530 Q/TOF (Agilent Technologies, Inc.) was used in positive and negative ionization modes. Acquisition was done in All-Ions fragmentation mode using collision energies (CE) 0, 10, 20, and 40 eV (scan rate 4 spectra/s) for the target and suspect screening (see below). The 0 eV channel was used to collect precursor ion information, while the higher CE channels were used to obtain fragment ion information simultaneously. Details of the analytical settings are found in Table S2.3.

Method Validation. The optimized extraction and analytical method was validated by extracting a triplicate of NIST SRM 2585 dust (standard reference material). A spike recovery experiment was done by adding a mixture (500 ng) of all 132 target compounds to the NIST SRM 2585 dust, letting the solvent dry overnight, and extracting following the procedure described above. Absolute recovery was calculated by dividing the area of the prespiked sample by the area of a postspiked sample, that is, a NIST dust extract spiked immediately before instrumental analysis. This experiment was also conducted in triplicate. Finally, a triplicate of a method blank was extracted by use of an inert silica material (Min-U-Sil, U.S. Silica Holdings Inc., Frederick, MD) as a dust surrogate. The same method validation approach was used on both analytical platforms.

Targeted Quantification Method. Quantification of the target chemicals by both LC-Q/TOF and GC-Q/TOF employed Agilent MassHunter Quantitative Analysis (B.07). In LC-Q/TOF, the [M + H]$^+$ or [M − H]$^-$ adduct was used as quantifier and, depending on the compound, the one or two most abundant fragments from the library spectrum were used as qualifiers in the All-Ion scans (exact mass window ±20 ppm). In GC-Q/TOF, the most abundant fragment was used as quantifier and two further fragments were used as qualifiers (exact mass window ±25 ppm).

Nontarget Screening by GC-Q/TOF. The 38 samples including method blanks were rerun in one randomized sequence using the same acquisition method as described above. Before and after the sequence, an alkane mix was run to calculate the retention time index (RI) of all nontarget features.

In a first step, nontarget features were extracted by spectral deconvolution with Agilent Unknowns Analysis software. The

software calculates a score based on the quality of the deconvolution (component shape quality). The software runs in batch mode, but corresponding features between samples are not grouped together (no binning and alignment). In a second step, the software compares spectra for each feature, using a spectral library, and calculates a match factor. In this study, the NIST 14 library[29] was used (unit mass resolution). All compounds with a component shape quality > 60, a NIST library match factor > 60, and a chromatographic peak width between 3 and 15 s were selected (parameters calculated by the MassHunter Unknown Analysis software; see Table S3.1 for details).

In a next step, features that were the same between the samples were grouped together manually because the software did not support this step in an automated way. This was done by comparing the candidate names as well as mass–retention time (RT) combinations. In general, mass deviations of ±50 ppm and RT deviations of ±0.2 min were found to be acceptable limits, based on the results of target compounds that were identified in the nontarget workflow. Unfortunately, the library match name of the same compound in two samples can be different if two compounds in the library have similar fragment spectra. Also, the reference mass (ion with highest intensity) can be different if two fragments have similar intensities. Therefore, this step had to be carried out with careful manual effort.

Long-chain alkanes and their acids, esters, and similar compounds were neglected from further selection, as they were considered not relevant for this project. For the selected compounds, the calculated RI was compared with the NIST library value (experimental or estimated). A deviation of ±2% in RI was considered acceptable, based on the experience with target compounds that were also detected by the nontarget approach. If the NIST library contained only an estimated RI, a deviation of ±10% in RI was acceptable. The second criterion was set arbitrarily because the confidence interval of the estimation by NIST varies significantly depending on the compound properties. All compounds with intensities lower than 10 times the intensity in the method blank were discarded.

Suspect Screening by LC-Q/TOF. Suspect screening was conducted with the Agilent MassHunter Qualitative Analysis software (version B.07) by applying the Find by Formula workflow, following the method described in Moschet et al.[28] Two curated spectral libraries, Agilent Forensic Toxicology Personal Compound Database and Library (PCDL) and Agilent Water Contaminant LC/MS PCDL, respectively containing 8000 and 1450 compounds with MS/MS spectra, were used. Briefly, compounds for which a chromatographic peak was found for their main adduct (mass accuracy ±10 ppm) and for which the isotope pattern gave a good match (score >70/100)[28] were selected (see Table S3.2 for details). Next, the exact masses from the five main fragments in the PCDL's MS/MS library spectra (CE 10, 20, 40) were searched in the high-energy scans by the software. If one or more fragments were present and coeluting with the parent (determined based on a coelution score in the software), the compound was automatically flagged as qualified. Compounds qualified in at least five out of the 38 samples and for which the intensity was higher than 10 times the intensity in the method blank were manually inspected. If possible, a reference standard was purchased for these tentatively identified compounds (confidence level 2)[30] for unambiguous confirmation.

