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Title

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Household dust as a repository of chemical accumulation: New insights from a comprehensive high-resolution mass spectrometry study

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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 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 non-target screening approaches using both LC-quadrupole time of flight (Q/TOF) and GC-Q/TOF. First, the extraction method was optimized to streamline detection of LC-Q/TOF and GC-Q/TOF amenable compounds and was successfully validated using over a hundred target compounds. Non-target screening with GC-Q/TOF was done by spectral deconvolution followed by a library search. Suspect screening by LC-Q/TOF was carried out using accurate mass spectral library. Finally, LC-Q/TOF non-target screening was carried out by extracting molecular features, acquiring tandem MS/MS spectra and performing compound identification using *in-silico* fragmentation software tools. In total, 258 chemicals could be detected in 38 dust samples; 166 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 (CASRN: 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.

Graphical Abstract

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 (e.g.[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 (non-targets) 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], non-target screening studies in other environmental media such as household dust are still rare. So far, the most thorough investigation of non-targets in dust has been done by Rager et al. (2016)[16] who investigated more than 50 dust samples by LC time of-flight (TOF) MS. They linked the proposed formulas to EPA's Distributed Structure-Searchable Toxicity (DSSTox) database. However, their identification was only based on molecular formula match, as they did not acquire MS/MS data. A recent study by Ouyang et al. (2017)[17] applied two-dimensional (LCxLC)-ToF MS in order to get a better separation of the non-target features. However, as they only looked into one dust sample, the generalizability of these results is limited. Other non-target studies specifically looked at flame retardants or brominated azo dyes in household dust[18–20]. Hilton et al. (2010)[21] used two dimensional GCxGC-MS coupled to electron ionization (EI) to investigate non-target chemicals in dust including phthalates, polycyclic

aromatic hydrocarbons, chlorinated compounds, brominated compounds, and nitro compounds.

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 physico-chemical properties and structures. Chemicals range from very polar and non-volatile surfactants to non-polar and semi-volatile 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 non-target screening workflow for polar to semi-polar chemicals analyzed by LC-HRMS as well as a target and non-target screening method for non-polar 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 non-target screening approaches on both platforms (LC-HRMS and GC-HRMS) are critically discussed and the complementary roles of the two platforms are acknowledged. The 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 PTFE container at −20°C until extraction. Dust samples were sieved (106 μm) and 100 mg were sonication extracted using hexane:acetone (3:1 v/v) and acetone (100%). The extract was evaporated, filtered and split into a *GC-fraction* and a *LC-fraction* which were run on the corresponding instruments (see SI-2.1 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 (Table SI-1 and Table SI-5.1). 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

The analysis on the GC-Q/TOF was carried out on an Agilent 7890B gas chromatograph using a HP-5MS (30 m × 0.25 mm, 025 μm) column coupled to an Agilent Q/TOF 7200B running in electron ionization (EI) mode. A 78 min runtime with a linear temperature gradient from 35°C 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 SI-2.2.

The analytical method for the LC-Q/TOF was taken from Moschet et al (2017)[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: positive ionization mode: A) ultrapure water plus 0.1% formic acid, B) acetonitrile plus 0.1% formic acid; negative ionization mode: A) ultrapure water plus 1 mM ammonium fluoride, B) acetonitrile. Ammonium fluoride in ultrapure water was chosen in negative mode because it had >10x 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 mode. Acquisition was done in *All-Ions* fragmentation mode using collision energies (CE) 0, 10, 20, and 40 eV (scan rate: 4 spectra/sec) 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 SI-2.3.

Method Validation

The optimized extraction and analytical method was validated by extracting a triplicate of the 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 pre-spiked sample by the area of a post-spiked sample, i.e., 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 using an inert silica material (MIN-U-SIL®, U.S. Silica Holdings Inc., Frederick, USA) as a dust surrogate. The same method validation approach was used on both analytical platforms.

Targeted Quantification Method

Quantification of the target chemicals on 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]- were used as quantifiers and - depending on the compound - the one or two most abundant fragments from the library spectra were used as qualifiers in the All-Ion scans (exact mass window ± 20ppm). In GC-Q/TOF, the most abundant fragment was used as quantifier and two further fragments used as qualifiers (exact mass window: ± 25ppm).

Non-Target Screening by GC-Q/TOF

The 38 samples including method blanks were re-run 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 non-target features.

