Environmental Science & Technology

Article

Cite This: Environ. Sci. Technol. XXXX, XXX, XXX−XXX

pubs.acs.org/est

Human Indoor Exposome of Chemicals in Dust and Risk Prioritization Using EPA's ToxCast Database

Ting Dong,[†,‡,∥] Yingdan Zhang,[‡,∥] Shenglan Jia,[§] Hongtao Shang,[§] Wenjuan Fang,[§] Da Chen,[*,†] and Mingliang Fang[*,‡,§,⊥]

[†]School of Environment, Jinan University, Guangdong Guangzhou, P. R. China 511443

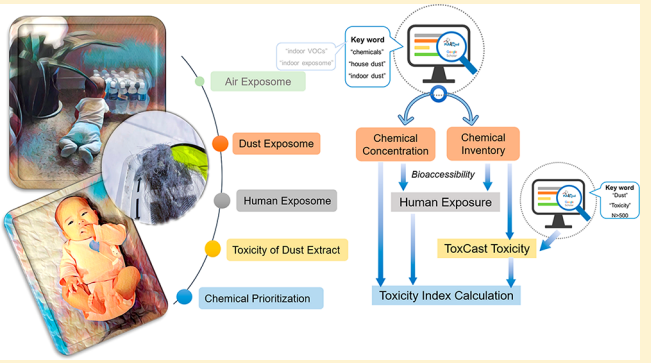
[‡]School of Civil and Environmental Engineering, Nanyang Technological University, Singapore, Singapore 639798

[§]Residues and Resource Reclamation Centre, Nanyang Environment & Water Research Institute, Nanyang Technological University, Singapore, Singapore 637141

[⊥]Singapore Phenome Center, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore 636921

Supporting Information

ABSTRACT: Humans spend most of their time indoors and thus have long-term exposure to chemicals. Dust is a sink for most indoor chemicals, and its ingestion is an important pathway for chemical uptake. Therefore, the chemical atlas from dust is an ideal environmental sample to investigate the indoor exposome and associated risk. In this study, we aimed to establish an indoor exposome database through comprehensive data mining on the occurrence of identified compounds in dust, and we prioritize chemicals of health concern. Through an extensive literature review (2849 articles), 355 chemicals and their concentrations were documented and analyzed for human exposure. Together with 81 compounds without concentration and 75 volatile organic compounds, we have established an indoor exposome database with 511 chemicals. Sixteen toxicological end points were selected for toxicity prioritization. Toxic equivalency factor (TEF)-based toxicity, calculated from EPA's ToxCast database, revealed a comprehensive atlas of the chemicals that had a primary contribution. Many of the prioritized compounds are currently neglected or are not actively studied. Overall, this investigation provides one of the most comprehensive analyses on chemical occurrence in indoor dust and prioritizes their chemical toxicity. Our findings can be used as a database for future exposome studies of the indoor environment and provide guidance for indoor risk assessments.



INTRODUCTION

The human exposome and related health effects have been a heavily researched topic in environmental studies in recent years. Chemical exposure, which is part of the overall human exposome, is challenging to study due to the extensive chemical inventory and their different exposure levels.[1] Taking the indoor environment as an example, numerous sources of chemical emissions in the indoor environment have been recognized, including construction/decoration material, furniture, utensils, personal care products, and human behaviors. Indoor dust has been increasingly examined as a critical environmental matrix for the characterization of indoor environmental quality, human indoor chemical exposure, and novel chemical occurrence, benefiting from its easy sampling method and accessibility.[2,3] Many semivolatile organic compounds (SVOCs), such as phthalates and flame retardants, are not chemically bound to their commercial products, and they may migrate over time, resulting in ubiquitous and abundant accumulation in dust. For example, phthalates, flame retardants, and plasticizers have been detected in dust at concentrations as high as mg/g dust. Therefore, indoor dust represents a pool of hundreds or thousands of chemicals to which humans are exposed on a daily basis.

Humans, especially infants and young children, spend the majority of their time (>95%) indoors where they are chronically exposed to the chemicals present in dust due to their increased hand to mouth activity, dermal contact, and crawling behavior.[4] The United States Environmental Protection Agency (EPA) estimates that children ingest 50 to 100 mg of dust per day indoors, suggesting a high chance of exposure to chemicals associated with dust particles. Dust ingestion has also been confirmed as a very important chemical uptake pathway in many studies. For example, serum

Received: February 8, 2019
Revised: May 10, 2019
Accepted: May 13, 2019
Published: May 13, 2019

DOI: 10.1021/acs.est.9b00280
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

concentrations of polybrominated diphenyl ethers (PBDEs) of toddlers and adults were significantly correlated with those detected in house dust.[5,6] Therefore, house dust is an environmentally relevant matrix for the investigation of chemical exposure and its associated risks in the indoor environment.

