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A quest to identify suitable organic tracers for estimating children's dust ingestion rates

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Abstract

Chemical exposure via dust ingestion is of great interest to researchers and regulators because children are exposed to dust through their daily activities, and as a result, to the many chemicals contained within dust. Our goal was to develop a workflow to identify and rank organic chemicals that could be used as tracers to calculate children's dust ingestion rates. We proposed a set of criteria for a chemical to be considered a promising tracer. The best tracers must be (1) ubiquitous in dust, (2) unique to dust, (3) detectable as biomarkers in accessible biological samples, and (4) have available or obtainable ADME information for biomarker-based exposure reconstruction. To identify compounds meeting these four criteria, we developed a workflow that encompasses non-targeted analysis approaches, literature and database searching, and multimedia modeling. We then implemented an ad hoc grading system and ranked candidate chemicals based on fulfillment of our criteria (using one small, publicly available dataset to show proof of concept). Initially, five chemicals (1,3-diphenylguanidine, leucine, piperine, 6:2/8:2 fluorotelomer phosphate diester, 6:2 fluorotelomer phosphate diester) appeared to satisfy many of our criteria. However, a rigorous manual investigation raised many questions about the applicability of these chemicals as tracers. Based on the results of this initial pilot study, no individual compounds can be unequivocally considered suitable tracers for calculating dust ingestion rates. Future work must therefore consider larger datasets, generated from broader measurement studies and literature searches, as well as refinements to selection criteria, to identify robust and defensible tracer compounds.

Keywords

dust; tracers; non-targeted analysis; multimedia modeling; children; exposure; indoor; indirect ingestion; workflow; tracer identification

INTRODUCTION

Dust ingestion can be a major route of chemical exposure for young children because of the way children interact with their environment (e.g., longer times spent on the floor and unique mouthing behaviors) [1,2,3]. Children aged 6 months to 3 years place their hands and objects into their mouths several times a day [3, 4], substantially increasing their potential chemical exposure through the non-dietary ingestion route [1,2,3]. Chemicals from personal care products (PCPs), household products (e.g., cleaners, pesticides), electronic appliances, furniture, and building materials can be released from their original sources and partition into dust [5, 6], making it an important exposure medium for children.

Three methodologies are routinely used to estimate dust and soil ingestion: (i) tracer elements, (ii) lead (Pb) biokinetic model comparisons, and (iii) activity patterns [1,2,3]. The tracer element methodology uses earth elements, such as aluminum, lanthanum or silicon, to quantify amounts of soil and dust ingested by analyzing children's feces and urine together with soil and dust samples from their environment. A common challenge with this approach is that earth elements are found in substantial quantities in food, soil, and other media that people ingest, making it difficult to isolate the fraction that is coming from dust.

The Pb biokinetic model comparison methodology uses the concentrations of Pb measured in blood or urine and compares them with estimates from a biokinetic model that describes human exposure to Pb via inhalation, ingestion, and dermal contact with dust and soil. Usually inputs include Pb concentration and bioavailability in food, and various environmental media and intake parameters for ingestion [7,8,9,10]. The main challenge associated with biokinetic modeling is that the approach requires a highly accurate accounting of all sources of Pb.

The activity pattern methodology uses information about hand- and object-to-mouth activities, time spent in various microenvironments, and other exposure factors to estimate soil and dust ingestion. One of the main limitations of the activity pattern approach is that estimates for soil and dust ingestion rely heavily on the quality and quantity of available data used to calibrate the model [1,2,3].

All three approaches provide useful information, but generally fail to distinguish between dust and soil ingestion estimates. To our knowledge, only two previous studies have attempted to distinguish between soil and dust ingestion. Calabrese and Stanek [11] attempted to distinguish between soil and dust ingestion using a comparison of element ratios. According to their findings, the element ratios measured in children's feces were more like those measured in soil than dust, indicating that soil ingestion occurs at higher quantities than dust ingestion. However, the study did not provide an estimate for dust ingestion. Özkaynak et al. [12] conducted a modeling study using the activity pattern methodology and the Stochastic Human Exposure and Dose Simulation model for multimedia pollutants (SHEDS-Multimedia) to estimate separate ingestion rates for soil and dust by taking into account the pathway of exposure, source type, and population group. To the best of our knowledge, this is the only study to provide separate estimates for dust and soil ingestion rates for children aged 3 to <6 years. It should be clarified, however, that the

evaluation of the modeling estimates was made by comparing the findings of the study to previous studies of soil and dust ingestion estimates using earth elements as tracers. Such an evaluation may be sufficient when comparing total estimated soil and dust ingestion to analytical data, but it does not allow for an assessment of the soil and dust ingestion estimates separately.

Ideally, a tracer for dust ingestion should be found primarily in dust and not be present in substantial quantities in other media that children contact or ingest. Previous targeted analysis studies have reported measurements for a plethora of organic and inorganic substances in dust. Some examples are polybrominated diphenyl ethers (PBDEs) [6], per- and polyfluoroalkyl substances (PFAS) [5], several pesticides [13], chemicals from PCPs [14], and heavy metals [15]. Recently published non-targeted analysis (NTA) studies have indicated that house dust contains thousands of chemicals of varying structures and properties [16, 17]. Given the findings from these targeted and NTA studies, our research objective was to develop a workflow to prioritize chemicals found in dust based on their suitability as tracers for estimating children's dust ingestion rates.