In a first step, non-target features were extracted by spectral deconvolution using 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 score. 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 seconds were selected (parameters calculated by the MassHunter Unknown Analysis software, see SI-3.1 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 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 the target compounds that were identified in the non-target 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.

Long-chain alkanes, their acids, esters and similar compounds were neglected from the further selection as they were considered as 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 the target compounds that were also detected by the non-target approach. If the NIST library only contained 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 ten times the intensity in the method blank were discarded.

Suspect Screening by LC-Q/TOF

Suspect screening was conducted using the *Agilent MassHunter Qualitative Analysis* software (version B.07) by applying the "Find by Formula" workflow following the method described in Moschet et al. (2017)[28]. Two curated spectral libraries, *Agilent Forensic Toxicology Personal Compound Database and Library (PCDL)* and *Agilent Water Contaminant LC/MS PCDL*, containing 8,000 and 1,450 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 SI-3.2 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 co-eluting 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 ten 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.

Non-Target Screening by LC-Q/TOF

A) Recursive Feature Extraction—All samples including the method blanks and the NIST reference dust were re-run 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/sec. Agilent Profinder software (version B.08.00) was used to extract non-target 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, i.e., 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. All parameter settings are found in SI-3.3

B) 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 ten times the intensity of the blank sample. In order to focus on compounds ubiquitously present in dust, all features present in at least 37 of the 38 samples were selected for further identification.

C) Compound identification using in-silico fragmentation—The samples with the highest intensities of the selected features were re-run in targeted MS/MS mode (CE=20) by triggering the [M-H]$^-$ or [M+H]$^+$ mass of the selected feature at the measured RT. Using the MS/MS information, the features were tentatively identified (if possible) using 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 a different algorithm and different filtering and weighting options (details on parameter settings see SI-3.4). 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 (± the 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 based on 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 based on 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 (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 to run batches of 20 compounds.

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, e.g. plausibility check of the retention time based on the predicted $logK_{ow}$ 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 (Table SI-4.1, Details for each compound in Table SI-4.2). The extraction was somewhat biased towards non-polar compounds by the selected solvents (hexane:acetone 3:1 and 100% acetone). However, more polar solvents 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 (SI-4.1). 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, organophosphate flame retardants, skin oils) and background contamination in the method blank 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 two), but higher for compounds measured in positive ionization mode (60% > factor of two). 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 Non-Target Screening

The deconvolution of the GC-EI-MS chromatograms produced about 3000 to 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 (CASRN: 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 co-elution 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 method section) led to 75 compounds with detections in multiple samples (see SI-5.2). 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, pyrethroids, phthalates) that were already confirmed; the remaining 27 were identified uniquely through this non-targeted workflow (see SI-5). For instance, 7,9-Di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione (CASRN: 82304-66-3) – a leachable from plastics - has not been reported in dust before, but is of increasing interest because of detections in water (leached from pipes) and in airborne particles[37]. For 17 of the non-targets, 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] (SI-5.1 and SI-5.2 for details) based on 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 applying the automatic filter criteria and after manual inspection (see SI-5.2). The approach is discussed in detail for water samples in Moschet et al. (2017)[28]. Seventeen of them were already quantified in the

target screening, six were target chemicals from the GC-Q/TOF and two were non-targets identified by GC-Q/TOF. For 52 suspects, a reference standard was purchased; 43 of them were unambiguously confirmed by matching RT; 9 were rejected due to non-matching RT. The remaining 28 compounds remain tentatively confirmed with confidence level 2[30].

One example of a positively identified compound is the fungicide imazalil (CASRN: 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 (Fig. 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 SI-6) co-elute 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.

These results show the efficiency of suspect screening using 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 - e.g. diphenylhydramine (CASRN: 58-73-1), miconazole (CASRN: 22916-47-8), diclofenac (CASRN: 15307-86-5) - which have previously not been investigated in house dust, were detected by this approach.