Both targeted and untargeted analysis of environmental chemicals in dust have been extensively investigated in recent decades. Targeted analysis has the advantages of high sensitivity but has reduced compound coverage, whereas untargeted analysis is challenged by lower sensitivity and extensive work for chemical identification and characterization. A simple search with the keywords "chemical" and "dust", "house dust", or "indoor dust" in search engines, including PubMed and Web of Science, resulted in over 5000 publications. The concepts of "indoor exposome" or "dust exposome" representing the summation of one's lifetime indoor exposure to chemicals or microbes, have been introduced in several recent reviews with great significance in characterizing human indoor exposure.[1,7] The meta-analysis of indoor chemical levels in dust has been nicely investigated in a few previous studies, showing ubiquitous indoor exposure to many legacy or emerging contaminants.[2,3,8] However, most of those studies were conducted either in the U.S. only,[8] or studying a few targeted compounds.[2] There is a global monitoring boom of environmental chemicals in the past decade and many known or novel compounds have been identified due to the advance of analytical techniques. To provide a more complete database for human indoor exposome research, it is of great scientific interest to further conduct a comprehensive review on the occurrence and levels of all identified compounds in indoor dust. More importantly, additional relevance is to associate chemical exposure in indoor environments with toxicity and to prioritize chemicals with the highest health concern. EPA's ToxCast has previously been used to prioritize approximately 1800 pure chemicals based on activity assays with more than 700 high-throughput end points.[9,10] On the basis of the human indoor exposome and the activities of the compounds from ToxCast database, we can bridge the gap in the risk assessment of prioritized toxic compounds at environmentally relevant levels.

In summary, the aims of the current study included the following. First, we conducted an extensive literature search on the occurrence and levels of both organic and inorganic chemicals in the indoor dust worldwide. Second, we estimated human exposure to these chemicals by considering dust ingestion, dermal contact, and bioaccessibility. Third, the concentrations of those compounds were combined with ToxCast in vitro bioassays to prioritize the chemicals in terms of toxicity, using different end points. Overall, we believe that this study is the first to provide useful information to characterize the "exposome" of house dust, and the results can be used as guidance for future exposure studies and indoor risk assessments.

METHODS

Chemical Search. To investigate the occurrence and levels of organic and inorganic chemicals in house dust, we conducted an extensive literature search on in-house dust chemicals worldwide. The search criteria and workflow are described in detail in Text S1 in the Supporting Information (SI). Briefly, we only included the studies using mass spectrometry based analytical method during our manual screening of the possible literature hits. We also excluded the samples from polluted areas (e.g., e-waste and production industry) or special environment area (e.g., agricultural pesticide spraying region). The chemicals in the search results were assigned to one of the following categories: (1) environmental phenols (n = 16 chemicals plus 2 with unknown concentrations), (2) flame retardants (n = 62 plus 1 unknown), (3) fungicides (n = 13 plus 2 unknown), (4) herbicides (n = 7 plus 1 unknown), (5) pesticides/insecticides (n = 34 plus 19 unknown), (6) metals (n = 12), (7) musks (n = 12), (8) polychlorinated biphenyls (PCBs) (n = 21), (9) polycyclic aromatic hydrocarbons (PAHs) (n = 31), (10) dioxins (n = 30), (11) personal care products (n = 17 plus 10 unknown), (12) endogenous compounds (n = 4 plus 6 unknown), (13) perfluorinated compounds (n = 20), (14) plasticizers (n = 27 plus 4 unknown), (15) polycyclic aromatic compound (PACs) (n = 23), (16) siloxanes (n = 15), (17) food additives (n = 5 unknown), (18) azo dyes (n = 8 unknown), (19) volatile organic compounds (VOC, n = 75) and (20) others (n = 11 plus 23 unknown). The final list after manual screening resulted in 2849 publications. The median concentration, standard deviation, sample size, and study location (country or region) were extracted from the literature. The concentration of each compound was calculated based on the sample size weighted median concentrations. The concentration variation was estimated either by inter- or intra (if there is only one study) -standard deviations and standard errors weighted by sample size from the literature. The final list is presented in the SI Table S1, including chemical name, CAS registry number, formula, exact mass, weighted median concentration, weighted standard deviation (error), study numbers, and category.

Human Dust Exposure Model. The human dust exposure assessment was evaluated, mainly considering nondietary dust ingestion and dermal adsorption. The human daily exposure to each documented chemical in the dust was calculated by the equations reported in the Agency for Toxic Substances and Disease Registry's Public Health Assessment Guidance Manual.[11] The exposure factor distributions (e.g., dust ingestion rate and body weight) referred to the U.S. EPA's Exposure Factors Handbook for adults.[12] Exposure uncertainty and variability were simulated by Monte Carlo from assigned exposure factors and measured contaminant concentrations.[13] The input parameters were randomly drawn from corresponding probability distributions. Thereafter, Monte Carlo simulations were performed 100 000 times to calculate the daily dose (μg/kg/day) and estimate exposure (μg/day) via nondietary dust ingestion and dermal absorption. A further description of the dose calculations and Monte Carlo input parameters is summarized in Text S2 in the SI.