MATERIALS AND METHODS

The criteria

In order to identify potential tracers, we developed a set of evaluation criteria. Ideal tracers must: (1) be ubiquitous in dust; this criterion ensures that we can monitor the tracers across a broad geographical area, in both a variety of populations and locations; (2) be unique to dust and not present in measurable amounts in other media such as soil, food, water, and children's PCPs; this criterion ensures that the tracers do not reflect exposure from other pathways; (3) be measurable as a biomarker, either directly or as a metabolite, in an accessible biological medium; this criterion ensures that we can generate surrogate measures of internal dose; and (4) have well-defined absorption, distribution, metabolism, and excretion (ADME) properties; this criterion enables us to reconstruct external exposures from biomarker measures.

The case study

For our proof-of-concept case study, we used a small, publicly available dataset generated by Moschet et al. [16], who collected and analyzed 38 dust samples from homes in California, using both NTA and targeted analysis methodologies. This research group also collected and analyzed eight soil samples from areas adjacent to the same homes, three composite food samples, and one composite PCP sample as part of a contract with EPA (#EP-16-W-000173; see Supplementary Information (SI) for additional details on sample collection and processing). To the best of our knowledge, this dataset was the only dataset available containing data on multimedia samples (dust, soil, food, and PCPs) and results from both NTA and targeted analysis methodologies for use in our proof-of-concept case study.

To address the first criterion (ubiquity), we sorted all dust compounds based on detection frequency and selected those with a detection frequency ≥90% (34/38 samples) for further consideration (Supplementary Information Spreadsheet: SIS). To address the second

criterion (uniqueness), we compared the chemicals found in the dust samples to those found in the soil, food, and PCP samples. Furthermore, we queried the literature and selected data sources (e.g., databases and reports (Table S1)) to determine whether chemicals from the Moschet et al. [16] dataset had been previously reported in food, soil, and drinking water. To complement the literature and database searching, and to further understand the behavior of these chemicals, we developed a multimedia model that describes chemical fate in both the indoor and outdoor environments. Implementation of this model allowed us to focus on chemicals not expected to partition into either indoor air or outdoor soil. Finally, addressing the third and fourth criteria, we conducted a literature review to ascertain whether measurable biomarkers and ADME data exist for chemicals of interest.

Targeted and non-targeted analysis

The methods and materials for the dust sample extraction and analysis are presented in detail in Moschet et al. [16]. Details on how the composite soil, food, and PCP samples were prepared and extracted are presented in the SI. Instrument and data analysis methods for the composite soil, food, and PCP samples were the same as those used for the dust samples. Briefly, samples were analyzed using gas chromatography (GC)—quadrupole time-of-flight mass spectrometry (QTOF MS) and liquid chromatography (LC)—QTOF MS, with both targeted and NTA (including suspect screening) approaches. Target chemicals included select PBDEs, organophosphate flame retardants (OPFR), phenols, polycyclic aromatic hydrocarbons (PAHs), phthalates, UV filters, fragrance components, pesticides, plasticizers, parabens, biocides, PFAS, surfactants, and skin oils. For NTA using GC-QTOF MS, the analysis was performed via spectral deconvolution followed by a library search [18]. For NTA using LC-QTOF MS, a first analysis matched observed molecular features to compounds within two Agilent Personal Compound Database and Libraries (PCDLs): Forensic Toxicology and Agilent Water Contaminants (containing about 10,000 chemicals). A second analysis enabled compound determination by use of two in silico fragmentation software tools: Agilent Molecular Structure Correlator and MetFrag [19]. Using this assortment of analytical techniques and compound identification strategies, the study samples were screened for the presence of tens-of-thousands of compounds. After manual review, 271 unique chemical features were identified in the dust samples (with thousands of additional features requiring further review). One-hundred sixty-three were confirmed with reference standards ([20], Level 1), and the remaining 108 were classified as tentative identifications ([20], Levels 2–4) [16].

Data processing and ranking

We developed a workflow to address our four criteria and an ad hoc grading system for ranking chemicals based on how well they met these criteria (Fig. 1). To establish if a chemical was ubiquitous in the sampled dust, we selected compounds with a detection frequency of ≥90% (137/271). We then restricted our focus to those chemicals with an entry in EPA's CompTox Chemicals Dashboard (hereafter, the "Dashboard") (90/137). It is possible that chemicals without a Dashboard entry could still be useful tracers. It would be difficult, however, to assess their uniqueness to dust without having Dashboard-provided information on sources, uses, and properties. Of the 90 unique compounds meeting our

initial selection criteria, 60 were Level 1 identifications (i.e., confirmed using reference standards) and 30 were Level 3 identifications ([20] SIS, column: M).

To establish if a chemical was unique to dust, we first searched the literature to see if the chemical was previously reported in indoor air, drinking water, food/beverages, or soil. For the literature search, we used SciFinder (CAS, American Chemical Society) and conducted the searches between December 2018 and March 2019. We searched for each chemical using its CAS number and the key words: "*indoor air*", "*drinking water*", "*food*", and "*soil*". Outdoor air was not included in our literature search because we assumed that the concentrations of chemicals in outdoor air are negligible when compared to chemical concentrations in indoor air. We refined our search to include only studies published in peer-reviewed journals and written in English. First, we examined article titles and abstracts for the searched key words. In most studies, the desired information was provided in the abstract. In some instances, we read the entire article to ensure the chemical was found in the medium of interest. PCPs were not considered in the literature searches because presence in a PCP would not necessarily disqualify a chemical from being a potential tracer. For example, if a PCP is meant only for adult use (e.g., shaving foam), then children would not be expected to have direct exposure, and the chemicals within that PCP could still qualify as tracers. Ultimately, manual review of PCPs as exposure sources was performed for compounds tagged as promising tracers.

In addition to searching the published literature, we searched data from available public sources (Table S1) for evidence of the presence of specific chemicals in various media. If a chemical was reported in a medium of interest, either from the literature or public sources, it was flagged with the letter "A" (indoor air), "W" (drinking water), "F" (food), and "S" (soil) (SIS, columns: AB-AE and AH-AK). One point was given each time a chemical was found absent (based on a lack of reporting) in a medium of interest (up to 4 points total for each chemical).

