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Article

Screening of Indoor Transformation Products of Organophosphates and Organophosphites with an in Silico Spectral Database

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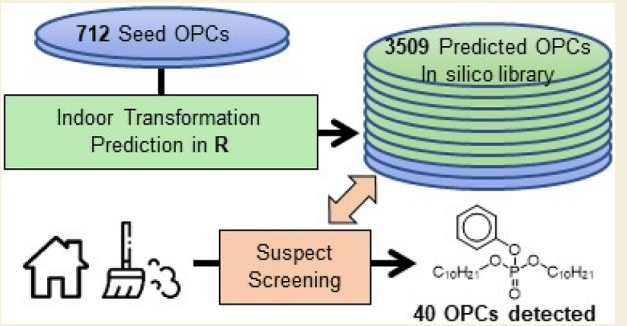
ABSTRACT: Numerous transformation products are formed indoors, but they are outside the scope of current chemical databases. In this study, an in silico spectral database was established to screen previously unknown indoor transformation products of organophosphorus compounds (OPCs). An R package was developed that incorporated four indoor reactions to predict the transformation products of 712 seed OPCs. By further predicting MS^2 fragments, an in silico spectral database was established consisting of 3509 OPCs and 28,812 MS^2 fragments. With this database, 40 OPCs were tentatively detected in 23 indoor dust samples. This is the greatest number of OPCs reported to date indoors, among which two novel phosphonates were validated using standards. Twenty-four of the detected OPCs were predicted transformation products in which oxidation from organophosphites plays a major role. To confirm this, the in silico spectral database was expanded to include organophosphites for suspect screening in five types of preproduction plastics. A broad spectrum of 14 organophosphites was detected, with a particularly high abundance in polyvinyl chloride plastics and indoor end-user goods. This demonstrated the significant contribution of organophosphites to indoor organophosphates via oxidation, highlighting the strength of in silico spectral databases for the screening of unknown indoor transformation products.



KEYWORDS: *high-resolution mass spectrometry, organophosphorus compounds, nontargeted analysis, indoor transformation, oxidation*

INTRODUCTION

Organophosphorus compounds (OPCs) are of public and regulatory concern due to their environmental persistence and high toxicities.[1−3] Hundreds of OPCs with diverse chemical structures have been widely used in the past decades as pesticides, plasticizers, antioxidants, and organophosphate flame retardants (OPFRs). The production of OPFRs, in particular, has increased since the phase-out of polybrominated diphenyl ethers, and the worldwide consumption of OPFRs was estimated to be 500,000 t in 2011.[4] OPCs exert toxicity through multiple mechanisms including the inhibition of serine esterase and proteases[1,5,6] and the activation of nuclear receptors.[7−9] The covalent modification of serine residues on endogenous proteins (e.g., acetylcholinesterase) by OPCs via the electrophilic phosphorus center is of particular concern, as this process can result in toxic effects even at low concentrations.[5,10] Thus, investigation of the environmental occurrences of OPCs is important due to the potential exposure risks.

While targeted analysis studies have made important contributions to the monitoring of OPCs,[11−15] nontargeted analysis with high-resolution mass spectrometry (HRMS) can provide the complementary benefit of identifying unknown OPCs in a systematic way. Two recent studies have successfully employed characteristic fragments (e.g., $[H_4PO_4]^+$) of OPFRs to discover a dozen previously unrecognized OPFRs in indoor dust.[16,17] While this nontargeted analysis strategy is effective for screening organophosphates, many C−P bond-containing phosphonate compounds could be missed as a result of the stability of the C−P bond during collision-induced dissociation in a mass spectrometer. In addition, coeluting compounds such as highly abundant phospholipids produce the same $[H_4PO_4]^+$ fragment, which would lead to increased signal interference. More recently, another nontargeted analysis strategy was employed to screen halogenated OPFRs by relying on their diagnostic isotopic peaks.[18] Three previously unrecognized chloroalkyl OPCs were detected in house dust with this method.[18] While these nontargeted analysis methods made important progress,

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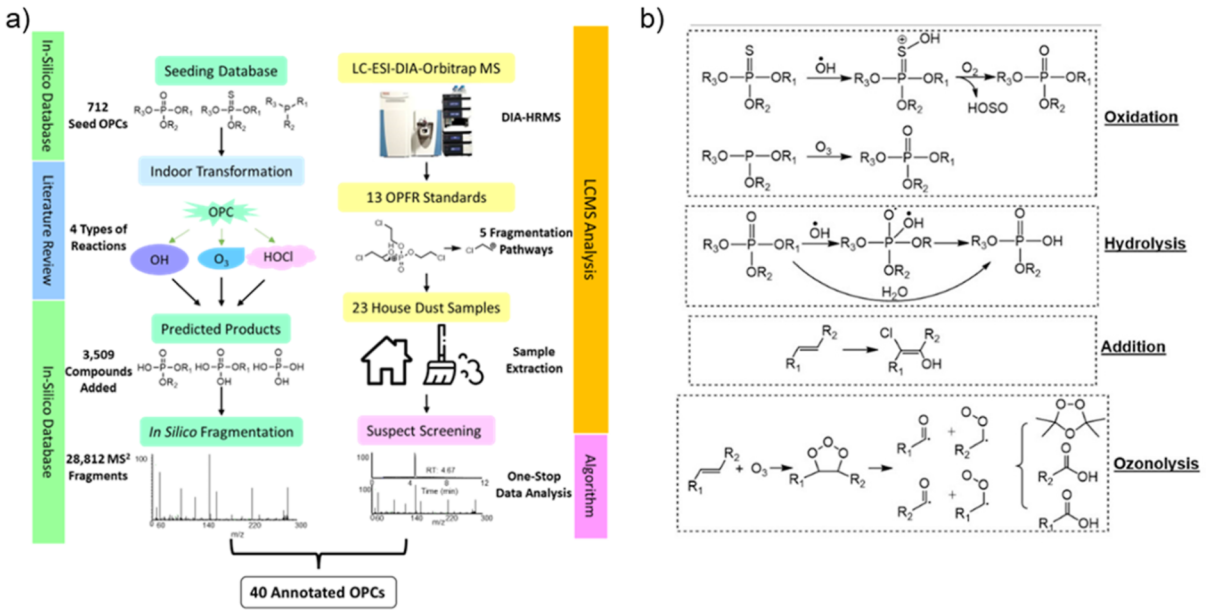