The bioaccessibility of pollutants was considered when predicting the internal exposure concentrations of indoor dust chemicals. We originally adopted a previously published bioaccessibility empirical model[14,15] to predict human absorption that included the parameters of bioaccessibility,[16] and we found large discrepancies with some experimental data (not shown). We finally used a bioaccessibility model from our previously published experimental data,[17] and the log K_{ow} value was used to predict the bioaccessibility of each chemical, which was estimated using EPI suite (EPIWEB 4.1). For chemicals with log K_{ow} values higher than 8, bioaccessibility was assigned as 0.2; for chemicals with log K_{ow} values lower than 5, bioaccessibility was given as 0.8. For chemicals with log K_{ow}

DOI: 10.1021/acs.est.9b00280
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

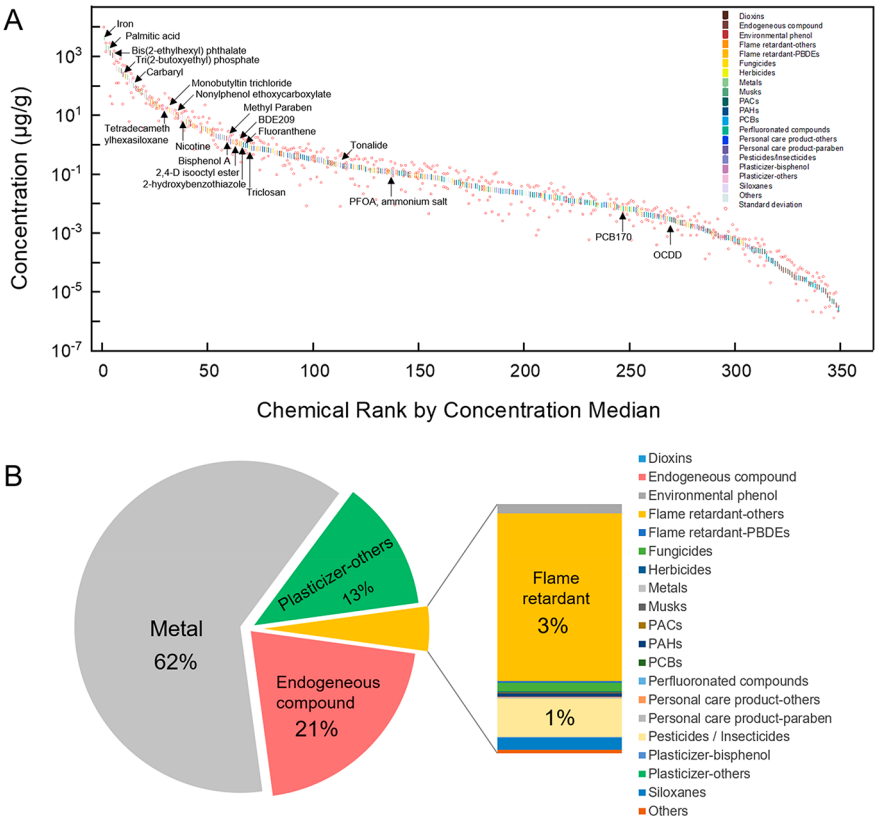


Figure 1. Occurrence and levels of indoor dust chemicals. (A) The curve represents the cumulative distribution of chemical concentrations from all chemical categories with available concentrations (total, n = 355; endogenous compounds, n = 4; environmental phenols, n = 16; flame retardants-PBDEs, n = 14; flame retardants-others, n = 48; fungicides, n = 13; herbicides, n = 7; pesticides/insecticides, n = 34; inorganic metals, n = 12; musks, n = 12; PAHs, n = 31; PCBs, n = 21; dioxins, n = 30; perfluorinated compounds, n = 20; personal care product-parabens, n = 6; personal care product-others, n = 11; plasticizers-bisphenol, n = 9; plasticizers-others, n = 18; PACs, n = 23; siloxanes, n = 15; others, n = 11). The chemical with the highest concentration in each chemical category is labeled. (B) Contribution of each chemical category to the total indoor dust chemicals, by percent.

values between 5 and 8, bioaccessibility was estimated by linear normalization based on the following equation:

$$B_a = a + \frac{(b - a) \times (8 - \log K_{ow})}{(8 - 5)}$$

where B_a is the normalized bioaccessibility in humans, and a and b are constants that were assigned as 0.2 and 0.8 in this study. For heavy metals without log K_{ow} values, their bioaccessibility was estimated based on values from previous studies.[18,19]

ToxCast Search and Toxicity Index Calculation. The EPA iCSS ToxCast Dashboard was employed to evaluate the endocrine-related activity and other toxicities of house dust chemicals. In vitro and in vivo toxicity tests using indoor dust, as well as their component compounds, was extensively summarized (Text S3 in SI) from previous studies. On the basis of these reviews, the targeted assays covering the aryl hydrocarbon receptor (AhR), androgen receptor (AR), estrogen receptor alpha (ERα), nuclear factor of kappa light polypeptide gene enhancer in B cells (NFκB1), and peroxisome proliferator-activated receptor gamma (PPARγ) were chosen for further study. The toxicity potential or prioritization of each chemical was represented as a toxic equivalency (TEQ), which was estimated by multiplying its human exposure amount (weighted median concentration) by the toxic equivalency factor (TEF). A chemical's TEF was calculated from its respective AC_{50} in relation to the most potent positive control that was retrieved from the EPA iCSS ToxCast Dashboard. The chemical with the minimal AC_{50} is considered as a positive control, and its TEF is referred to as 1. The TEQ values of each chemical and its percentage in the total TEQ were estimated based on the below equations:

$$TEF_i = AC_{50min} \div AC_{50i}$$

$$TEQ_i = TEF_i \times \text{weighted median concentration}_i$$

and

$$TEQ_i\% = TEQ_i \div TEQ_{total} \times 100\%$$

RESULTS

Chemical List, Concentration, and Variability in Dust. The occurrence and levels of indoor dust chemicals were investigated using extensive literature review. In total, 511 chemicals were prioritized for their occurrence in house dust, among which concentrations were documented for 355 chemicals (SI Table S1−S3). The documented indoor dust chemicals were estimated for their concentrations in dust by calculated the weighted median concentration from each study. In general, the concentrations of the documented indoor dust chemicals ranged from 2.6 × 10^{-6} to 4.3 × 10^3 μg/g—a staggering 9 orders of magnitude (Figure 1A). For most chemical categories, the range of concentrations was 4 to 5 orders of magnitude and was mainly centered between 5 ×