To further examine "uniqueness" (Fig. 1), we compared chemicals deemed "ubiquitous" in the dust samples to those measured in analyzed food, soil, and PCP samples. If a chemical was found in the analyzed samples it was flagged with the letter "F" (food), "S" (soil), and "P" (PCPs) (SIS, columns: AF-AH). When a chemical was not found in these media, it received 2 points for each medium. The higher grade in this step gave more weight to the analytical data as compared to the literature data.

Chemicals not found in a particular medium in either the public data sources or the literature may truly be absent from food, soil, indoor air, and drinking water. It is also possible, however, that specific chemicals have yet to be monitored in these media. Furthermore, mere detection of a chemical in a medium without any quantitative information should not disqualify a chemical from being a suitable tracer. If, for example, a given chemical is present in soil at a concentration 1000 times lower than in dust, then uptake from soil would be relatively insignificant.

Modeling calculations describing the fate of chemicals (due to their properties) can provide estimates of chemical partitioning for quantitative evaluation of likely tracer concentrations

in dust and other media (indoor air, soft surfaces, hard surfaces, wallboard, outdoor air, and soil). For this reason, we employed a multimedia model that describes the fate of chemicals in both the indoor and adjacent outdoor environments. In this study, our model is a residential model (not a global model) and the outdoor air and soil compartments cover only the adjacent compartments next to the modeled house. A detailed description of the model, environmental parameters (including physicochemical properties), parameterization methods, and evaluation procedures are presented in the SI (text, Fig. S1, Tables S2–S4) and the SIS (columns: N-S).

Chemicals that partition into indoor air in substantial quantities would make inhalation a contributing route of exposure in addition to dust ingestion, making that chemical an unlikely tracer. The expected presence of a chemical in indoor air was assessed by estimating the fraction of chemical partitioning into air relative to other compartments. If the amount of chemical in indoor air exceeded 75% of the total amount, then the chemical received 0.25 points; if the percentage was between 50 and 75%, the chemical received 0.5 points; if it was between 25 and 50%, the chemical received 0.75 points; and if it was between 0 and 25%, the chemical received 1 point (Fig. 1). This step prioritized the selection of chemicals that do not partition into indoor air in substantial quantities.

The points for the modeling calculations (0.25–1) were equivalent to the point values assigned from the literature/database search. For example, if a chemical was absent from indoor air in the literature/database search, it received 1 point. In a similar way, if the same chemical was predicted to be absent in indoor air based on the modeling calculations, it received 1 additional point. We decided to weigh these criteria equally since both approaches are theoretical and there were no obvious reasons to prioritize one approach over the other.

Similarly, the model was used to assess the prevalence of chemicals in soil relative to dust. For that comparison, we used the ratio of the predicted concentration of a chemical in dust to that in soil (C_{dust}/C_{soil}). Chemicals with a log (C_{dust}/C_{soil}) from −1 to 1 received 0.25 points; from 1 to 3 received 0.5 point; from 3 to 5 received 0.75 points; and from 5 to 7 received 1 point (Fig. 1). This step ensured that chemicals with a low presence in soil were prioritized over chemicals with a high presence in soil. The reason we used a concentration ratio (C_{dust}/C_{soil}) and not a percentage of chemical amount (as used for indoor air) is because soil is a much larger compartment than dust and percentages of chemical amounts would not provide useful information with regards to ingestion rates. For example, if a chemical partitions at higher quantities in soil compared to dust, the concentration of that chemical in soil could still be much lower than in dust due to size dilution and its contribution through ingestion could still be minimal compared to dust.

Finally, for criteria related to biomarkers and ADME parameters (iii and iv, respectively), we conducted a literature review to find information on biomarkers and metabolism. This step ensured that chemicals with available information regarding biomarkers and ADME parameters were prioritized over those without that information. Literature search procedures/criteria for biomarkers and ADME were similar to those used for presence in environmental media. We used SciFinder and searched each chemical using its CAS number

and the key words "*biomarker*", "*absorption*", "*distribution*", "*metabolism*"and "*excretion*". The rest of the search process was as previously described. Chemicals with a known measurable biomarker received 1 point. Chemicals for which ADME parameter information was available also received 1 point. These criteria were weighted lower than others (1 vs. 2 points for analytical data) because absence of information should not disqualify a chemical from being a potential tracer (Fig. 1). For many chemicals, biomarker and ADME studies have simply not been conducted.

Multimedia modeling

The model used to evaluate partitioning of candidate tracers was a steady-state, non-equilibrium model of chemical partitioning in both the indoor and outdoor residential environments. The model was a modified version of the model developed by Webster et al. [21]. In our version, dust is a distinct compartment and the model also includes outdoor air and soil. The outdoor compartments are outdoor air and soil adjacent to the house as opposed to global/regional air and soil compartments. The model, shown schematically in Fig. 2, was built on the fugacity approach introduced by Mackay [22] and first applied to the indoor environment by Bennett and Furtaw [23]. Fugacity, f (Pa), is directly related to concentration, C (mol), and can be described as the tendency of a chemical to leave a certain compartment or the partial pressure of a chemical in a certain compartment. Fugacity is related to concentration through the fugacity capacity, Z (mol/m^3 Pa) as $C = fZ$. Fugacity capacity is defined as the capacity of a compartment to retain a chemical based on the physicochemical properties of the chemical and the properties of the compartment.