Nontarget Screening by LC-Q/TOF. *Recursive Feature Extraction.* All samples, including method blanks and NIST reference dust, were rerun in triplicate in positive and negative modes in randomized order. For five samples, three individual extraction replicates were run in addition. This resulted in 149 injections in both positive and negative modes. The acquisition followed procedures described above, but only the full scan (CE = 0 eV) was acquired with a scan rate of 1.5 spectra/s. Agilent Profinder software (version B.08.00) was used to extract nontarget compounds by the Batch Recursive Feature Extraction workflow. In brief, the software searches and identifies molecular features in the first sample. A feature is a group of corresponding ions, that is, adducts and isotopes of the same compound, that form a chromatographic peak at a certain RT. All detected features are stored in a list with their exact monoisotopic mass and RT. Next, the software searches all features in the subsequent samples. The detected features in all samples are compared, the exact masses and RT are aligned, and the corresponding features are binned together. This results in a list of features and their presence in corresponding samples. In a second step, the average exact masses and RT of the consensus feature list are scanned in each sample to check if any feature has been missed in the first round (recursive feature extraction). All parameter settings are found in Table S3.3

Selection of Relevant Features. The feature list was imported into Mass Profiler Professional (MPP, version 14.0, Agilent Technologies, Inc.), which is a statistical analysis software package designed to evaluate high-resolution mass spectrometry data. To improve robustness, features were discarded if they were not found in at least two out of three replicates or if the highest intensity in the samples was less than 10 times the intensity of the blank sample. To focus on compounds ubiquitously present in dust, all features present in at least 37 of the 38 samples were selected for further identification.

Compound Identification by in Silico Fragmentation. The samples with the highest intensities of the selected features were rerun in targeted MS/MS mode (CE = 20) by triggering the $[M - H]^-$ or $[M + H]^+$ mass of the selected feature at the measured RT. By use of the MS/MS information, features were tentatively identified (if possible) by two in silico fragmentation software packages: Agilent Molecular Structure Correlator (MSC) and the program MetFrag[31] (online version https://msbi.ipb-halle.de/MetFragBeta/ and MetFragR http://c-ruttkies.github.io/MetFrag/projects/metfragr). Both software tools have the same principle but different algorithms and different filtering and weighting options (for details on parameter settings, see Table S3.4). Briefly, input parameters for both programs are the exact mass of the $[M - H]^-$ or $[M + H]^+$ ion and the list of the acquired MS/MS fragment masses and relative intensities. The software searches all compounds with the corresponding exact mass (±chosen mass error, in this case ±10 ppm) in a database. In this study, MSC searched the ChemSpider database (www.chemspider.com), and MetFrag was set to search PubChem (https://pubchem.ncbi.nlm.nih.gov). In a next step, the fragmentation pattern of every candidate is simulated on the basis of a given fragmentation algorithm, and a match score between the acquired and predicted MS/MS spectra is calculated. If no other criteria are selected, the candidates are ranked on the basis of this fragmenter score.

In MSC, candidates can be ranked by the number of data sources in ChemSpider. MetFrag has more options in this

respect. The number of references and patents from PubChem can be integrated in a weighted score, and the user can define the importance of each score by a weighting factor. In addition, a suspect list [comma-separated values (.csv) file containing InChIKeys] can be added. In this case, a candidate that is listed on the suspect list is ranked higher compared to a candidate that is not listed. These weighting options help in selecting the correct compound if there are multiple candidates with similar fragmenter scores due to similar structures. In this study, the weighting factor for the fragmenter score was 1.0, for the number of references 0.125, for the number of patents 0.125, and for the suspect list 0.25. The suspect list in this study was a merged list of all suspect exchange lists from the NORMAN network (http://www.norman-network.com/?q=node/236[32]), an unpublished temporary list from DSSTox (desalted compounds, received from Mark Strynar, EPA) and the CPCP database[27] (>18 000 compounds). The online version of MetFrag cannot be used in a batch mode. Therefore, MetFragR was used and a batch version was programmed.