DOI: 10.1021/acs.est.9b00280
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

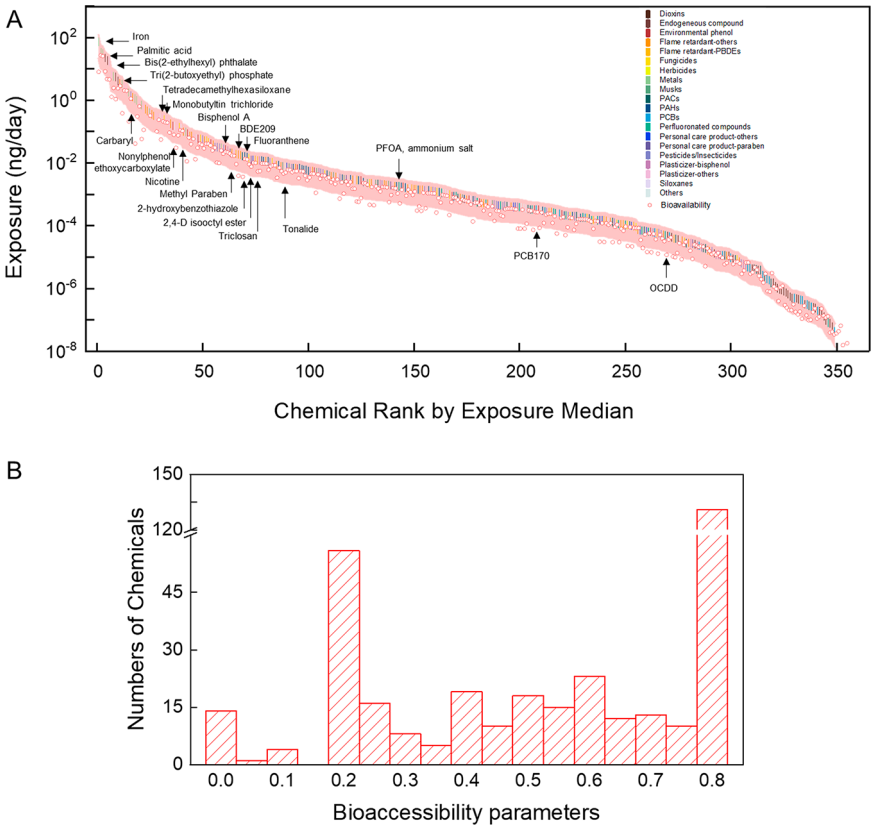


Figure 2. Human cumulative exposure to chemicals in indoor dust. (A) The documented indoor dust chemicals are ranked by the predicted median exposure (ng/day) for adults. The bar indicates the median exposure to each chemical; the pink area represents the exposure range (5−95%) derived from the Monte Carlo simulations. The chemicals with the highest exposure level in each chemical category are labeled. The red dots indicate the median human bioaccessibility (ng/day) for chemicals. (B) Histogram of bioaccessibility distribution for all tested chemicals in the study.

10^{-3} μg/g and 6 μg/g. As shown in Figure 1A, heavy metals (total inorganic heavy metal: iron and titanium) and endogenous compounds (e.g., fatty acids) showed the highest abundances (from 1.3 to 4.3 × 10^{3} μg/g); polychlorinated biphenyls (PCBs) and polychlorinated dibenzo-*p*-dioxins and dibenzofurans (dioxins) showed the lowest concentrations in dust (from 2.6 × 10^{-6} to 1.9 × 10^{-2} μg/g). Meanwhile, the composition of dust chemicals was evaluated by chemical category, which indicated that heavy metals (62.3%) are the most abundant chemicals, followed by endogenous compounds (20.7%), plasticizers (12.7%), flame retardants (2.94%), and pesticides/insecticides (0.67%) (Figure 1B). The rest of the categories accounted for less than 0.5% of the total indoor dust chemicals.

As it is well-known that chemical concentrations in dust can vary greatly between samples, we further investigated the variation of the documented indoor dust chemicals based on the median values from different studies. Among the 280 chemicals with more than (including) two studies, 200 compounds (71.4% of the total) showed relative standard deviation of less than 100% of the median concentration (Figure S1). Therefore, most of the indoor dust chemicals showed prevalent occurrence worldwide, with similar levels within 1 order of magnitude, although the variation was usually large in each individual study. The remaining prioritized chemicals, which were reported at levels below detection limits or were not quantitatively evaluated in the original studies, were not included for downstream exposure and toxicity analysis.