Figure 1. Scheme for the screening of indoor transformation products of OPCs; (a) 40 OPCs and their transformation products were detected in 23 house dust samples using a newly developed suspect screening analysis algorithm. Left side: construction of an in silico spectral database of OPCs consisting of 3509 predicted OPCs and 28,812 predicted MS^2 fragments. Right side: LC-ESI-DIA-Orbitrap was employed to analyze the house dust extracts and a scoring algorithm was used to detect OPCs. (b) Four predominant indoor transformation pathways of OPCs.

they are constrained to halogenated OPCs or organophosphates. A more robust nontargeted analysis strategy is needed to enhance the coverage of those OPCs with diverse structures and distinct fragmentation pathways.

In addition, many new OPCs might be formed through indoor transformations. For instance, a recent study reported the rapid oxidation of organophosphite antioxidants to organophosphate esters in an indoor environment.[19] This was further confirmed by the detection of highly abundant tris(2,4-di-*tert*-butylphenyl)phosphate in outdoor PM2.5 as the oxidation product of antioxidant Irgafos 168.[20] A more recent study also reported the global distribution of photooxidation products of OPFRs across 18 megacities.[21] Transformation products can be more toxic than their parent compounds, for example, the oxidation of phosphorothioates (P═S) to phosphates (P═O) increases the electrophilicity of the phosphorus center thereby increasing their toxicity.[1] Identification of these indoor transformation products poses a challenge to existing suspect screening analysis workflows, as the vast majority of these compounds exist outside current chemical databases.

This study aims to establish a suspect screening workflow (Figure 1a) to cover both commercial OPCs and their transformation products. First, an in silico spectral database was established by predicting the indoor transformation products and MS^2 fragments of the seed OPCs curated from the Toxic Substances Control Act (TSCA) database. Then, the in silico spectral database was incorporated into a previously developed scoring algorithm[22] to screen OPCs and their transformation products in indoor dust. Lastly, inspired by the ubiquitous indoor occurrence of oxidation products, the in silico spectral database was expanded to the screening of organophosphites in plastics.

MATERIALS AND METHODS

Chemicals and Reagents

Authentic standards of OPCs and their mass-labeled standards (Table S1 in the Supporting Information) were purchased from Wellington Laboratories Inc. (Guelph, ON, Canada). Dichloromethane, methanol, and acetone were all "Omni-Solv" grade and were purchased from EMD Chemicals (Gibbstown, NJ, USA).

Sample Collection and Treatment

Twenty-three samples of dust were collected from 23 Canadian houses. Field blanks were also prepared to monitor potential background contamination. The method to collect dust samples was described in a previous study.[7] In brief, the equivalent of the entire floor-surface area was sampled in each room. All sampling components upstream of the extraction thimble were cleaned after each sampling event. Five types of plastic polymers, including high-density polyethylene, low-density polyethylene (LDPE), polyethylene (PET), polyvinyl chloride (PVC), and polypropylene, were obtained in the form of preproduction pellets. These preproduction pellets have been used to manufacture many downstream end-user plastic products in North America. In addition, 5 indoor PVC end-user plastic products, including two PVC pipes, one inflatable children's toy, one laptop table mat, and one mask container (Figure S1), were also included in this study.

The primary objective of this study was to screen for unknown transformation products rather than quantification and, thus, a simple sample extraction method without solid-phase extraction (SPE) cleanup was used for the analysis of OPCs to reduce the loss of compounds during cleanup. Approximately, 0.05−0.1 g of product or house dust samples was loaded into 15 mL Falcon tubes and extracted by shaking with 4 mL of acetonitrile for 30 min[23] 1 mL aliquots of extracts were then blown to dryness under a gentle stream of N_2 and reconstituted in 200 μL of methanol for instrumental analysis.

Instrumental Analysis

Aliquots of extracts were analyzed using a Q Exactive ultrahigh resolution mass spectrometry (UHRMS, Thermo Fisher Scientific, San Jose, CA, USA) equipped with a Vanquish UHPLC system (Thermo Fisher Scientific), as described in the Supporting Information. Data were acquired using electrospray ionization (ESI)

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in both positive and negative ion modes across a total mass range of m/z 150−1000. Data were acquired in data-independent acquisition (DIA) mode, as described in Supporting Information.