For our study, we built a steady-state non-equilibrium model (level 3). The main assumption of a level 3 model is that the chemicals are emitted at constant rates and not always at equilibrium. Since we are dealing with a diverse set of chemicals that do not have well-characterized emission routes, we assumed that all emissions occur first in indoor air, followed by dust and other compartments. Even though this may not be true for all chemicals, emitting the chemicals first to indoor air gives us the worst-case scenario for presence in indoor air. This is important because we want to ensure that chemicals we use as tracers for dust ingestion are not capturing other exposure routes, such as inhalation. It is important to note that the indoor air compartment contains both gas and particulate phases. A similar approach on emission scenarios has been previously presented by Liagkouridis et al. [24].

For the model calibration and evaluation, we used two datasets: Rudel et al. [25] and Newton et al. [26]. The Rudel et al. [25] dataset contains measurements of 88 diverse chemicals found in dust and air and the Newton et al. [26] dataset contains measurements for brominated flame retardants (n = 14) found in indoor and outdoor air, dust, and soil. The physicochemical properties of the chemicals used in the modeling calculations were the partition ratios between octanol and water (K_{OW}) and air and water (K_{AW}) and the half-lives of the chemicals in air (Th_A) and soil (Th_S). K_{OW} and K_{AW} were obtained from the OPEn structure—activity/property Relationship App (OPERA) through EPA's CompTox Chemicals Dashboard [27], and Th_A and Th_S were obtained from EPA's EpiSuite [28].

RESULTS

Of the 271 chemical features identified in Moschet et al. [16], 137 had a frequency ≥ 90% (Fig. 1). We obtained predicted physicochemical properties for 90 of these proposed structures via searches on the Dashboard. These 90 chemicals, along with the associated information, category scores, and final scores are presented in the SIS. Of the 90 chemicals, 60 were confirmed using chemical standards and 30 were tentatively identified by in silico predicted MS/MS spectra or plausible fragments.

Based on our searches of the literature and public data sources (Table S1), we found 67 chemicals (out of 90) reported in food, 55 in soil, 52 in drinking water, and 45 in indoor air (Fig. 1, 2 and SIS, columns: AB-AE for database and AI-AP for literature, AW for point assignment).

Based on laboratory analyses, 23 chemicals were measured in PCPs, 17 chemicals were measured in food, and 9 chemicals were measured in soil (Fig. 1). When a chemical was not measured in PCPs, food, or soil (SIS columns: AF-AH) it received 2 points for each medium. The increased weight at this stage prioritized the analytical data over the literature review information.

Our modeling calculations indicated that, for most chemicals, walls and surfaces were expected to be the main sinks in the indoor environment (Fig. 3a, SIS columns T-Z). Even though partitioning in dust and soil occurred at substantially smaller quantities (Fig. 3b), these compartments are of greater interest due to their function as exposure media. Calculations for presence of chemicals in indoor air (SIS column V) showed that 87 of the 90 chemicals are expected to partition at low quantities (0–25%, 1 point, Fig. 1) (Fig. 3c). Zero chemicals are expected to partition at medium-low quantities (25–50%, 0.75 points), two are expected to partition at medium-high quantities (50–75%, 0.5 points), and one at high quantities (75–100%, 0.25 points). This is reasonable since our list contains primarily semi-volatile organic compounds. Calculations for presence in dust relative to soil showed that 12 chemicals are expected to partition at low concentrations in dust relative to soil (log C_{dust}/C_{soil} = −1 to 0.5; 0.25 points), 25 chemicals at medium-low (log C_{dust}/C_{soil} = 0.5 to 2; 0.5 points), 28 at medium-high (log C_{dust}/C_{soil} = 2 to 3.5; 0.75 points), and 25 at high (log C_{dust}/C_{soil} = 3.5–5) concentrations in dust (Fig. 1 and SIS, column AA).

During our literature search, biomarker information was found for 50 chemicals and ADME information was found for 48 chemicals (SIS, columns: AS-AT). It should be noted that, for the majority of the chemicals in the dataset, there are no available human ADME studies and we often relied on in vitro and in vivo studies. For ADME parameters, often there are available studies on metabolism and excretion, but no studies on absorption and distribution. If during our search we found information on metabolism and excretion, or only one of the two, but not on absorption or distribution, we marked that chemical as having information on ADME parameters.

After compiling all information, nine chemicals with a score ≥12 were grouped as “highly likely tracers”, 29 chemicals with a score <12 and ≥10 were grouped as “likely tracers”, 29 chemicals with a score <10 and ≥8 were grouped as “unlikely tracers”, and 23 chemicals

with a score <8 were grouped as “very unlikely tracers” (SIS, column BA). Examples of chemicals from each group were (i) 1,3-diphenylguanidine (highly likely tracer), (ii) fipronil (likely tracer), (iii) triclosan (unlikely tracer), and (iv) linoleic acid (highly unlikely tracer). For 5 of the 9 chemicals classified as “highly likely tracers”, we found some information about their biomarkers and ADME parameters. These chemicals were 1,3-diphenylguanidine, leucine, piperine, 6:2/8:2 fluorotelomer phosphate diester, and 6:2 fluorotelomer phosphate diester (SIS, columns: AS-AT, BA). The other chemicals identified as “highly likely tracers” were 1-hydroperfluoroheptane, salnacedin, palmitoylethanolamide, and pentaethylene glycol; we were not able to locate any biomarker and ADME information for these chemicals.

Using our workflow and ad hoc grading system, we omitted 85 chemicals from further consideration as potential tracers. These chemicals were classified by Moschet et al. [16] as surfactants (n = 23), cosmetics (n = 15), natural products (n = 12), plasticizers (n = 10), flame retardants (n = 8), pesticides (n = 5), polyfluorinated compounds (n = 5), human metabolites (n = 3), industrial chemicals (n = 2), and unknowns (n = 2). Notwithstanding human metabolites (which are likely not suitable as tracers for reasons described below) surfactants had the highest overall score (mean = 10.7), with 19 out of 23 compounds having a score of 10 or higher (Fig. S2), making them at least “likely tracers”. Most of these chemicals were seldom found in other media (based on the literature search, database search, and laboratory analysis). Yet, only one compound was a confirmed identification, with the remaining compounds labeled as tentative identifications (SIS). With eventual confirmation using standards, and additional data on available biomarkers and ADME, it is possible that individual surfactants may meet the criteria for tracer selection.