Human Exposure and Bioaccessibility Evaluation via Dust Ingestion. Human exposure to the chemicals associated with indoor dust was predicted from Monte Carlo simulations by correlating the chemical concentration in dust with its bioaccessibility (Figure 2A). In general, the estimated human daily exposure to indoor chemicals ranged from 4.30 × 10^{-8} to 71.78 ng/day, ranging 9 orders of magnitude. Heavy metal iron, which had a median exposure of 71.78 ng/day, constituted the highest exposure level for adults, followed by the endogenous compound palmitic acid (22.07 ng/day) and the plasticizer bis (2-ethylhexyl) phthalate (16.29 ng/day). Dioxins had the lowest exposure levels, which generally ranged from 10^{-8} to 10^{-5} ng/day. The profile for human exposure was similar to the distribution pattern of a chemical's concentration in dust. The human bioaccessibility for adults is predicted to be systematically lower than the total exposures. As shown in Figure 2B, the bioaccessibility was less than 0.3 for 91 chemicals among the 355 tested chemicals, between 0.3 and 0.5 for 43 chemicals, and the remaining 221 chemicals showed a bioaccessibility higher than 0.5. Overall, the bioaccessible fractions were highly correlated with the concentration, and were unlikely to change the prioritization of the chemical by ranking risk.

Chemical Toxicity Prioritization Using EPA's ToxCast Database. Published papers were extensively reviewed to understand the toxicological effect of house dust exposure on

DOI: 10.1021/acs.est.9b00280
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

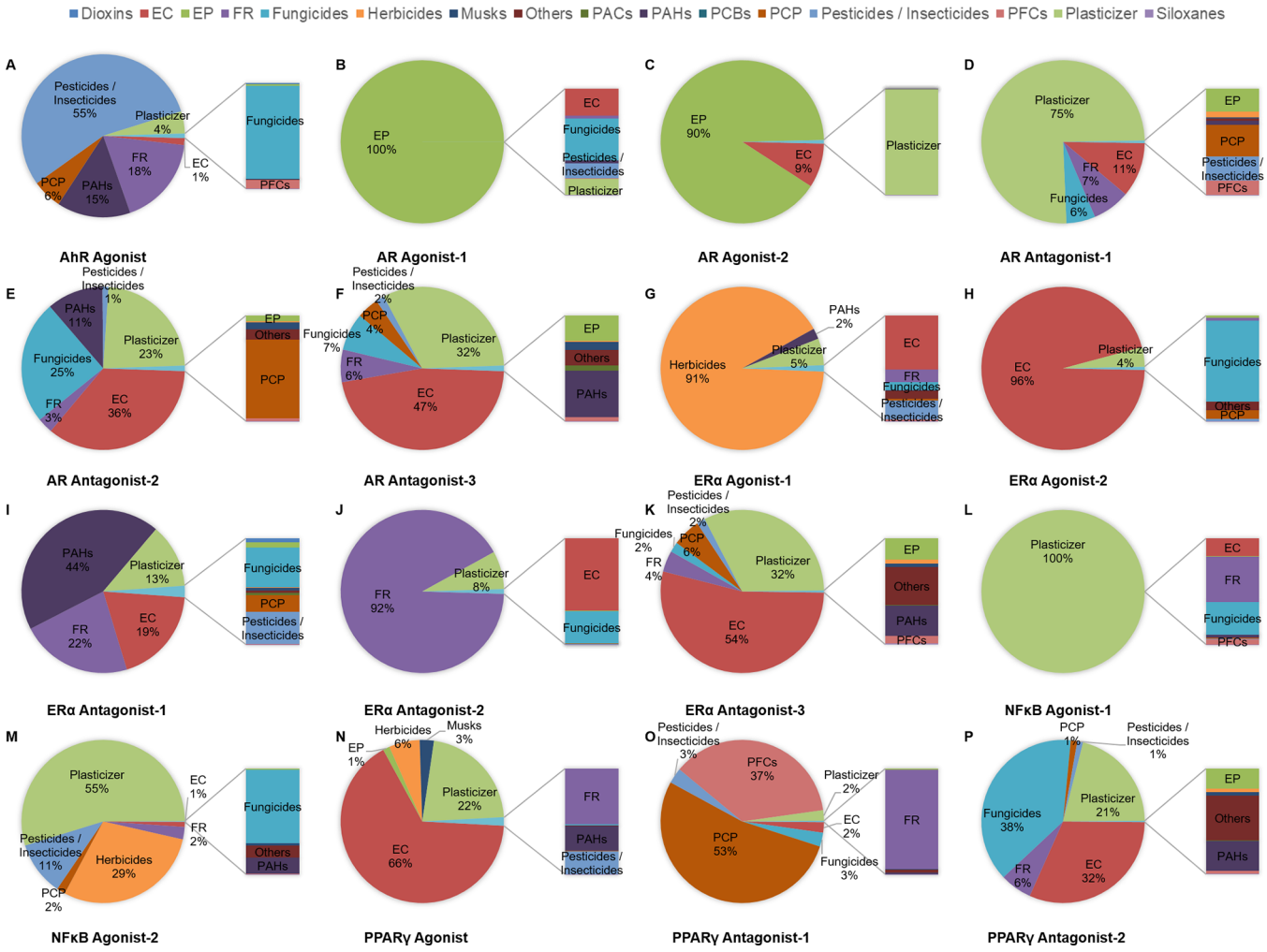


Figure 3. Toxicity contributions from chemicals in dust (different assay end point, based on category). EC: Endogenous compounds, EP: Environmental phenols (excluding bisphenols and parabens), FR: Flame retardants, PAHs: Polycyclic aromatic hydrocarbons, PCBs: Polychlorinated biphenyls, PFCs: Perfluorinated compounds, PCP: Personal care product, and PACs: Polycyclic aromatic compounds. Percentage of all second plots <2%.