The candidate list for each feature was manually checked and the most plausible structure was selected. In cases where it was determined to be necessary or advantageous, additional lines of evidence were considered, for example, plausibility check of the retention time based on the predicted log K_{ow} value or the MS/MS match score from the fragmentation prediction software CFM-ID (http://cfmid.wishartlab.com).[33]

■ RESULTS AND DISCUSSION

Method Validation Procedure for Targeted Analytes. Method validation showed good absolute recoveries (extraction recovery of a triplicate spike sample): above 75% for more than 80% of the 76 GC-Q/TOF target compounds and above 50% for more than 80% of the 56 LC-Q/TOF compounds (summary in Table S4.1; details for each compound in Table S4.2). The extraction was somewhat biased toward nonpolar compounds by the selected solvents (hexane/acetone 3:1 and 100% acetone). However, a more polar solvent such as methanol would not have meshed well with a single sequential extraction because of its immiscibility with hexane and its elevated boiling point. Nevertheless, method detection limits (MDL) were generally lower for LC-Q/TOF compounds. In total, 50% of all compounds had MDLs below 10 ng/g dust and 80% had MDLs below 100 ng/g dust (Table S4.1). These MDLs are comparable with MDLs from previous literature studies.[8,34−36] Compounds with higher MDLs either had extremely high concentrations in the dust (phthalates, organo-phosphate flame retardants, skin oils) or they had limited sensitivity in GC-EI-MS mode (pyrethroids, phenols). Precision (standard deviation of replicates) was <20% for 95% of all compounds. In addition, the accuracy of the concentrations could be checked for 14 compounds for which certified concentrations in the SRM 2585 dust were available (i.e., deviation of the measured value from the certified value). For 12 out of 14 compounds, accuracy was <25%. The only exceptions were phenanthrene and pyrene, for which concentrations were underestimated by 33% and 26%, respectively. In LC-Q/TOF, ion suppression due to matrix load was low for most compounds measured in negative ionization mode (90% < factor of 2) but higher for compounds measured in positive ionization mode (60% > factor of 2). Therefore, the use of appropriate internal standards was absolutely necessary to accurately quantify the compound concentrations.
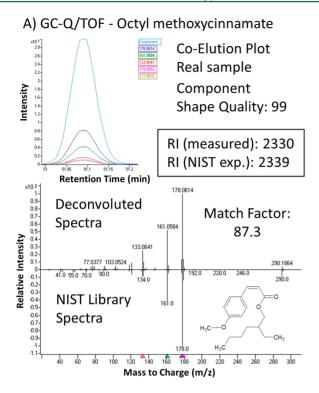
Overall, the quality control parameters of this simple and extremely broad extraction method followed by two untargeted analytical methods show that the compound classes previously described to be present in dust can be efficiently and accurately extracted and detected.

Results of GC-Q/TOF Nontarget Screening. The deconvolution of the GC-EI-MS chromatograms produced about 3000−5000 features per sample; roughly 300 of these compounds per sample had a NIST library hit (component shape quality >60, library match factor >60). An example compound, octyl methoxycinnamate (CAS 5466-77-3), a UV-filter later confirmed with a reference standard, is shown in Figure 1A. The perfect deconvolution (component shape quality 99) is indicated by the coelution plot of the five main fragments. The good match with the hit in the NIST library (match factor 87.5) is underlined by the differential plot. In addition, the experimentally derived RI in the NIST library perfectly matches with the measured RI in this study. The compound was detected in 36 out of 38 dust samples.

The manual grouping and prioritization (see Materials and Methods section) led to 75 compounds with detection in multiple samples (see Chart S5.2). Twenty-six of them were discarded due to high presence in the blank or RI deviation above the selected criterion. Twenty-two of the remaining 48 compounds were target compounds (BDE, OP-FR, pyreth-roids, phthalates) that were already confirmed; the remaining 27 were identified uniquely through this nontargeted workflow (see Chart S5.2). For instance, 7,9-di-*tert*-butyl-1-oxaspiro-(4,5)deca-6,9-diene-2,8-dione (CAS 82304-66-3), a leachable from plastics, has not been reported in dust before, but it is of increasing interest because of detection in water (leached from pipes) and in airborne particles.[37] For 17 of the nontargets, a reference standard could be purchased and all identifications were confirmed by matching RT. For the remaining 10 compounds, no reference standard could be purchased; they remain tentatively identified with confidence level 2[30] (see Table S5.1 and Chart S5.2 for details) on the basis of matching EI spectra and RI values.