Quality Control and Quality Assurance

To avoid contamination of samples, all equipment was rinsed regularly with methanol. Two procedural blanks were incorporated into the analytical procedure. Background contamination from blanks was subtracted from samples for subsequent data analysis, and those compounds with abundances less than 3 times the background abundance in blanks were considered nondetects. Where possible, OPCs were quantified using authentic standards: tris(2-chloroethyl) phosphate (TCEP); tris(1,3-dichloro-isopropyl) phosphate (TDCIPP); triphenyl phosphate (TPhP); tris(4-methylphenyl) phosphate (TMPP); 2-ethylhexyl diphenyl phosphate (EHDPP); tris(2-ethylhexyl) phosphate (TEHP); tris(2-butoxyethyl) phosphate (TBOEP); tris(2,4-di*tert*-butylphenyl) phosphate (AO168═O); bis-(2,4-di*tert*-butylphenyl) pentaerythritol diphosphate (AO626═O_2); triisodecyl phosphate (TIDP); bis(2,4-di*tert*-butylphenyl phosphate (B2,4DtBPP); and diphenyl phosphate (DPhP). However, many of the compounds annotated in house dust are novel species that have not been previously documented. Therefore, authentic standards were not available, and TBOEP was used to semi-quantify compounds detected in positive ion mode, as TBOEP was the most abundant OPC detected in selected house dust. DPhP was used to semi-quantify compounds detected in negative ion mode. This semi-quantitative strategy has been frequently used in nontargeted studies.[7] Method detection limits (MDLs) were defined to be three times the average concentration in the procedural blanks, for OPCs (e.g., AO626═O_2) detected in procedural blanks.[24] For other OPCs that were not detected in the blanks, MDLs were calculated by a 99% confidence of y-intercept divided by the slope of the calibration curve.[25] The MDLs for all of the OPCs ranged from 1.63 to 32.4 ng/g. Strong signal suppression (−32.5 to −60.2%) was observed, as SPE cleanup was not incorporated to avoid the loss of unknown OPCs. To improve the semiquantification accuracy, mass-labeled standards (TBOEP-d_{27}, TCEP-d_{12}) were spiked into the acetonitrile extracts before LC−MS/MS analysis. Relative recoveries for OPCs with surrogate standards ranged from 71.5 to 110%.

In Silico Spectral Database

To curate manufactured OPCs, the "MS-ready" library constructed from the TSCA database in our recent study was used, consisting of 23,235 compound SMILES.[22] The TSCA database maintained by the U.S. EPA contains all existing chemicals in the United States that do not qualify for an exemption or exclusion under TSCA. A total of 712 OPCs were recognized by screening for P−O bonds from the SMILES data of the TSCA chemicals. These 712 manufactured OPCs were used as the "Seed" compounds to predict their indoor transformation products.

To predict transformation products, the "indoortransformer" R package was developed (https://github.com/PengGroup/indoortransformer). Four major indoor transformation pathways were considered for OPCs, including oxidation,[19] hydrolysis,[26] HOCl electrophilic addition,[27] and ozonolysis.[28] The SMILES of each seed compound was taken as the input and was converted to an "SDFset" object using the "ChemmineR" package. Unsaturated C−C double bonds were subjected to HOCl addition and ozonolysis reactions, phosphite, and phosphorothioate groups were subjected to oxidation reactions, and phosphate ester bonds were subjected to hydrolysis reactions. Iterative transformations were performed when multiple reactive moieties were present in the same OPCs. For instance, for a simple triester OPC with three different side chains, three diesters and three monoesters were predicted to form via successive hydrolysis reactions. A total of 3509 putative indoor transformation products of OPCs were predicted via the "indoortransformer" package, consisting of 230 oxidation products, 1399 hydrolysis products, 825 products of oxidation followed by hydrolysis, and 1055 products of further sequential reactions including ozonolysis and HOCl addition.

To predict the MS^2 fragments of OPCs, three fragmentation pathways were used for positive ion mode data, and two fragmentation pathways for negative ion mode, based on the observed fragmentation patterns of 13 authentic OPC standards (Table S1). A total of 28,812 MS^2 fragments were predicted for all 4100 OPCs. Xlog P values were also calculated for all of the OPCs using the "rcdk" R package, and these were used to predict LC retention times. Xlog P was calculated using an additive model with molecular descriptors and chemical similarity as described in a previous study.[29] Strong correlations (R^2 > 0.8) were observed in Xlog P and retention times and 21 model compounds (see the full list in Table S3) which were used to calibrate the linear relationship. Nontargeted screening was performed using an R algorithm developed in a recent study[22] which automatically matched peak features to the established in silico spectral database (see Supporting Information for details).

Statistical Analyses

All statistical analyses were performed using either R or GraphPad Prism (version 7.0.4, GraphPad Software Inc., San Diego, CA, USA). In all cases, results were considered significant if p < 0.05 when calculated using t-test functions in R or GraphPad Prism.

RESULTS AND DISCUSSION

Construction of an In Silico Spectral Database for OPCs and Transformation Products

Five predominant indoor transformation pathways have been documented for OPCs, including oxidation of the phosphorus center,[19] hydrolysis,[26] ozonolysis,[28] electrophilic addition of HOCl,[27] and hydrogen abstraction by $^{\bullet}$OH (Figure 1b and Table S2).[30,31] However, the indoor concentrations of $^{\bullet}$OH (5 × 10^4 molecules cm^{-3}) are 2−3 orders of magnitude lower than outdoors (5−10 × 10^6 molecules cm^{-3}).[31] In addition, hydrogen abstraction initiates complicated radical chain reactions[32−34] which might introduce large uncertainties on transformation product prediction. Thus, hydrogen abstraction by $^{\bullet}$OH was not considered in the present study. With these defined indoor transformation pathways, the "indoortransformer" R package was established to predict the transformation products of 712 commercial OPCs from the TSCA database. A total of 3509 indoor transformation products of OPCs were predicted to form, consisting of 230 oxidation products, 1399 hydrolysis products, 825 products of oxidation followed by hydrolysis, and 1055 products of further sequential reactions including ozonolysis and HOCl addition. Note that the number of putative transformation products is about 5 times greater than that of native OPCs, demonstrating the potential existence of many previously unrecognized OPCs.