endocrine disruption, disease occurrence, and immune activity in vitro, in vivo, or in humans (see details in Text S5 in SI). On the basis of a summary of this review, 16 Tox21 assays from EPA iCSS ToxCast Dashboard were used to assess the bioactivity of 355 documented chemicals in this study. The total 16 assays covered one AhR agonist, two AR agonists, three AR antagonists, two ERα agonists, three ERα antagonists, two NFκB1 agonists, one PPARγ agonist, and two PPARγ antagonists (SI Table S4). Notably, 51.3% of the 355 chemicals of interest were not tested across all of the 16 assays. The 173 tested chemicals were classified into 16 categories, including endogenous compounds (n = 4), environmental phenols (excluding bisphenols and parabens) (n = 10), flame retardants (n = 22), fungicides (n = 10), herbicides (n = 6), musks (n = 6), PAHs (n = 19), PCBs (n = 1), dioxins (n = 1), perfluorinated compounds (n = 11), personal care products (n = 16), pesticides/insecticides (n = 29), plasticizers (n = 21), PACs (n = 6), siloxanes (n = 3), and others (n = 8).

The contributions by individual chemicals were analyzed for each assay. Interestingly, each end point showed obviously different chemical toxicity prioritization, and had its own dominant contributor(s). In the AhR agonist assay, the bioactivity scores ranged from <0.1% to 44.23% for the 173 tested indoor dust chemicals. Among these chemicals, pesticides/insecticides contributed 55.0% (Figure 3A), within which cypermethrin was the dominant contributor, accounting for 44.23%, followed by flame retardants (17.8%) and PAHs (14.6%) (Figure 4). In the AR agonist-1 assay and the AR agonist-2 assay, environmental phenols made the most significant contribution, > 99.9% and 90.5%, respectively (Figure 3B and C); and almost all of the contribution was attributed to 4-nitrophenol (Figure 4). In the AR antagonist-1 assay, plasticizers (75.4%), endogenous compounds (10.7%) and flame retardants (7.5%) were the three main contributors (Figure 3D). The dominant contributors are diisononyl phthalate (DINP) (51.3%) and bis (2-ethylhexyl) phthalate (DEHP) (19.8%) in plasticizers, myristic acid (MA) (8.2%) in endogenous compounds and tri (2-butoxyethyl) phosphate (TBOEP) (6.1%) in flame retardants (Figure 4). In the AR antagonist-2 assay, the important contributions were from endogenous compounds (35.6%), fungicides (24.5%), plasticizers (23.4%) and PAHs (11.2%) (Figure 3E). The most dominant chemicals in each category were dibutyltin dichloride (DBTC) (21.2%) in fungicides, palmitic acid (PA) (15.6%), and oleic acid (OA) (13.1%) in endogenous

DOI: 10.1021/acs.est.9b00280
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

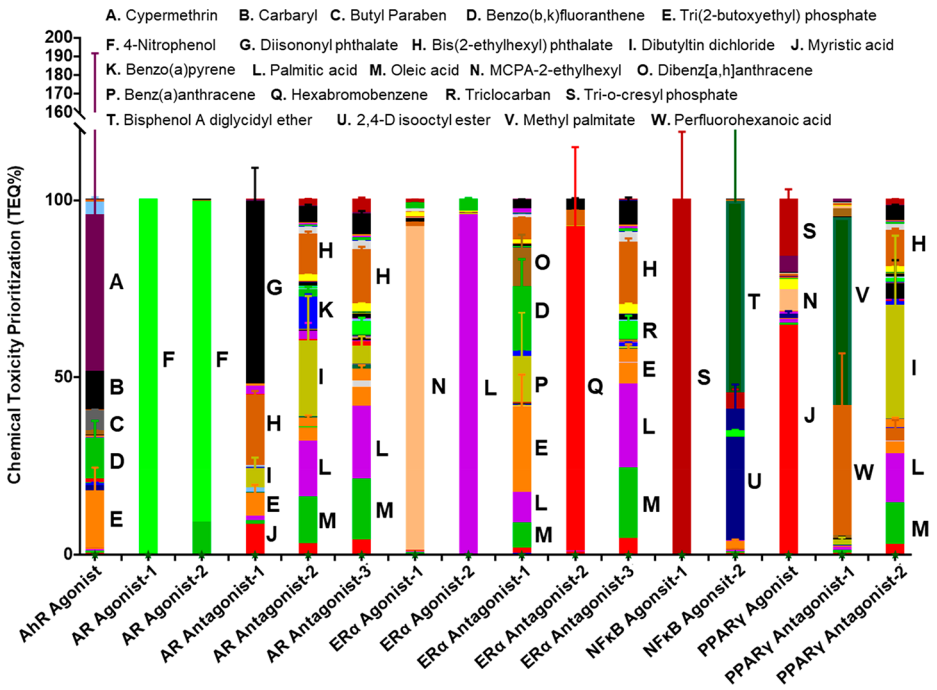


Figure 4. Contribution (%) of indoor chemical exposome in each assay. Bars represent the TEQ% of all tested chemicals in each assay, and error bars represent the weighted standard error.

compounds, DEHP (11.6%) in plasticizers and benzo(a)-pyrene (B(a)P) (8.8%) in PAHs (Figure 4). The AR antagonist-3 assay showed a similar chemical distribution pattern as the previous two AR antagonist assays; the top contributor was endogenous compounds (46.7%), followed by plasticizers (32.3%), fungicides (7.4%), and flame retardants (6.5%) (Figure 3F), and the dominant chemical in each corresponding category was PA (20.6%), DEHP (15.2%), DBTC (5.1%), and TBOEP (3.3%) (Figure 4).