Results of LC-Q/TOF Suspect Screening. The screening of the LC-Q/TOF chromatograms acquired in the All-Ions fragmentation workflow with two PCDLs containing almost 10 000 chemicals with MS/MS spectral information led to 97 tentatively identified compounds after application of automatic filter criteria and after manual inspection (see Chart S5.2). The approach is discussed in detail for water samples in Moschet et al.[28] Seventeen of them were already quantified in the target screening, six were target chemicals from the GC-Q/TOF, and two were nontargets identified by GC-Q/TOF. For 52 suspects, a reference standard was purchased; 43 of them were unambiguously confirmed by matching RT, and nine were rejected due to nonmatching RT. The remaining 28 compounds remain tentatively confirmed with confidence level 2.[30]

One example of a positively identified compound is the fungicide imazalil (CAS 35554-44-0, molecular formula $C_{14}H_{14}Cl_2N_2O$), which is used to preserve citrus fruits and is likely to be carcinogenic to humans (Figure 1B). The mass error was +4.5 ppm and the isotope pattern explains the two Cl atoms, which resulted in an isotope match score of 97 out of 100. In addition, the five main fragments (see Figure S6.1) coelute with the $[M + H]^+$. The compound was unambiguously confirmed by matching retention time of a reference standard. It was detected in 29 of the 38 dust samples.

A) GC-Q/TOF - Octyl methoxycinnamate

Co-Elution Plot
Real sample
Component
Shape Quality: 99

RI (measured): 2330
RI (NIST exp.): 2339

Deconvoluted Spectra

Match Factor: 87.3

NIST Library Spectra

B) LC-Q/TOF - Imazalil

Real Sample

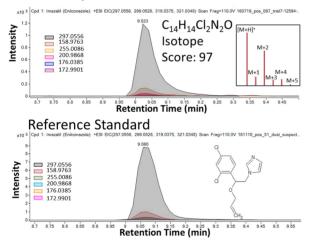$C_{14}H_{14}Cl_2N_2O$
Isotope Score: 97

Reference Standard

Figure 1. (A) Example of UV-filter octyl methoxycinnamate (CAS 5466-77-3) detected by GC-Q/TOF (nontarget screening). (Top) Co-elution plot of five main deconvoluted fragments in a real sample. (Bottom) Differential plot between deconvoluted spectrum and NIST library spectrum. The match factor was calculated by MassHunter Unknown Analysis software. The identity of the compound was later confirmed by a reference standard. (RI = retention time index; exp = experimental.) (B) Example of the fungicide imazalil (CAS 35554-44-0) detected by LC-Q/TOF (suspect screening). $[M + H]^+$ and five main fragments from the All-Ions scans (see Figure S6.1) are assessed in a real sample (top) and in the reference standard (bottom). (Inset) Isotope pattern match including the monoisotopic mass $[M + H]^+$ and five isotopes (M + 1 to M + 5). Black lines reflect the measured isotopes; red boxes reflect the theoretical isotope pattern. Due to their good overlap, the two lines are hardly distinguishable.

These results show the efficiency of suspect screening by use of curated spectral libraries and automated software workflows,

allowing identification of dozens of compounds without procuring thousands of standards or optimizing target methods. For example, 21 pharmaceuticals—such as diphenylhydramine (CAS 58-73-1), miconazole (CAS 22916-47-8), and diclofenac (CAS 15307-86-5)—that have previously not been investigated in house dust were detected by this approach.

Results of LC-Q/TOF Nontarget Screening. *Quality Control in Nontarget Screening by LC-Q/TOF.* The recursive feature extraction of the 149 triplicate injections detected 13 340 individual features in negative mode and 14 588 features in positive mode. Features that were found in only one out of three replicates (roughly 30% of total features) and features present in the blank (roughly 10%) were discarded, leading to new total numbers of features of 7701 in negative mode and 9326 in positive mode (see Chart S5.2). Identification of all these features is not feasible,[15] so a statistical analysis, explained below, was used to focus on relevant compounds.