Another major challenge for nontargeted analysis is that experimental MS^2 spectra are not available for the majority of the OPCs, especially for transformation products. Several programs have been developed to predict the in silico MS^2 spectra of compounds, including machine learning-based CSI:Finger ID,[35] and combinatorial fragmentation-based MetFrag software.[36] Schreckenbach et al. employed a fragment prediction tool to successfully detect multiple OPCs in electronic waste dust, including the resorcinol bis-(diphenylphosphate) (RDP).[37] However, current MS^2 spectral prediction software is not specifically trained for OPCs and is prone to high false discovery rates. Fortunately, the major fragmentation pathways of OPCs are highly predictable. By manually inspecting the MS^2 spectra of 13 OPCs whose authentic standards are available (Table S1), five predominant fragmentation pathways were clearly observed (Figure S2). With these five defined fragmentation pathways, the "indoortransformer" package (https://github.com/PengGroup/

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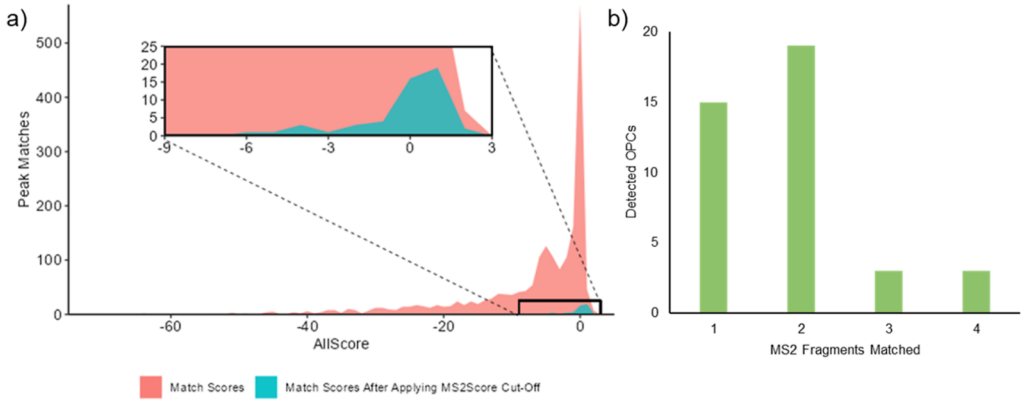

Figure 2. Detection and scoring of 40 OPCs in indoor house dust using the in silico spectral database. (a) Distributions of top-ranked total scores for all compound matches. The blue area demonstrates the distribution of 45 high-confidence hits with at least one matching MS^2 fragment. (b) Number of fragments detected for the final list of 40 annotated OPCs.

indoortransformer) was used to predict the MS^2 fragments of all 4100 OPCs including seeding compounds, for a total of 28,812 MS^2 fragments. To further enhance the confidence of suspect screening analysis, the retention times of all 3509 OPCs were predicted based on their calculated Xlog *P* values as in previous studies.[22] Thus, an in silico spectral database of OPCs was constructed consisting of 4100 compounds, 28,812 MS^2 fragments and 4100 retention times (see Supporting Information Data 1 to download the database).

Benchmarking the In Silico Spectral Database

Next, the in silico spectral database was applied to the screening of OPCs in 23 Canadian house dust samples in combination with LC-Orbitrap-based suspect screening (Figure 1a). A one-stop scoring algorithm developed in a previous study[22] was employed herein to control false discovery rates by scoring each database match according to several criteria, including exact m/z (mzscore), isotope distributions (isoscore), adducts (adductscore), MS^2 fragments (MS^2score), and retention time matching (RTscore), respectively (see Supporting Information for details). The algorithm was first benchmarked with 13 OPCs whose authentic standards are available. Seven of these OPCs were detected in the house dust samples via manual inspection: TDCPP, DPHP, TPHP, TBOEP, EHDPP, TMPP, and TEHP. Then, by matching to the in silico spectral database, six out of the seven were automatically detected in the house dust samples by the screening algorithm. TEHP was the only compound missed by the algorithm because its MS^2 fragment was not detected, even through manual inspection, due to the low abundance. Due to the lack of authentic standards, MS features incorrectly predicted as one of the 7 compounds were considered false positives. With the small benchmarking data set of 13 OPCs, we rationalized the selection criteria for OPC identification with a detection sensitivity of 6/7 and false discovery rate of 0/7: Allscore > −6.0 and MS^2score > 0. Future studies are warranted to thoroughly assess the false discovery rate using more authentic standards.

We then moved forward to the screening of unknown transformation products in the same house dust extracts by matching all peak features to the in silico spectral database. Among >60,000 peak features, 2932 initial hits were obtained using MS^1 matching to the in silico spectral database, within a mass tolerance of 2 ppm. After the score criteria were applied, a total of 45 OPCs were annotated as high-confidence hits. The Allscore of 45 OPCs ranged from −5.28 to 1.83, greater than 764 initial hits (Figure 2a). MS^2 fragment is essential to further exclude false identifications, and 15, 19, 3, and 3 hits were supported by 1, 2, 3, and 4 MS^2 fragment matches (Figure 2b), respectively. Five diesters were manually excluded as in-source fragments of triesters, and 40 final identities were obtained (see the compound list in Supporting Information Data 2). This demonstrated an estimated false discovery rate of 11.1% (5/45) of the automatic algorithm arising from in-source fragments. Among 40 detected OPCs, 16 compounds were detected as raw seed chemicals, while 24 OPCs were detected as transformation products formed through oxidation and/or hydrolysis. Not surprisingly, many relatively new OPCs (e.g., DIDPP, **39**) were also reported in three very recent nontargeted analysis studies,[16−18] which cross-validated our method.