In the ERα agonist-1 assay, herbicides had the highest contribution (91.3%) (Figure 3G), and MCPA-2-ethylhexyl was the main dominant contributor (91.3%) (Figure 4). Endogenous compounds were the dominant contributors in the ERα agonist-2 assay, which accounted for 95.5% (Figure 3H), within which the contribution was mainly from PA (Figure 4). In the ERα antagonist-1 assay, PAHs (43.7%), flame retardants (22.1%), endogenous compounds (19.2%), and plasticizers (12.7%) were the most vital contributors (Figure 3I), and the most abundant chemicals were TBOEP (21.9%) and three PAHs, including benzo(b,k)fluoranthene (B(bk)F) (18.2%), benzo(a)anthracene (BA) (13.1%), and dibenzo(a,h)anthracene (DB(a,h)A) (10.8%) (Figure 4). In the ERα antagonist-2 assay, flame retardants were the most critical contributors (91.6%) (Figure 3J), and the representative chemical was hexabromobenzene (HBB) (91.5%) (Figure 4). In the ERα antagonist-3 assay, the most important contribution came from endogenous compounds (53.8%), followed by plasticizers (32.4%) and personal care products (5.6%) (Figure 3K); and the representative chemical in each respective category was PA (23.7%), OA (19.8%), DEHP (17.5%), and triclocarban (TCC) (5.2%) (Figure 4). In the NFκB agonist-1 assay, plasticizers were the most important contributor (>99%) (Figure 3L), and all of the contribution was from tri-*o*-cresyl phosphate (TOCP) (>99.9%) (Figure 4). In the NFκB agonist-2 assay, the top three contributors were plasticizers (54.7%), herbicides (29.3%), and pesticides/insecticides (10.7%) (Figure 3M), and the three most abundant chemicals were bisphenol A diglycidyl ether (BADGE) (54.1%), 2,4-D isooctyl ester (29.3%), and chlorpyrifos (6.1%) (Figure 4). In the PPARγ agonist assay, endogenous compounds (66.2%), plasticizers (21.9%), and herbicides (6.1%) were three main contributors (Figure 3N), and the most abundant chemical in each respective category was MA (64.3%), TOCP (16.1%), and MCPA-2-ethylhexyl (6.1%) (Figure 4). In the PPARγ antagonist-1 assay, personal care products (53.0%) and perfluorinated compounds (36.7%) were two dominant contributors (Figure 3O), and the corresponding dominant chemicals were methyl palmitate (MP) (52.9%), and perfluorohexanoic acid (PFHxA) (36.7%) (Figure 4). In the PPARγ antagonist-2 assay, the most critical contributions came from fungicides (38.5%), endogenous compounds (31.6%), and plasticizers (20.9%) (Figure 3P), and the most abundant chemicals were DBTC (32.2%), PA (13.9%), OA (11.6%), and DEHP (10.3%), respectively (Figure 4).

DISCUSSION

In this study, we first conducted an extensive literature search on the occurrence and levels of chemicals existing in indoor dust worldwide. Second, we estimated human exposure to these chemicals by considering dust ingestion, dermal contact, and bioaccessibility; and third, through a combination of the concentration and ToxCast in vitro activity assay, the toxicity of chemicals was prioritized in terms of different end points. Overall, we have built up an indoor dust exposome database with 511 chemicals, among which 355 have their levels found in indoor dust. The exposome database, conceptually and practically, provides a holistic view of exposome monitoring targets. It also provides input data for future large-scale multimedia modeling for air pollutants. The risk prioritization can also provide supporting information for pollution mitigation control.

DOI: 10.1021/acs.est.9b00280
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

In previous reviews on dust samples, the number of chemicals was usually less than 20−40.[2,3,8,20−22] The search result from this study is much more recent and comprehensive, covering most of the key chemical groups found in indoor dust. Although most chemicals showed high heterogeneity in their occurrence and levels, heavy metals, endogenous compounds, plasticizers, pesticides/insecticides, flame retardants, and siloxanes were the most abundant chemical groups. The abundant accumulation of these chemicals is mainly due to their wide range of sources in daily life and their characteristic of being persistent in the environment. For example, flame retardants are broadly applied in daily life and have been focused on in recent decades. A number of flame retardants showing significant adverse health effects in humans and animals have been or are being phased out (e.g., PBDEs). However, health concerns raised by flame retardants remain due to the persistence and accumulation of legacy flame retardant chemicals, especially at low exposure levels. Additionally, the health effects of alternative flame retardants that are replacing the phased-out chemicals remain unclear at indoor exposure levels.