As classical quality control using validation parameters (e.g., recovery, accuracy) is not possible when doing nontargeted analysis. Data quality assessment needs to be demonstrated differently; two proxies for this are described in this section. Only after the reproducibility and accuracy of the screening approach is verified should statistical analysis or compound identification be performed.

The first approach is to examine the reproducibility of features among replicate samples, for example, by principal component analysis (PCA; see Figure 2 for negative ionization mode and Figure S7.1 for positive ionization mode). The plot shows that the injection replicates cluster close together
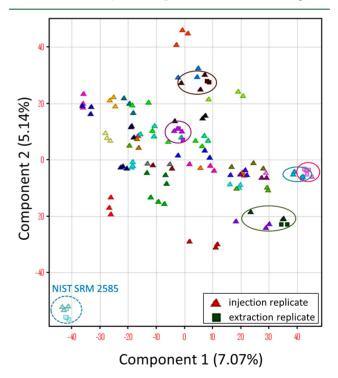

Figure 2. Principal component analysis (PCA) of detected nontarget features in 38 dust samples and the NIST SRM 2585 dust sample on LC-Q/TOF in negative ionization mode. Different colors indicate different samples. Each sample was injected in triplicate (triangles). Total number of features: 7701 (blank subtracted). Samples indicated with a colored circle had additional extraction replicates (squares). The indicated light blue sample is the NIST SRM 2585 reference dust sample.
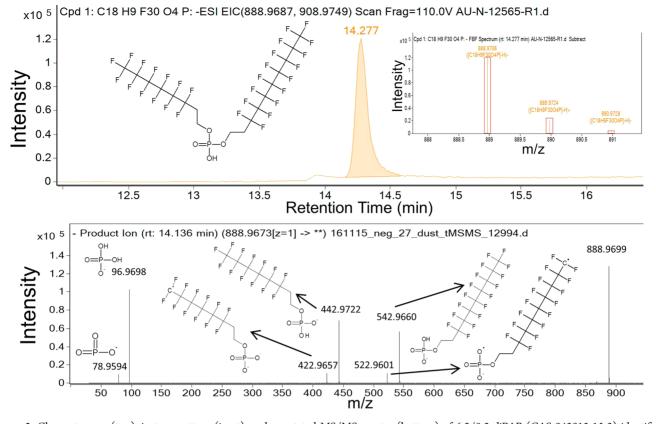
Figure 3. Chromatogram (top), isotope pattern (inset), and annotated MS/MS spectra (bottom) of 6:2/8:2 diPAP (CAS 943913-15-3) identified by the in silico fragmentation software MetFrag by a complete nontarget approach in LC-Q/TOF negative ionization mode. MetFrag fragmenter score, 177; number of explained peaks, 8; number of references/patents (PubChem), 0/0; suspect list, no; mass error of precursor mass, 1.3 ppm; mass error of fragment masses, 0.2 ppm (m/z 542.9659) to 4.7 ppm (m/z 78.9590). The estimated log K_{ow} (10.6, Jchem for Excel) is consistent with the measured RT of 14.1 min.. The feature was detected in ≥37 out of 38 samples and was later confirmed by a reference standard (see Figure S10.7).

(triangles with the same color). The clustering is clearly visible, although components 1 and 2 only explain <10% of the variation, which is due to the fact that several thousand features are compared. This shows that (i) RT and mass accuracies were stable over the 4-day run of the 149 injections and (ii) the recursive feature extraction algorithm grouped the features accurately and reproducibly. The RT shifts of the internal standards throughout the sequence were <0.2 min in negative mode and <0.4 min in positive mode (Figure S7.2). Figure S7.1 shows that the grouping of extracted features was not as good in positive mode as in negative mode, which can be partly explained by less stable RTs. Potential explanations include higher matrix loads in positive mode compared to negative mode or less stable instrument conditions.

The extraction replicates of the five selected samples (squares in Figure 2, indicated with a colored circle) also grouped within similar distances to the injection replicates of the same samples. This means that dust is homogeneous enough to obtain similar results when different subsamples are extracted multiple times.

The second approach is to check for known chemicals in the untargeted feature list. Most of the targets and suspects that were detected in the dust samples were found as features in the unfiltered feature list (40 out of 48 compounds with >5 detections in negative mode, 21 of 30 compounds in positive mode). Reasons for missing a compound could be that it fell below the selected intensity threshold or it occurred in the blank. The automated criteria were set more stringently than

for manual evaluation of the data; thus, the automated evaluation leads to higher detection limits.[10]

However, the fact that most target compounds were found shows that relevant compounds were isolated by use of the recursive extraction algorithm and not just compounds with much higher intensities such as surfactants (see next section).