Compared to previous nontargeted analysis studies,[16−18] the current study reported the largest number of OPCs in indoor dust to date. This should primarily be attributed to the expanded chemical coverage of the in silico spectral database. For instance, C−P bond phosphonates do not produce the $[H_4PO_4]^+$ fragment and cannot be captured by characteristic fragment-based nontargeted analysis. Seven phosphonates were detected in house dust for the first time, including (5-ethyl-2-methyl-2-oxido-1,3,2-dioxaphosphinan-5-yl) methylphosphonate (PMMMP, m/z = 287.0804, Figure 3a) and di-PMMMP (m/z = 449.1251, Figure 3b). The two chemicals have been recently detected in children's car seats but have never been reported in indoor environment.[12] Authentic standards were purchased to confirm the identities of PMMMP and di-PMMMP. The MS^2 spectra of the detected features in the house dust sample were well matched to the authentic standard of di-PMMMP, by detecting three high abundance fragments at m/z 97.0053, 177.0674, and 273.0646 (Figure 3a). As expected, all three high abundance fragments were formed via the cleavage of P−O or C−O bonds while the P−C bond remains stable during CID. Similarly, the identity of PMMMP was also confirmed by its authentic standard (Figure 3b).

Wide Spectrum of Transformation Products Formed through Oxidation and Hydrolysis

Hydrolysis Products. Nine OPCs including **5**, **8**, **9**, **11**, **16**, **17**, **18**, **37**, and **40** were tentatively identified as the hydrolysis products from seeding OPCs. Eight of them, except for

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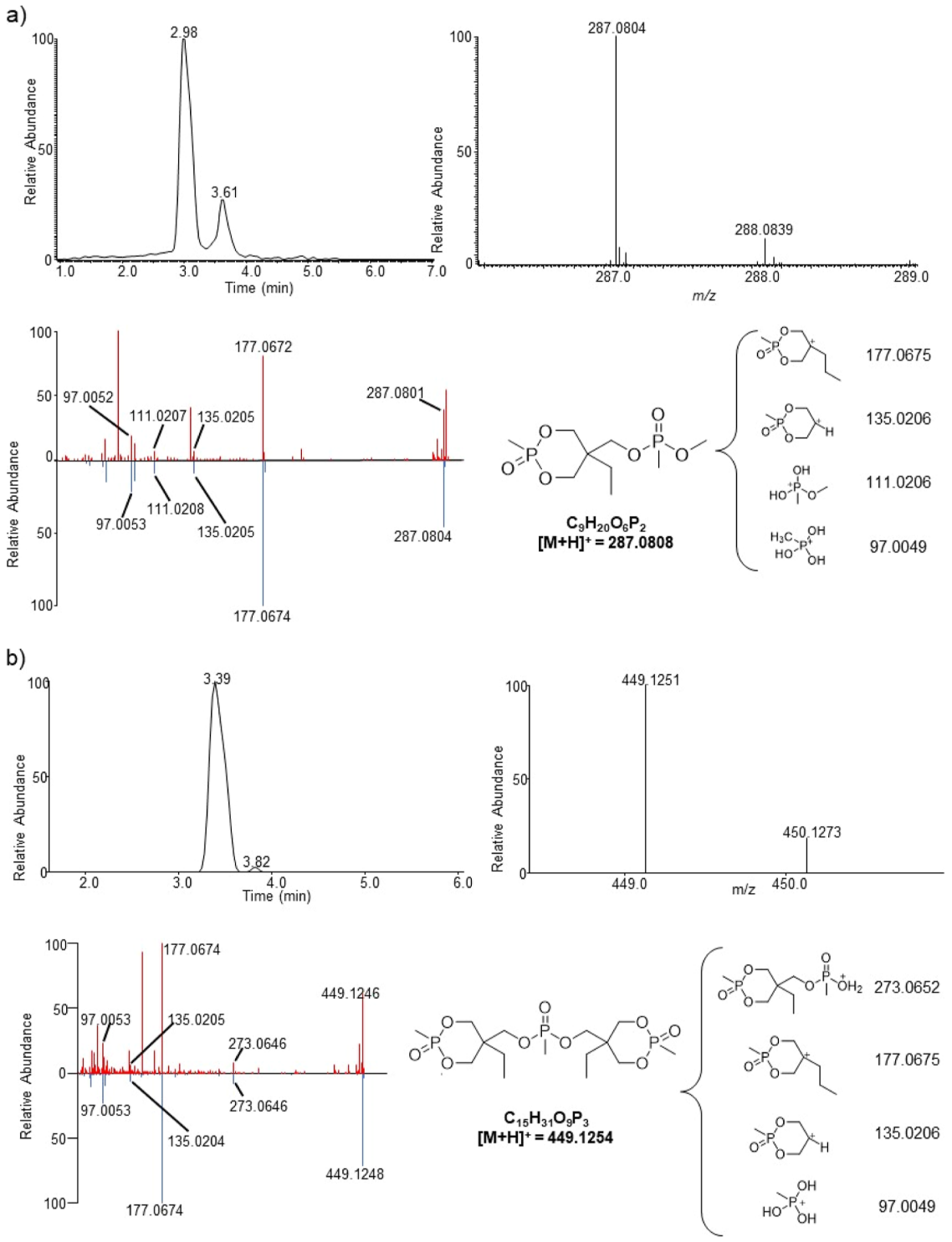

Figure 3. Validation of PMMMP and di-PMMMP using their authentic standards. (a) Chromatogram, MS^1 and MS^2 spectra of PMMMP in representative house dust. (b) Chromatogram, MS^1 and MS^2 spectra of di-PMMMP in a representative house dust. The MS^2 spectra were shown for both representative house dust (red) and authentic standard (blue).

compound **40**, were diesters formed through one-step hydrolysis. The predominance of diesters, rather than monoesters, is not surprising, as the deprotonated hydroxyl largely increases the electron density of phosphorus atom for nucleophilic attack compared to triesters.[38] Interestingly, the compound **40** was recently identified as a hydrolysis product of RDP (**39**) in the sediment of Taihu Lake.[25] Similarly, a strong correlation was observed between RDP and OPC **40** (R^2 = 0.73, $p < 0.001$, Figure S3), demonstrating OPC **40** as a potential hydrolysis product of RDP. Alternatively, previous studies have also reported diesters as impurities in commercial products.[39] Future studies are warranted to discriminate the contributions of the two sources to indoor diesters.