Results of LC-Q/TOF Non-Target Screening

A) Quality Control in Non-Target Screening using 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, respectively. Features that were only found in one out of three replicates (roughly 30% of total features) and features present in the blank (roughly 10%) were discarded leading to a new total number of features of 7,701 in negative mode and 9,326 in positive mode (see SI-5.2). 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 non-targeted analysis, data quality assessment needs to be demonstrated differently; two proxies for this are described below. 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, e.g., using principal component analysis (PCA; see Fig. 2 for negative ionization mode, and Fig. SI-7.1 for positive ionization mode). The plot shows that the injection replicates cluster close together (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 four day run of the 149 injections and ii) that 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 (SI-7.2). Fig. SI-7.1 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 Fig. 2, indicated with a colored circle) also grouped within similar distances to the injection replicates of the same samples. This means that dust is homogenous enough to obtain similar results when extracting different sub-samples 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 due to occurrence in the blank. The automated criteria were set more stringently than when manually evaluating the data; thus, the manual evaluation leads to lower detection limits.[10]

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

B) Homologous Series Identification—The total ion chromatogram of the dust samples suggested that homologous series of compounds were present (SI-8), so all features were searched for homologues using 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 (SI-8). Most prominent in negative mode were homologues with a mass defect of 44.0262, i.e. (-$CH_2CH_2O)_n$ (~50% of the homologues). The most prominent homologues in positive mode were identified with a mass defect of 14.0156, i.e. (-$CH_2)_n$ (~40% of the homologues). Cleaning agents usually contain surfactants with a homologous series of compounds. They have been detected in different environmental media (e.g.[39]), and it is expected that surfactants end up in the dust. Examples of surfactants with (-$CH_2CH_2O)_n$ chains are alcohol polyethoxylates (AEOs) and polyethyleneglycols (PEGs); examples of surfactants with (-$CH_2)_n$ chains are linear alkylbenzenesulfonates (LASs) and sulfophenyl carboxylic acids (SPCs)[11, 40, 41] One way to identify expected surfactants is to use the NORMAN exchange list[32] that contains surfactants previously identified in waste water[11] using 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.

C) Compound Identification using In-Silico Fragmentation Software—As it is impossible to identify several thousands of non-target 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 method section). These included 611 features in negative mode and 284 in positive mode. To further refine that

selection, ubiquitous features with stable intensities amongst the samples (coefficient of variation CV<75%) and features with significant intensity fluctuations amongst the samples (CV>200%) were selected. This led to 129 features in negative mode and 99 features in positive mode (see SI-5.2). 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 using the two in-silico fragmentation software packages MSC and MetFrag. An example of a compound identified by using both packages is the ionic surfactant N-Lauroylsarcosine (SI-9.1; mass 270.2068, RT 10.5 min), which is used in shampoos and shaving foam and which 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 (CASRN: 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 rank 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 logKow (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 (SI-10).

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 non-targeted 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, CASRN: 943913-15-3, see Fig. 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, CASRN: 27619-97-2), 6:2diPAP (CASRN: 57677-95-9, see SI-10) – were detected by the non-target 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 (CASRN: 28343-61-5), which has not been detected in house dust before (Fig. SI-9.2). 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 with the highest number of references and patents.

With this approach, 75 compounds were tentatively identified with a proposed structure either in negative or positive ionization mode, (see table SI-5). Four of them were already identified by the target or suspect approach (bisphenol A, dexpanthenol, fipronil-sulfone, triclocarban). For 16 non-target candidates, a reference standard could be purchased. Twelve compounds were confirmed by matching RT and matching MS/MS spectra (SI-10). In addition to the aforementioned compounds, these were: vanillin (CASRN: 121-33-5), genistein (CASRN: 446–72-0), palmidrol (CASRN: 544-31-0), linolenic acid (CASRN: 463-40-1), palmitic acid (CASRN: 57-10-3), leucine (CASRN: 61-90-5), and piperine (CASRN: 9-62-2). Four compounds were not confirmed (methyl-2-octynoate, cinnamic acid, diphenyl phosphate, 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 SI-5.1).