Homologous Series Identification. Total ion chromatograms of the dust samples suggested that homologous series of compounds were present (Figures S8.1 and S8.3), so all features were searched for homologues by use of the software EnviHomolog (www.envihomolog.eawag.ch).[38] Interestingly, 50% of the features in negative mode and 30% of the features in positive mode were identified as homologues by the software (Figures S8.2 and S8.4). Most prominent in negative mode were homologues with a mass defect of 44.0262, that is, $(-CH_2CH_2O)_n$ (~50% of the homologues). The most prominent homologues in positive mode were identified with a mass defect of 14.0156, that is, $(-CH_2)_n$ (~40% of the homologues). Cleaning agents usually contain surfactants with a homologous series of compounds. They have been detected in different environmental media,[39] and it is expected that surfactants end up in the dust. Examples of surfactants with $(-CH_2CH_2O)_n$ chains are alcohol polyethoxylates (AEO) and poly(ethylene glycol)s (PEG); examples of surfactants with $(-CH_2)_n$ chains are linear alkylbenzenesulfonates (LAS) and sulfophenyl carboxylic acids (SPC).[11,40,41] One way to identify expected surfactants is to use the NORMAN exchange list[32] that contains surfactants previously identified in wastewater[11]

by a suspect screening approach. Although numerous other types of surfactants and also other compounds with homologous series, such as polyfluorinated or polyhalogenated compounds, might be present in dust,[42] the identification of these individual compounds is outside the scope of this study.

Compound Identification by in Silico Fragmentation Software. As it is impossible to identify several thousands of nontarget features,[15] we have chosen to prioritize features that were ubiquitous in the dust samples. Therefore, features present in ≥37 out of 38 samples were selected and identified, if possible (see Materials and Methods section). These included 611 features in negative mode and 284 in positive mode. To further refine that selection, ubiquitous features with stable intensities among the samples (coefficient of variation CV < 75%) and features with significant intensity fluctuations among the samples (CV > 200%) were selected. This led to 129 features in negative mode and 99 features in positive mode (see Chart S5.2). Good MS/MS spectra were acquired for 57 features in negative mode and 75 features in positive mode. The remaining features had insufficient intensity or no/poor fragments.

The features with good MS/MS spectra were examined with two in silico fragmentation software packages, MSC and MetFrag. An example of a compound identified by both packages is the ionic surfactant *N*-lauroylsarcosine (section S9.1; mass 270.2068, RT 10.5 min), which is used in shampoos and shaving foam and has not been detected in house dust before. MS/MS information first helped to confirm the molecular formula, with both MSC and MetFrag producing top candidates with the formula $C_{15}H_{29}NO_3$. The isotope pattern score of 99.7 in the MS full scan supported this. In MSC, the top candidate *N*-lauroylsarcosine (CAS 15535-18-9) had a fragment match score of 87.5 (mass error −1.2 ppm), with 95% of the fragments being explained by its structure. In MetFragR, the compound had a fragmenter score of 70.7, only ranked 33 among all candidates. However, the compound had the highest number of references and patents and was listed on the custom suspect list. Therefore, the compound had the highest rank with the weighted score. The estimated log K_{ow} (4.5, MetFrag output) is consistent with the measured RT of 10.5 min. *N*-Lauroylsarcosine reference standard was purchased, and its identity was confirmed with matching RT and MS/MS spectra (Figure S10.5).

This example illustrates how multiple pieces of evidence support correct identification. MetFrag was frequently favored over MSC due to its wider range of program capabilities. Nonetheless, both software packages are very useful in identifying chemicals through the nontargeted workflow.

Another tentative compound identification later confirmed with a reference standard was the emerging organofluorine compound 6:2/8:2 diPAP (polyfluoroalkyl phosphoric acid diester, CAS 943913-15-3; see Figure 3). Although the isotope pattern of 6:2/8:2 diPAP is not distinctive because it does not contain Cl or Br atoms, the negative mass defect indicates the presence of multiple F atoms. The eight top fragments of 6:2/8:2 diPAP could all be explained by its structure, with the compound receiving the highest fragmenter score by MetFrag. In this case, neither the suspect list nor the number of references/patents helped because none of the candidates had any entries. Two other emerging organofluorine compounds, 6:2 fluorotelomer sulfonic acid (6:2 FTSA, CAS 27619-97-2; see Figure S10.4) and 6:2diPAP (CAS 57677-95-9; see Figure S10.6), were detected by the nontarget approach and later

confirmed by a reference standard. Emerging organofluorine compounds, especially diPAPs, have recently been found in dust samples in high concentrations and detection frequencies[43] and are an underestimated source of human exposure to polyfluorinated compounds.