Oxidized Products. Seven OPCs (**3**, **12**, **14**, **22**, **27**, **35**, and **39**) were tentatively identified as oxidation products from seed organophosphites, including three previously reported:[19]

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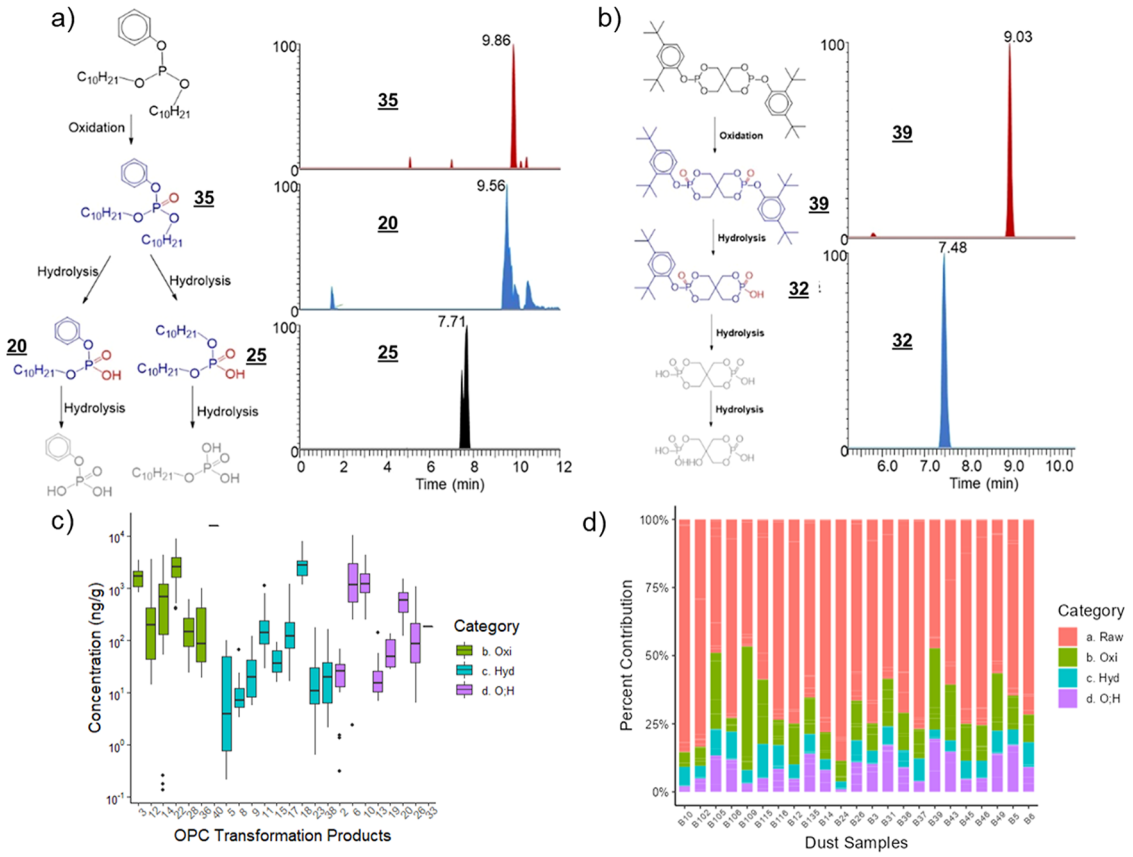

Figure 4. Representative OPCs detected formed through indoor transformations. (a) Proposed transformation pathways of diisodecyl phenyl phosphite (DDePhPi) and representative chromatograms of three detected transformation products. Detected compounds are highlighted in blue. Modification of functional groups are highlighted in red. Gray structures indicate proposed transformation products not detected by the algorithm. (b) Proposed transformation pathways of AO626 and representative chromatograms of two detected transformation products. (c) Estimated concentrations of 40 OPC transformation products in house dust. (d) Percentage contributions of raw OPCs and transformation products in house dust. In the box-whisker plot, the box represents 1−3 quartiles; the midcourt line represents the median.

TCEP (**14**), phenyl dodecyl phosphate (PhDDeP) (**35**, Figure 4a), and AO626═O_2 (**39**, Figure 4b). Two of the seven detected OPCs, including AO626═O_2 (**39**) and decyl diphenyl phosphate (DeDPhP) (**27**), should be exclusively formed through oxidation, as only their organophosphite analogs are included as commercial chemicals in the TSCA database. Supporting this, AO626═O_2 was confirmed in two recent studies as the oxidation product of antioxidant AO626.[19,20] As for the five other OPCs (e.g., PhDDeP), both organophosphates and organophosphites are included in the TSCA database. This demonstrated the potential contributions of both primary and secondary (i.e., transformation) sources to the indoor occurrence of the five OPCs. This highlighted the importance of detecting organophosphites to confirm the contributions of secondary sources.