Comparison of LC-Q/TOF and GC-Q/TOF workflows for detecting unknown chemicals

The identification of compounds using GC and LC techniques provides complimentary yet unique capabilities while providing a complete chemical profile of dust samples. Both analyses provide several thousands of detected non-target 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 the molecular ion information while GC-EI-MS generally does not, necessitates distinct non-targeted screening workflows. Both platforms have advantages and drawbacks. The biggest advantage in GC-EI-MS is that the fragment spectra are very reproducible and that libraries containing over 200,000 compounds are available. In addition, relative RT are very reproducible, so that normalized RI can be calculated when using a standard column and a simple temperature gradient. 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 used for LC-Q/TOF. Also, this makes it much more difficult to detect *unknown unknowns*, i.e., 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 non-target 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 (low energy EI, PCI, 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 co-eluted to form a specific spectrum. Further advances in joint non-target screening by LC-HRMS and GC-HRMS depend critically on the 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 a 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 non-targets) as well as 204 compounds by LC-Q/TOF (42 targets, 79 suspects, 83 non-targets, see SI-5.2)). 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 Fig. 4. As expected, GC-amenable compounds are generally in the higher $logD_{ow}$ range than LC-amenable compounds. However, there are quite a few exceptions: e.g. diPAPs, dioctadecylamine with high $logD_{ow}$ detected by LC-Q/TOF, or triethyl citrate and coumarin with lower $logD_{ow}$ detected by GC-Q/TOF (see SI-5.1). 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 Fig. 4 and SI-5.1). 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 the Findings in the Dust Samples

To the authors' 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 SI-5.1). In total, 271 compounds were detected in at least one dust sample; 163 of them could be confirmed by a reference standard, the other 108 compounds remain tentatively identified (37 with probably structure, 55 tentative candidates, 16 unequivocal molecular formula; confidence level 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 non-dermally

applied pharmaceuticals is more surprising. Finally, the detection of different emerging polyfluorinated compounds, plasticizers and other environmental contaminants indicates that non-target screening approaches using HRMS are critical in the detection of compounds that can potentially affect humans. The results of this multi-step 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.
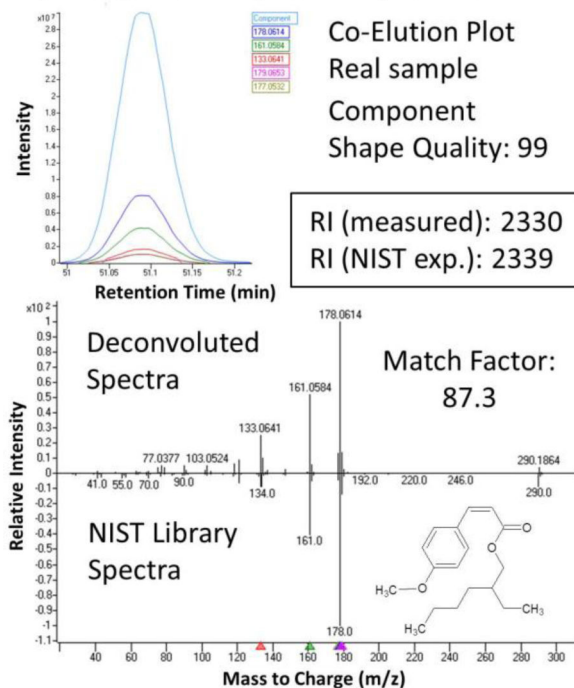
Acknowledgements

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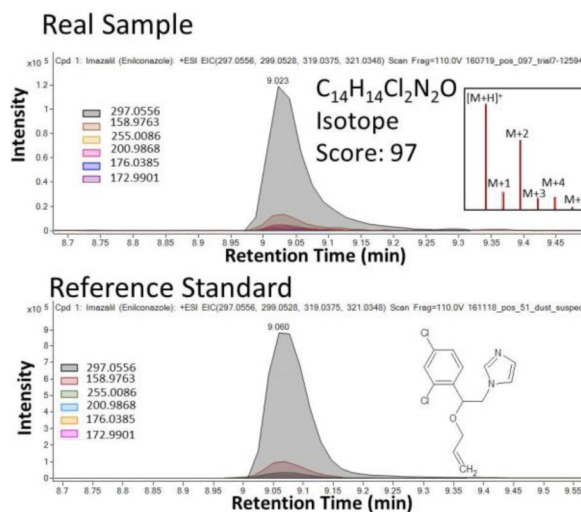
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A) GC-Q/TOF - Octyl methoxycinnamate