Not surprisingly, the lowest final scores were observed for flame retardants (mean = 8.7), cosmetics (mean = 8.2), and natural products (mean = 6.9). Despite having biomarker and ADME data (and thus elevated final scores), natural product chemicals were frequently found in multiple media as part of the laboratory analysis and the literature search (SIS). Compared to natural products, consumer product chemicals were found less often in food as part of the laboratory analysis. These chemicals were, however, frequently found in PCPs as part of the lab analysis, and in all media as part of the literature search. Flame retardant chemicals were seldom found in media based on the database queries and lab analyses. Yet, each flame retardant chemical was reported in the literature as being previously found in air, drinking water, food, and soil. Taken together, these results clearly show the value of using independent data streams to vet chemicals for further consideration as useful tracers.

DISCUSSION

Building the workflow

Previous studies of children’s dust ingestion have failed to distinguish between contributions from dust and soil. Considering that both dust and soil are important contributors to children’s chemical exposures, there is a need to develop methods to distinguish between the two sources. In light of this need, we developed a multifaceted workflow to identify chemicals that can be used as potential tracers to estimate children’s dust ingestion. Our workflow is comprised of laboratory analyses, literature reviews, and multimedia modeling,

ensuring that prioritization is based on a weight of evidence, using independent data streams. Our workflow utilizes a holistic assessment that integrates both qualitative (NTA and literature/database reviews) and quantitative (multimedia modeling) characteristics. The workflow is designed to be applicable to any dataset. In this study, we applied the workflow to the Moschet et al. [16] dataset, and discuss our findings, limitations, and recommendations.

Workflow application

Results from the Moschet et al. [16] dataset suggest that house dust contains organic chemicals that are ubiquitous across samples collected in California, and that a subset of these ubiquitous compounds are not likely to appear (in measurable amounts) in other media that children contact (SIS). Initially, we identified five chemicals that satisfied all four selection criteria: 1,3-diphenylguanidine, leucine, piperine, 6:2/8:2 fluorotelomer phosphate diester, and 6:2 fluorotelomer phosphate diester (SIS). Of these, 1,3-diphenylguanidine and leucine had the highest scores (score = 13), suggesting they are the most promising tracers. For each candidate tracer, we searched the literature for their primary uses and occurrence in consumer products. Additionally, we evaluated their occurrence in consumer products via the Dashboard [27], where we searched for each chemical and looked for potential uses under the tabs “Exposure” and “Product and use categories”. Even though these chemicals scored highly using our ad hoc grading system, and therefore appeared to satisfy our selection criteria, further evidence from our final in-depth review suggests they are not suitable tracers for estimating dust ingestion rates.

1,3-diphenylguanidine is a synthetic chemical used in the vulcanization of rubber; it is therefore commonly linked to rubber products. It is found in shoe soles and tires [29], synthetic rubber gloves used by healthcare workers, and goalkeeper gloves [30]. It is known to cause dermatitis upon skin contact [31, 32]. At the time of our literature search, 1,3-diphenylguanidine had not been reported in indoor air, food, or soil. We found one study from China [33] reporting that 1,3-diphenylguanidine leached from high density polyethylene materials used in drinking water pipes; it is unclear if that exact material is used in the United States. 1,3-diphenylguanidine was not found in the food, soil, or PCP samples from the analytical part of our study, suggesting minimal contribution from these media towards aggregate exposure. The analytical data are in good agreement with our modeling calculations, which estimated concentrations of 1,3-diphenylguanidine in soil near homes to be about 4 log units lower than concentrations in dust (SIS). While these findings reinforce our belief that exposure to 1,3-diphenylguanidine through soil ingestion is not expected to be a substantial pathway compared to that of dust ingestion, we have a limited understanding of total exposure potential for 1,3-diphenylguanidine in the outdoor environment. For example, soil near driveways or roadways may contain 1,3-diphenylguanidine coming from car tires. Depending on the air concentrations of 1,3-diphenylguanidine near driveways/roadways, the inhalation pathway may potentially contribute to the overall 1,3-diphenylguanidine exposure for commuters. Since this is something that remains to be confirmed through future research, 1,3-diphenylguanidine cannot, at this time, be considered a suitable tracer.

Leucine, despite receiving a high score, would not be a suitable tracer, as it is an endogenous chemical in humans. In any sort of observational human exposure measurement study, it would be impossible to distinguish between the fraction coming from dust ingestion and the fraction produced internally. This observation suggests that a filter step in the workflow may be needed to address compounds internally produced in humans. Indeed, five compounds (out of 90) are considered here as possible tracers, despite a general lack of suitability based on their origin (SIS, column H). Future applications of this workflow should consider and address endogenous compounds early in the workflow by matching compound identifiers against entries in well-known human metabolite libraries (e.g., the Human Metabolome Database) [34,35,36,37].