Products Formed through Oxidation and Hydrolysis. Eight OPCs (**2**, **6**, **10**, **13**, **20**, **21**, **25**, and **32**) were formed through two-step indoor transformations including oxidation and hydrolysis. For instance, PhDDeP (**35**) as the oxidation product of phenyl dodecyl phosphite (PhDDePi) was detected together with its two hydrolysis diesters (**20** and **25**) (Figure 4a). The identities of the two hydrolysis products were supported by their shorter retention times (9.56 and 7.71 min) than those of PhDDeP (9.86 min). Similarly, the diester (**32**) of AO626═O_2 (**39**) was detected at high abundances. Its identity was partly supported by the shorter retention time (7.48 min) compared to native AO626═O_2 (9.03 min) (Figure 4b). Monoester hydrolysis products were not observed for PhDDeP or AO626═O_2, probably due to the decreasing hydrolysis rates of diesters, as mentioned above.

In summary, among the 40 OPCs, 24 compounds were predicted as indoor transformation products. Due to the lack of standards for most of the OPCs, we used TBOEP and DPhP as the standards to estimate the concentrations in positive and negative ion modes, respectively. While there were large variations in concentration, oxidation products were detected at higher concentrations than hydrolysis products (Figure 4c). Overall, these 24 transformation products accounted for 11−53% of total OPC abundance in the house dust samples (Figure 4d), demonstrating the significant contributions of indoor transformation.

Wide Range of Organophosphites Detected in PVC Plastics

While OPC oxidation products of the OPC were detected as the predominant indoor transformation products, their seed organophosphites were not detected in the house dust samples, likely due to their rapid oxidation to organophosphates. To investigate the potential occurrences of organophosphites in the indoor environment, preproduction pellets of five types of plastic commonly used in the manufacture of consumer goods were obtained: HDPE, LDPE, PP, PET, and PVC. It was presumed that any organophosphite antioxidants present inside newly produced plastics would have had minimal

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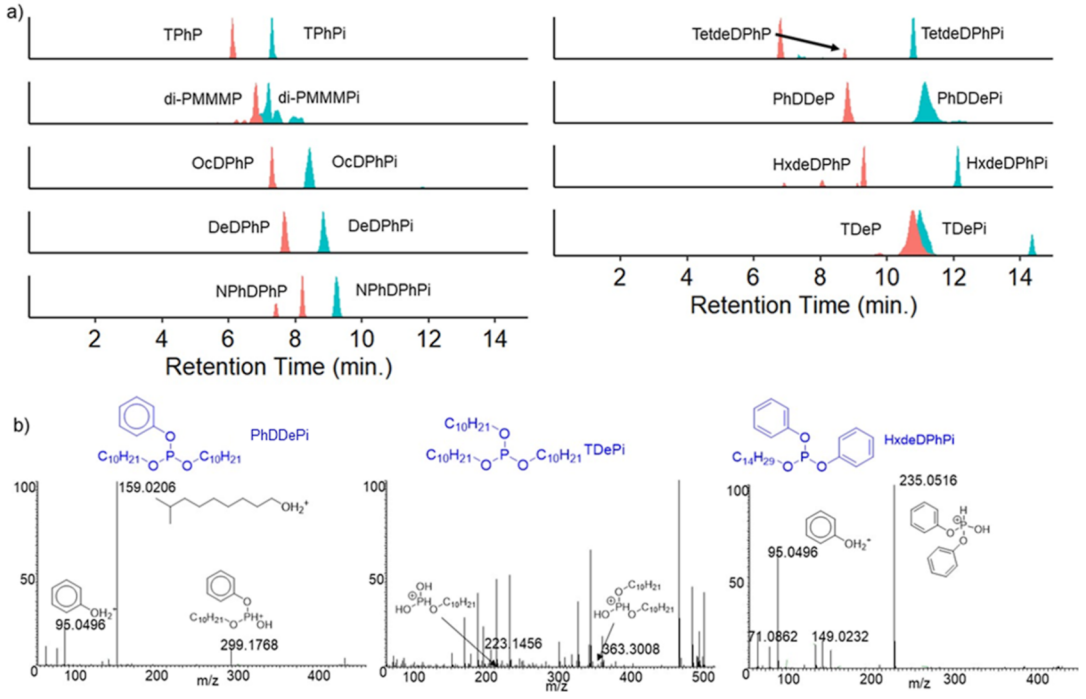

Figure 5. Screening of organophosphites in plastics. (a) Representative chromatograms of organophosphate (red) and organophosphite (green) analogs annotated in preproduction PVC plastics. (b) MS^2 spectra of three representative organophosphites.

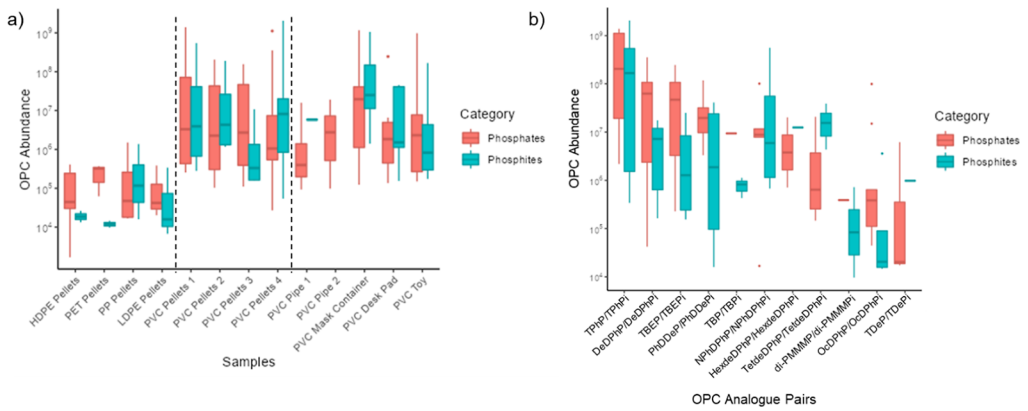

Figure 6. Abundances of organophosphates and organophosphites in plastics. (a) Abundances in preproduction and end-user plastics. (b) Abundances of paired organophosphates and organophosphites in plastics.