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 the UV-filter octyl methoxycinnamate (CASRN: 5466-77-3) detected by GC-Q/TOF (non-target screening). Top: Co-elution plot of five main deconvoluted fragments in a real sample. Bottom: Differential plot between deconvoluted spectra and the NIST library spectra. 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 (CASRN: 35554-44-0) detected by LC-Q/TOF (suspect screening). [M+H]+ and five main fragments from the *All-Ions* scans (see SI-6) 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.
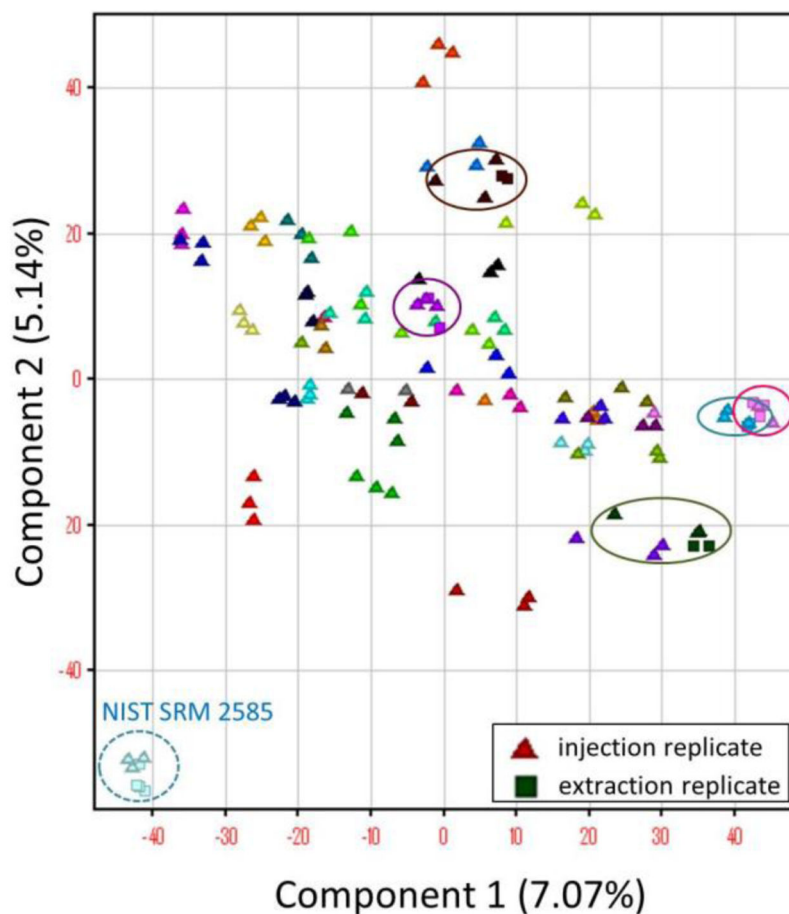
Fig. 2.
Principal component analysis (PCA) of the detected non-target features in 38 dust samples and the NIST SRM 2585 dust sample on the LC-Q/TOF in negative ionization mode. Different colors indicate different samples. Each sample was injected in triplicate (triangles). Total number of features: 7,701 (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.