Piperine is a naturally occurring component of black pepper, previously found to be common in house dust [17, 38]. In addition to being present in foods, piperine is used as a small animal repellent [39] and a pharmaceutical enhancer [40, 41]. According to our findings, the presence of piperine in a child's diet may be difficult to predict. Specifically, despite its origins in black pepper, piperine was not measured in food samples in the laboratory component of our study. We note that the analyzed food samples were a composite of commonly eaten foods and not an extensive compilation of everything children eat (e.g., foods prepared at home and foods prepared and eaten outside the home). Thus, we are not able to rule out the dietary pathway as a means of children's exposure to piperine. Furthermore, piperine may have been diluted in the composite sample, the composite sample may have been missing foods eaten by the children which contained piperine, or the method detection limits may have rendered analysis of the piperine difficult. The laboratory component of our study further showed no piperine in soil samples; this is in good agreement with our modeling calculations that estimate piperine concentrations in soil to be 3.3 log units lower than in dust. These results support the notion that the soil ingestion pathway contributes little to aggregate piperine exposure. While we may be able to consider soil an unlikely exposure source for piperine, the fact that it is most likely found in some children's food renders it an unsuitable choice as a tracer.

6:2/8:2 Fluorotelomer phosphate diester (6:2/8:2 diPAP) and 6:2 fluorotelomer phosphate diester (6:2 diPAP) received 12.25 and 12 points, respectively, and ranked fourth and fifth on the list of potentially suitable tracers found in dust. Both chemicals belong to the larger group of PFAS. They are used to grease-proof food contact paper and have been previously reported in food [42, 43]. 6:2/8:2 DiPAP and 6:2 diPAP have been measured in dust samples from Canada [44] and in human serum samples from the United States, Canada, and Germany [42, 45], indicating the ubiquitous presence of these compounds in the environment. Only 6:2 diPAP has been reported in soil [46]. Interestingly, neither of these chemicals were detected in children's food, soil, or PCP samples in the present study. However, our dataset may have been too small to detect these PFAS chemicals. Our modeling calculations suggest that the estimated concentrations of 6:2/8:2 diPAP in soil are similar to those of dust, but that the estimated concentrations of 6:2 diPAP in soil were 3.9 log units lower than those in dust. Considering the somewhat conflicting information stemming from our laboratory, literature, and modeling resources, additional work may be needed to clarify whether these two chemicals have potential utility as tracers before considering them further.

Finding a potential tracer that met all evaluation criteria was challenging because dust is comprised of fine particles of solid matter (e.g., soil, sediment, plant pollen, human and animal hairs, human skin cells, food particles, and anything else found in the local [indoor and or outdoor] environment) and these particles may contain myriad chemicals. Specifically, dust may contain: pesticides used in the indoor environment, on agricultural commodities, or as pet treatments; PCPs adhered to sloughed skin; food residues (e.g., from cooking, crumbs, coffee grounds) with associated chemicals; and compounds used for food packaging and textile coatings. In short, much of what is found in dust gets there through other sources in the home, making it difficult to identify a candidate compound that meets all criteria to be considered a suitable tracer.

Workflow limitations

Our workflow combined laboratory, literature, and modeling resources to attempt to identify chemicals which would be suitable as tracers. We used an ad hoc grading system based on expert consideration and subjective cut points. If we had adjusted the range of cut points for each category, the number of “highly likely tracers” and “likely tracers” would have increased or decreased accordingly. Larger publicly available datasets and evaluations may be needed to determine the most appropriate cut points for future applications. Additional publicly available datasets would also provide more data and information to evaluate the workflow. In performing these additional evaluations, we may discover criteria that should be incorporated into the workflow. For example, as described previously, the use of specific filters could shift focus away from endogenous compounds that are not well-suited as tracers.

In addition to refining the workflow via additional evaluation, any chemical identified as a potential tracer requires further vetting. For the compounds we identified, there is a need to examine different datasets from other geographic locations to assess the tracers’ spatial and temporal variability. The application of our workflow on the Moschet et al. [16] dataset is a first step in this direction, but we acknowledge that dust samples collected from California may not be representative of other geographical locations. Dust chemical composition may vary from place to place depending on chemical use in the home and on construction materials used within buildings. Also, dust chemical composition may vary over time as chemical usage changes and consumer products are introduced or replaced by newer alternatives. Additional analytical research to confirm the absence of potential tracers in foods and beverages is also recommended. In this proof-of-concept work, we did not use specific search terms for “beverages” because we assumed the key word “food” would adequately cover a variety of dietary sources, including beverages. We also did not search for “milk” or “breast milk”. Future applications of the workflow should include a more exhaustive literature component with specific key words. The food samples collected in California may not be representative of other areas, as dietary habits can differ from place to place based on a variety of factors (e.g., availability, preferences, customs). Collection and analysis of children’s food from various locations will help shed light on this issue and ensure that dietary ingestion is not a measurable exposure pathway for potential tracers. Even though we accounted for dermal exposure through the analysis of PCPs, there may be instances where dermal exposure may contribute to non-dietary ingestion. Future

adaptations of the workflow should consider the dermal/non-dietary ingestion relationship when choosing a potential tracer. Finally, analysis of food packaging materials will be necessary to filter any potential tracers that come in direct contact with food, thus affecting dietary exposures.