Another example is the fungicide metabolite 4-hydroxychlorothalonil (CAS 28343-61-5), which has not been detected in house dust before (section S9.2). The isotope pattern indicated the presence of three Cl atoms, and the top five fragments could be explained by its structure. However, three structural isomers had the same fragmenter score by MetFrag. Of these, only 4-hydroxychlorothalonil was on the suspect list, accompanied by the highest number of references and patents.

With this approach, 75 compounds were tentatively identified with a proposed structure in either negative or positive ionization mode (see Table S5.1). Four of them were already identified by the target or suspect approach (bisphenol A, dexpanthenol, fipronil-sulfone, and triclocarban). For 16 nontarget candidates, a reference standard could be purchased. Twelve compounds were confirmed by matching RT and matching MS/MS spectra (see section S10). In addition to the aforementioned compounds, these were vanillin (CAS 121-33-5; Figure S10.1), genistein (CAS 446-72-0; Figure S10.3), palmidrol (CAS 544-31-0; Figure S10.8), linolenic acid (CAS 463-40-1; Figure S10.9), palmitic acid (CAS 57-10-3; Figure S10.10), leucine (CAS 61-90-5), and piperine (CAS 94-62-2; Figure S10.11). Four compounds were not confirmed (methyl-2-octynoate, cinnamic acid, diphenyl phosphate, and dibutyl phthalate). The remaining 55 compounds remain tentatively confirmed with confidence level 3.[30] Sixteen additional compounds were identified only by a proposed molecular formula (confidence level 4; see Table S5.1).

Comparison of LC-Q/TOF and GC-Q/TOF Workflows for Detecting Unknown Chemicals. The identification of compounds by GC and LC techniques provides complementary yet unique capabilities while providing a complete chemical profile of dust samples. Both analyses provide several thousands of detected nontarget features, and it is important to prioritize the most relevant features[15] either by statistical analysis or by previous knowledge about suspected occurrence of certain compounds.

The fact that LC-ESI-MS provides molecular ion information, while GC-EI-MS generally does not, necessitates distinct nontargeted screening workflows. Both platforms have advantages and drawbacks. The biggest advantage in GC-EI-MS is that the fragment spectra are very reproducible and libraries containing over 200 000 compounds are available. In addition, relative RT are very reproducible, so that normalized RI can be calculated when a standard column and a simple temperature gradient are used. Both help to tentatively identify known unknowns with high confidence when the compound is in the library, saving significant time, labor, and cost by avoiding the need to procure, prepare, and analyze every analytical standard. In this respect, a good deconvolution software package and/or a good separation is essential to obtain the correct spectrum. As a drawback, relatively few curated and reliable accurate mass library spectra are presently available. Another drawback is the low or missing molecular ion, which would otherwise allow use of the suspect screening approach similar to LC-Q/TOF. Also, this makes it much more difficult to detect unknown unknowns, that is, compounds that do not have an EI spectrum in the library.

LC-Q/TOF software processing tools are more advanced, making it easier to bin and align nontarget features in multiple samples. For compound identification, or for compounds lacking MS/MS spectra, the approach of acquiring MS/MS spectra and running an in silico fragmentation is promising, though still largely a manual effort. Interestingly, the hardware and software tools from classical GC-MS and LC-MS are increasingly being integrated into a single, simpler platform to maximize data processing and integrity. For example, a GC-HRMS operated with a soft ionization source [such as low-energy EI, positive chemical ionization (PCI), or atmospheric-pressure chemical ionization (APCI)][20,44] generates data that are comparable with LC-ESI-MS/MS data. On the other hand, the All-Ions fragmentation workflow uses elements from the GC-EI-MS where multiple fragments are coeluted to form a specific spectrum. Further advances in joint nontarget screening by LC-HRMS and GC-HRMS depend critically on optimization of the different software tools.