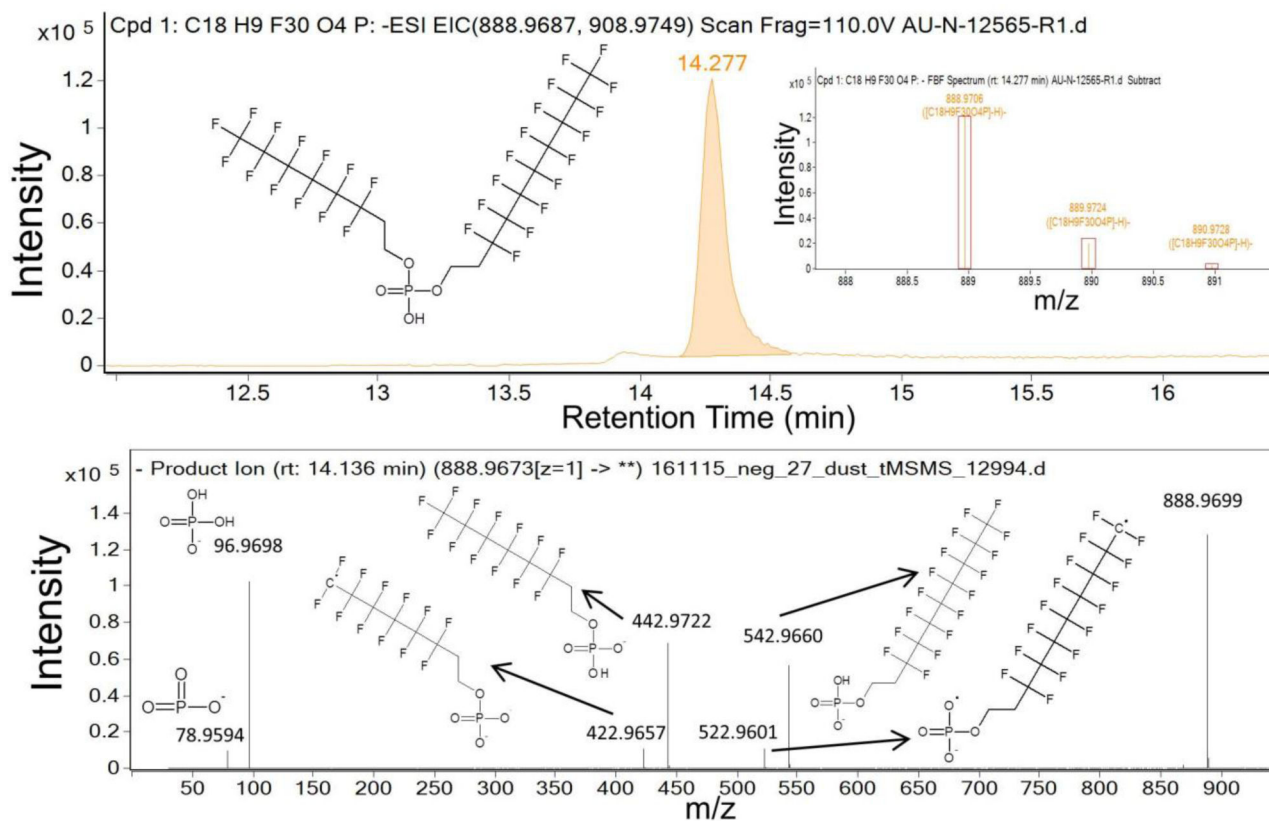
Figure 3:
Chromatogram (top), isotope pattern (inset) and annotated MS/MS spectra (bottom) of 6:2/8:2 diPAP (CASRN: 943913-15-3) identified by the in-silico fragmentation software MetFrag by a complete non-target approach in LC-Q/TOF negative ionization mode. MetFrag f*ragmenter score*: 177, number of 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 logKow (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 SI-10).
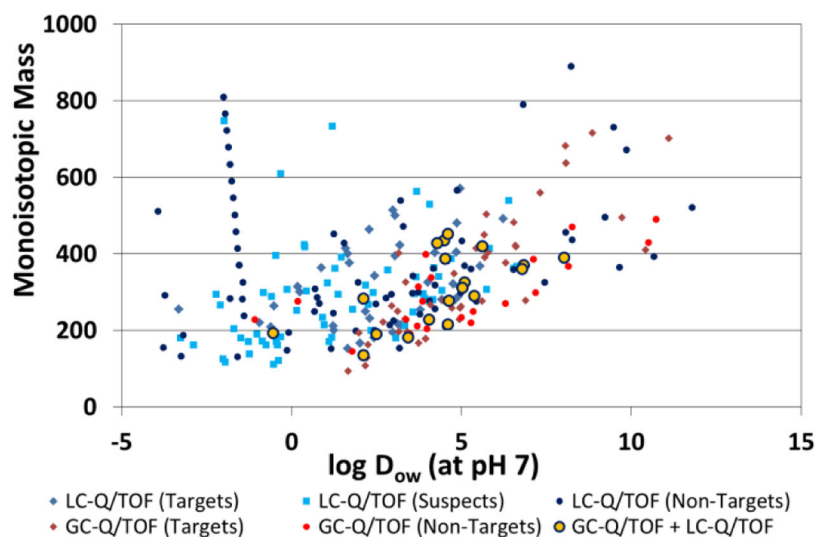
Figure 4.
Physico-chemical properties of detected chemicals by LC-Q/TOF, GC-Q/TOF and compounds detected by both platforms with the different identification workflows (target, suspect, non-target). The $logD_{ow}$ (at pH 7) was calculated by ChemAxon (JChem for Excel). See SI-5.1 for details. The homologous series between mass 200–800 at $logD_{ow} < 0$ are polyethylene glycol (PEG) surfactants that were detected by the LC-Q/TOF non-target approach.