CONCLUSIONS

This study demonstrates how multiple data streams can be used to identify compounds that may be suitable as tracers for calculating children's dust ingestion rates. Before any chemical can be deemed a suitable tracer, it will need further vetting, especially if used in an observational human exposure measurement study. Measurements of any chemicals in house dust and blood or urine, when carefully interpreted with ADME information, may ultimately allow the calculation of dust ingestion rates. Measurements of the same chemicals in food and soil will be necessary to ensure that intake from diet and soil are not contributing to aggregate exposure. The current study acts as a critical stepping stone for the design of a workflow to select candidate tracers. Based on the results of this initial pilot study, no individual compounds were identified as suitable tracers for calculating dust ingestion rates. Future work must therefore consider larger datasets, generated from broader measurement studies and literature searches, as well as refinements to selection criteria, to identify robust and defensible tracer compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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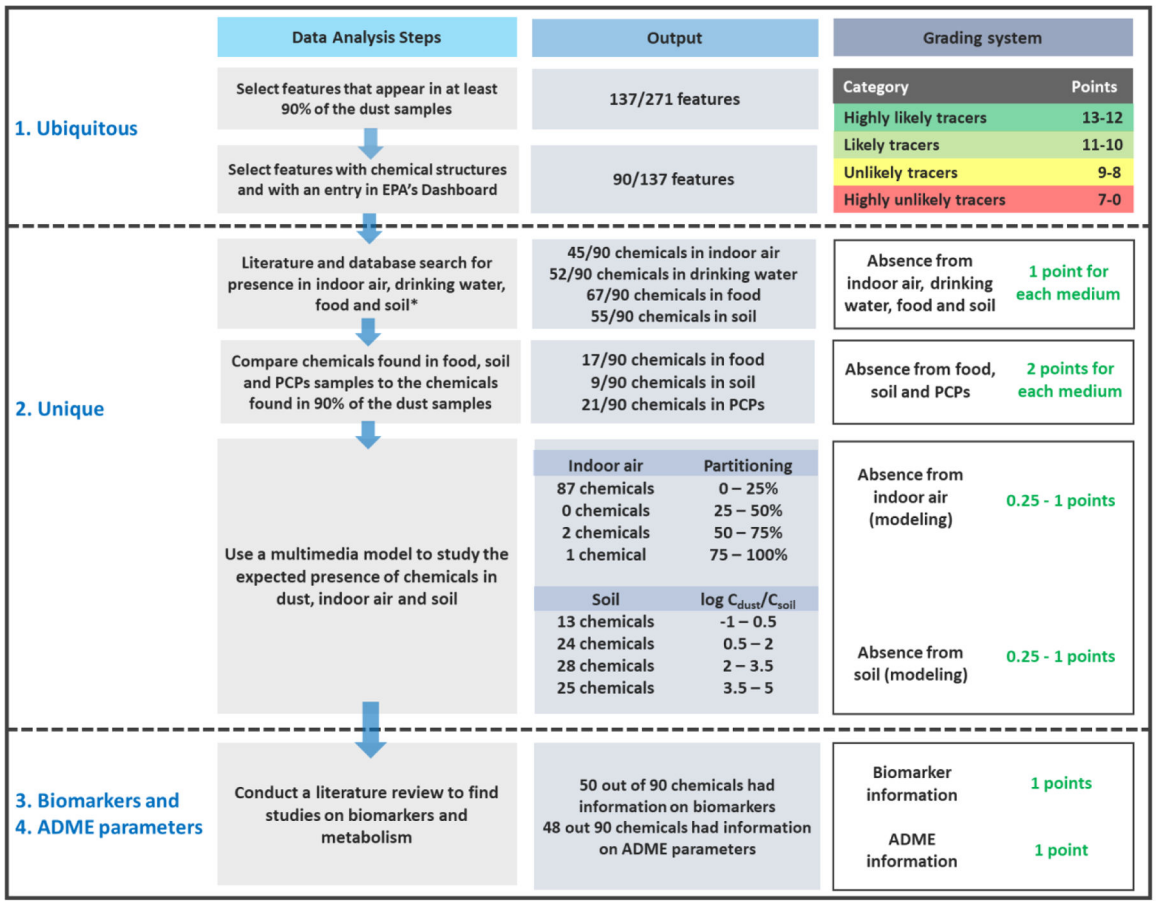

Figure 1:
Workflow for addressing the four criteria with outputs and grading system for each step.

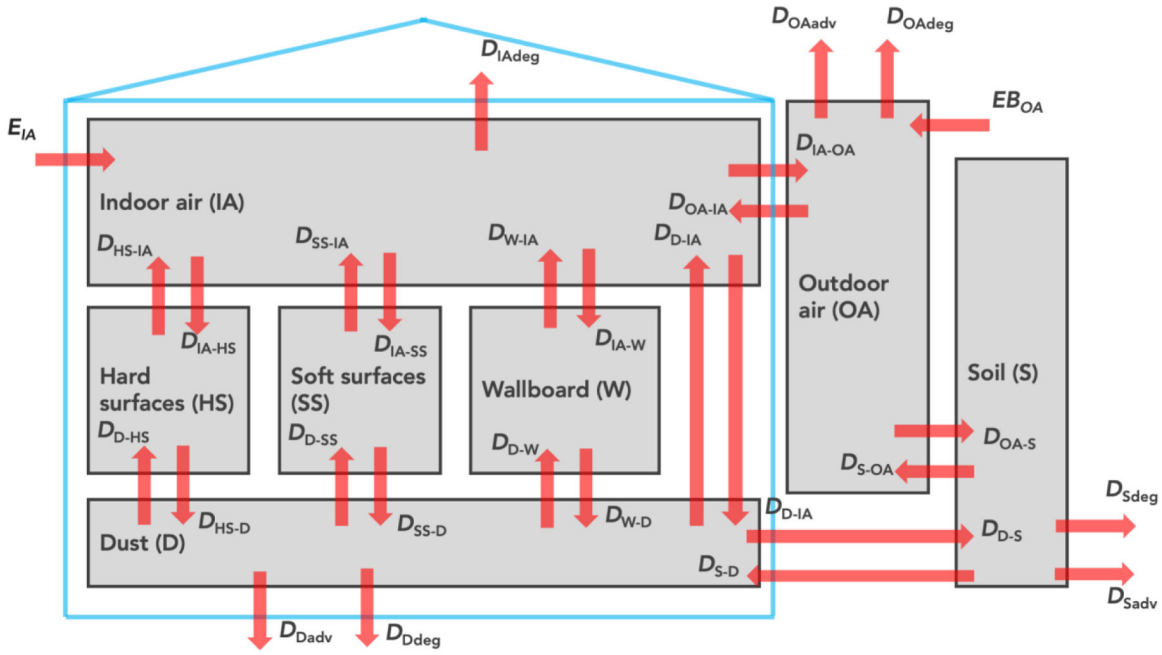

Figure 2:

Model diagram depicting the various compartments in the indoor and outdoor environment. The arrows show the fugacity rate descriptors for the intra-compartmental fluxes and the irreversible losses due to degradation (deg) and advection (adv). The fugacity rate descriptors between compartments are represented by the letter D and the initials for the compartments that the chemicals are moving from and to. For example, the fugacity rate descriptor from indoor air to dust is presented as $D_{\text{IA-D}}$ and the fugacity rate descriptor for degradation in dust is presented as D_{Ddeg}. The emissions are represented by the letter E and the initials of the compartment they occur in. In this model, the primary emissions occur in indoor air (E_{IA}) and background emissions occur in outdoor air (E_{OA}). Note that both the indoor and outdoor air compartments consist of both gas phases and particulate phases. Not to scale.

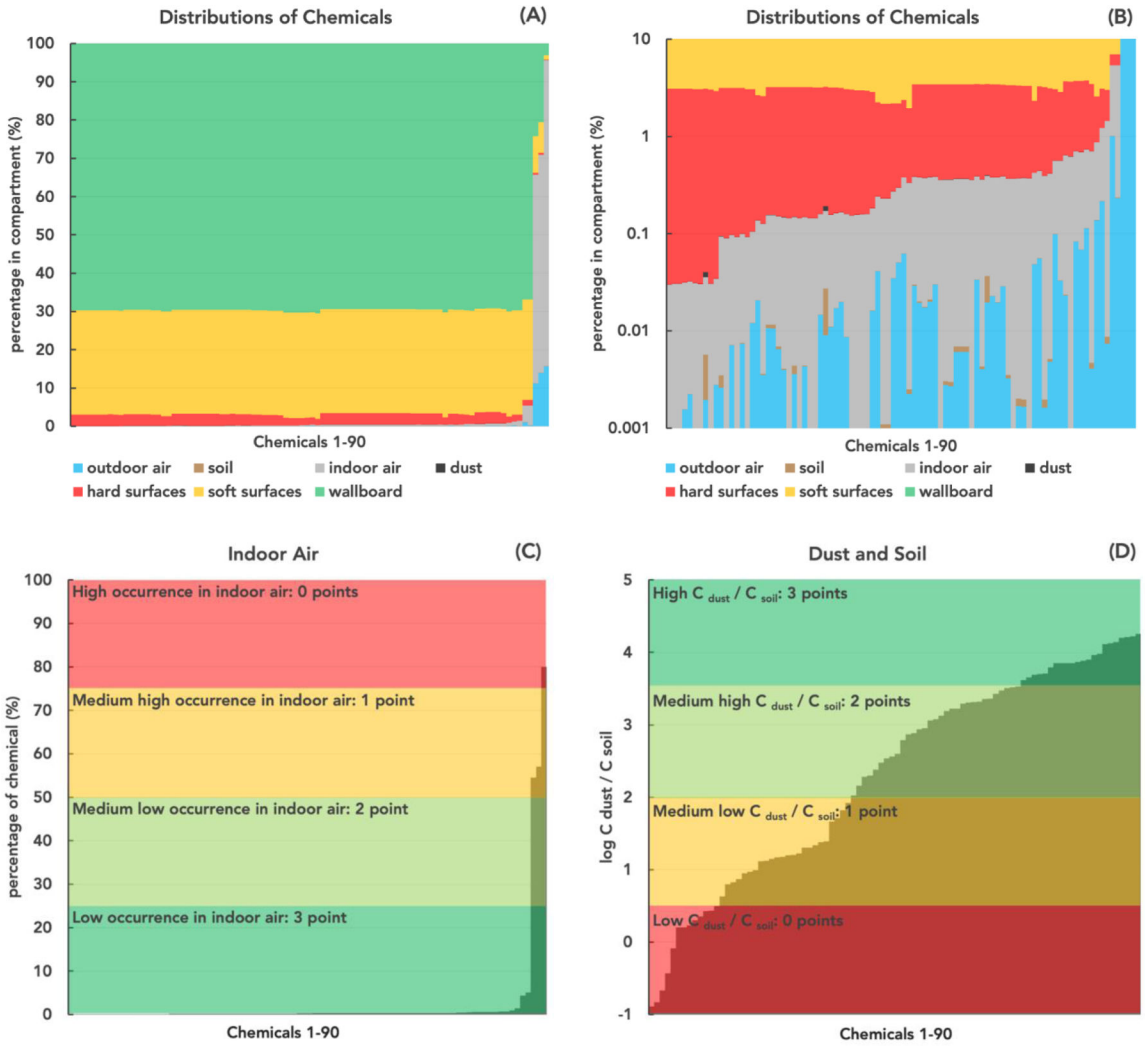

Figure 3:

Predicted distributions for all chemicals (panel A in natural space and panel B in log space and zoomed to <10%) in the indoor (grey = indoor air, black = dust, red = hard surfaces, yellow = soft surfaces, green = wallboard) and outdoor compartments (blue = outdoor air, brown = soil) ranked by amount present in indoor air from lowest (left) to highest (right). Each bar represents one chemical. Panel C shows the percentages of chemicals in indoor air, with chemicals ordered on the x-axis from lowest (left) to highest (right). Panel D shows the ratios between the concentrations of chemicals in dust and the concentrations of chemicals in soil (C_{dust} / C_{soil}), with chemicals ordered on the x-axis based on their presence in soil.