exposure to air. As expected, triphenyl phosphite (TPhPi) was detected with an even higher abundance than TPhP in the PVC plastic pellets (Figure S4a). The detection of TPhPi was confirmed using an authentic standard. These preliminary results indicated that freshly produced plastics might serve as an abundant source of organophosphites. To systematically screen for organophosphites, the existing in silico spectral database was expanded to include all commercial organophosphites from the TSCA database. Based on the MS^2 fragmentation of TPhPi (Figure S4), four major fragmentation pathways were predominantly observed via charge-induced fragmentations (e.g., m/z 95.0496), or rearrangements (e.g., m/z 235.0517). Inspired by the results, we incorporated these four fragmentation pathways to predict the MS^2 fragments for the organophosphites curated from the TSCA database.

The in silico spectral database was then applied to the screening of organophosphites in plastics. Across five preproduction plastics, 12 organophosphites were detected together with 21 organophosphates (Supporting Information Data 3), using the same scoring algorithm as mentioned above. The identities of organophosphites were supported by the consistently increased retention time over their organophosphate analogs (Figure 5a). Among the 12 organophosphites detected, only TPhPi and AO626 have been previously reported in indoor environments.[19] For instance, PhDDePi was detected as the second most abundant organophosphite, following TPhPi. The identity of PhDDePi was supported by the detection of both $[Ph + OH_2]^+$ and $[C_{10}H_{21} + OH_2]^+$ fragments (Figure 5b). The results confirmed the oxidation of PhDDePi as an important source of the high abundance of PhDDeP detected in house dust, as mentioned above. Similarly, TDePi and hexadecyl diphenyl phosphite (HxdeDPhPi) (Figure 5b) were also detected in PVC plastics at high abundances.

Among the five types of plastics, higher abundances of organophosphites were consistently detected in PVC. This was

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confirmed by screening three additional sources of preproduction PVC plastics from different manufacturers (Figure 6a). This trend is consistent with previous studies that PVC chemical additives are abundant compared to other plastics.[40] Inspired by the high abundances of organophosphites detected in preproduction PVC plastics, five freshly purchased end-user PVC plastics were also tested, including two water pipes, 1 laptop mat, 1 inflatable children's toy, and 1 mask container. Across all plastic samples, 29 organophosphates and 14 organophosphites were detected (Supporting Information Data 3). Within these compounds, there were 11 phosphate−phosphite analog pairs detected (Figure 6b), with TPhP and TPhPi detected at the highest abundance across all plastic samples. Ten of the 29 organophosphates detected in plastics were also detected in house dust as products of oxidation (TEP, TBP, TCEP, TPhP, DeDPhP, and PhDDeP) or oxidation followed by hydrolysis (DPrP, DPhP, DePhP, and HxdeP). In addition, for five out of the seven OPC oxidation products detected in house dust, their organophosphite analogs (i.e., TBPi, TPhPi, DeDPhPi, PhDDePi, and AO626) were also detected in the PVC plastics. This demonstrates the widespread occurrence of organophosphites in indoor plastics, supporting their contributions to indoor OPCs as a secondary source via oxidation. While two recent studies have reported the oxidation of organophosphites to organophosphates,[19,20] the current study employed nontargeted analysis and highlighted the importance of this oxidation pathway for a broader set of previously unrecognized organophosphites.

Implications

Previous nontargeted analysis methods have been focused on commercial compounds, but transformation products are difficult to cover mainly due to incomplete chemical databases. The study presented here establishes an in silico spectral database for the screening of unknown transformation products of OPCs. With this strategy, we reported the biggest number of OPCs in indoor dust and discovered a wide spectrum of previously unrecognized organophosphites. While the current study is focused on OPCs, the same strategy can be adapted to more chemical classes and transformation pathways. Indeed, Getzinger et al. recently reported an in silico spectral library for the transformation products of PFAS.[41] In parallel to these efforts from the analytical chemistry community, the U.S. Environmental Protection Agency (U.S. EPA) has established a web-based tool "Chemical Transformation Simulator (CTS)" for predicting transformation products of chemical contaminants, for example, hydrolysis.[42] This provides a great opportunity to understand the transformations of chemical contaminants in the environment by aggregating the efforts from both analytical chemistry and modeling communities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmeasuresciau.3c00039.

The Supporting Information provides text and figures addressing (1) LC−MS/MS analysis; (2) nontargeted data analysis; (3) list of 13 organophosphates; (4) list of 21 compounds used for retention time prediction; (5) summary of indoor reactions; (6) pictures of PVC end-user products; (7) fragmentation pathways of organophosphates; (8) RDP and its putative hydrolysis product; (9) organophosphites detected in PVC plastics (PDF)

(XLSX)

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Author Contributions

‖S.K. and W.C. contributed equally to the study. CRediT: **Steven Kutarna** conceptualization, data curation, methodology, project administration, writing-original draft, writing-review & editing; **Wanzhen Chen** conceptualization, data curation, investigation, methodology, writing-review & editing; **Ying Xiong** data curation; **Runzeng Liu** data curation, writing-review & editing; **Yufeng Gong** data curation, writing-review & editing; **Hui Peng** conceptualization, project administration, supervision, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

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