The results of this study show that both instrument types, LC-Q/TOF and GC-Q/TOF, are indispensable for complete identification of chemicals in a sample. In the 38 dust samples, we detected and identified 86 compounds by GC-Q/TOF (59 targets and 27 nontargets) as well as 204 compounds by LC-Q/TOF (42 targets, 79 suspects, and 83 nontargets; see Chart S5.2). The actual number of compounds present in the dust is much higher, though. For example, many hydrocarbons were detected on GC-Q/TOF, and numerous surfactants were detected by LC-Q/TOF. These chemicals were not further investigated.

The detected and identified compounds are shown in Figure 4. As expected, GC-amenable compounds are generally in the
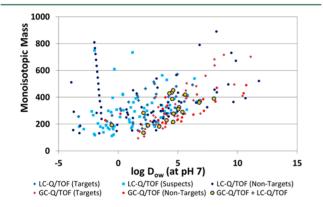

Figure 4. Physicochemical properties of chemicals detected by LC-Q/TOF, GC-Q/TOF, and both platforms with different identification workflows (target, suspect, and nontarget). The log D_{ow} (at pH 7) was calculated by ChemAxon (JChem for Excel); see Table S5.1 for details. The homologous series between mass 200 and 800 at log $D_{ow} < 0$ are poly(ethylene glycol) (PEG) surfactants that were detected by the LC-Q/TOF nontarget approach.

higher log D_{ow} range than LC-amenable compounds. However, there are quite a few exceptions; for example, diPAPs, dioctadecylamine with high log D_{ow} detected by LC-Q/TOF, or triethyl citrate and coumarin with lower log D_{ow} detected by GC-Q/TOF (see Table S5.1). There is also an overlap of compounds that can be detected by both instrument types. Sixteen of the 86 compounds that were detected by GC-Q/TOF were also detected in a comparable number of samples by LC-Q/TOF (target or suspect screening approaches; see Figure 4 and Table S5.1). Vice versa, three compounds that were

detected by LC-Q/TOF were also detected in a comparable number of samples by GC-Q/TOF. The chemicals detectable on both platforms were phthalates, organophosphate flame retardants, UV filters, and fipronil and its metabolites, which is consistent with results from a collaborative trial in water samples.[45]

Significance of Findings in Dust Samples. To our knowledge, this is the first study that investigated a large number of dust samples in such a comprehensive way. The detected compounds were categorized in compound classes, to the extent possible (see Table S5.1). In total, 271 compounds were detected in at least one dust sample; 163 of them could be confirmed by a reference standard, and the other 108 compounds remain tentatively identified (37 with probable structure, 55 tentative candidates, 16 unequivocal molecular formula; confidence levels 2−4).[30] The detected compounds belonged to the following use categories: 38 pesticides, 30 surfactants, 28 cosmetic products, 21 pharmaceuticals and drugs, 21 flame retardants, 17 plasticizers, 15 polyfluorinated compounds, and 22 other industrial chemicals. In addition, 21 human metabolites and 26 naturally occurring compounds were found. For 16 compounds, the use category was unknown, and for another 16 compounds, only the molecular formula could be assigned.

The detection of pesticides, surfactants, flame retardants, and plasticizers in the samples was not surprising, as they have been investigated in many previous studies.[1,4,24] However, the number of compounds and the fact that many of the compounds were detected in more than 50% of all dust samples was not expected. In addition, the detection of a large number of cosmetic products and pharmaceuticals was rather surprising. Except for parabens, cosmetic product constituents have not been investigated extensively in dust, although their occurrence can be expected due to their skin application. The detection of nondermally applied pharmaceuticals is more surprising. Finally, the detection of different emerging polyfluorinated compounds, plasticizers, and other environmental contaminants indicates that nontarget screening approaches using HRMS are critical in the detection of compounds that can potentially affect humans. The results of this multistep screening give new insights into the full chemical fingerprint of indoor dust, supporting future efforts to connect the results to chemical source profiles and health impacts.

■ ASSOCIATED CONTENT

ⓢ Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.7b05767.

> Additional text, 20 figures, and one table describing dust extraction, confirmation of subjects by library spectra, quality control in nontarget screening, homologous series detection, examples of tentatively identified compounds by in silico fragmentation, and confirmation of tentatively identified compounds (PDF)

> Ten tables and one chart listing details and validation of target compounds, instrument settings, software parameters, and all detected compounds (XLSX)

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Notes
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