Although the concentrations of chemicals varied greatly between dust samples, we have found that the median/mean values calculated from a large sample size did not vary greater than 1 order of magnitude between different countries. For some chemicals, such as plasticizers and flame retardants, which have common sources in global indoor environments, the RSD of their median concentrations are even less than 40%. The application of some pesticides and insecticides, such as allerthrin and esfenvalerate, might be unique across countries or households, resulting in a significant heterogeneous distribution. Therefore, we believe that the concentration profile from this large-scale literature review can be representative of the occurrence of these chemicals in indoor environments.

Human exposure to these prioritized chemicals was simulated, showing a similar distribution with that of chemical concentrations in the dust. Compared with dermal contact, dust ingestion was more important for the total exposure contribution. The bioaccessibility varied greatly between compounds; however, it did not significantly change human exposure and toxicological prioritization. This might be due to the fact that the log K_{ow} values of most compounds in dust are within the range of 3.0 to 8.0.

As another key component of this study, the potential health effects and the causal compounds of indoor dust were summarized, revealing several key biomarker assays. A total of 16 Tox21 assays were used to assess the bioactivities of 355 chemicals (excluding VOCs) collected from the literature review, among which 173 chemicals were tested across all 16 assays, showing different toxicity prioritization patterns. In the AhR agonist assay, cypermethrin, which accounted for 44.23%, was the principle AhR agonist activity contributor owing to its relatively lower AC_{50} (0.035 μM) and higher concentration (3.32 μg/g). Interestingly, the contribution from well-known potent AhR agonists, such as chlorinated/brominated dioxins and some PAHs, was negligible due to their low levels. For example, TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin), a potent AhR ligand, was also included in this study and had a much lower AC_{50} value (2.75×10^{-4} μM). However, TCDD did not show significant AhR agonist activity due to its low concentration (5.8×10^{-6} μg/g). This was consistent with previous reports showing that cypermethrin had an agonistic effect on AhR function by exposure to Hepa1.12cR cells.[23] Cypermethrin has been widely used as a pesticide, and the concentrations of cypermethrin in surface water can reach 2.8 μg/L.[24] Cypermethrin has been reported to be a well-known neurotoxicant. In vivo studies showed that cypermethrin exposure resulted in alterations of motor function and impairments of neurobehaviors in rodents.[25] In both the AR agonist-1 assay and the AR agonist-2 assay, 4-nitrophenol was responsible for the principle AR agonist activity owing to its extremely low AC_{50} (1.05×10^{-5} μM and 2.89×10^{-5} μM, respectively). In a quantitative high-throughput screening assay (qHTS), which was designed to identify small molecule agonists of the AR signaling pathway, 4-nitrophenol was also found to be an active AR agonist (from PubChem, BioAssay AID: 743053). The 4-nitrophenol is a phenolic compound that is mainly used to manufacture drugs, fungicides, insecticides, and dyes and to darken leather. Notably, the concentration of 4-nitrophenol in house dust was reported in only one study. Other than 4-nitrophenol, the main contributors in the AR agonist assays 1 and 2 were both DINP and DEHP (Figure S2). Three AR antagonist assays, based on different cell lines or reporters, showed similar chemical distribution patterns. In these three assays, the top contributors were all found to be plasticizers, fungicides, and endogenous compounds, although the contribution percentage varied. DEHP is a widely used high production volume plasticizers and is reported to be an endocrine-disrupting chemical with potent antiandrogenic activity,[26] which was consistent with our findings. DINP was another critical plasticizer in the AR antagonist assays. DINP is widely used in the plastics industry, food packaging, and children's toys and has been shown to disrupt the differentiation of androgen-dependent tissues in male rat offspring.[27] Interestingly, DBTC had the lowest AC_{50} values in all three assays, 0.090 μM, 0.027 μM, and 0.492 μM, which explained its important contributions. PA, OA, and MA are fatty acids that were first reported to be present in house dust by Fang et al.,[28] and their high contribution to AR antagonist activity was due to their high concentrations, 1320.5 μg/g, 1103.75 μg/g, and 244.08 μg/g, respectively. These fatty acids were detected in all of the 20 samples (100% detection). Besides the fatty acids, the second most important contributors in all three AR antagonist assays were DEHP, DINP, and DBTC (Figure S2).

Interestingly, the chemical contributions were significantly different in two ERα agonist assays. MCPA-2-ethylhexyl, which is a commonly used herbicide, was the major contributor to ERα agonist activities in the ERα agonist-1 assay, whereas fatty acid PA was the dominant contributor in the ERα agonist-2 assay. The AC_{50} for MCPA-2-ethylhexyl was 1.27×10^{-5} μM in the ERα agonist-1 assay, but 1000 μM in the ERα agonist-2 assay. Similarly, the AC_{50} for PA was 1000 μM and 0.505 μM in two assays, respectively. The different AC_{50} values of same chemical in these two assays may be due to different cell lines (HEK293T, a human kidney cell line, and BG1, a human ovary cell line) and different measurement times (24 h/48 h after chemical dosing). After excluding these two significant chemicals, the dominant contribution for the ERα agonist-1 assay was from plasticizers and PAHs, and was plasticizers and fungicides for the ERα agonist-2 assay (Figure S3). The three ERα antagonist assays also showed different toxicity patterns due to different contributors. Flame retardant TBOEP was the dominant contributor in ERα antagonist-1 assay due to its relatively high concentration (211.14 μg/g). Three PAHs, BA, B(bk)F, and DB(a,h)A, were also responsible for ERα

DOI: 10.1021/acs.est.9b00280
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

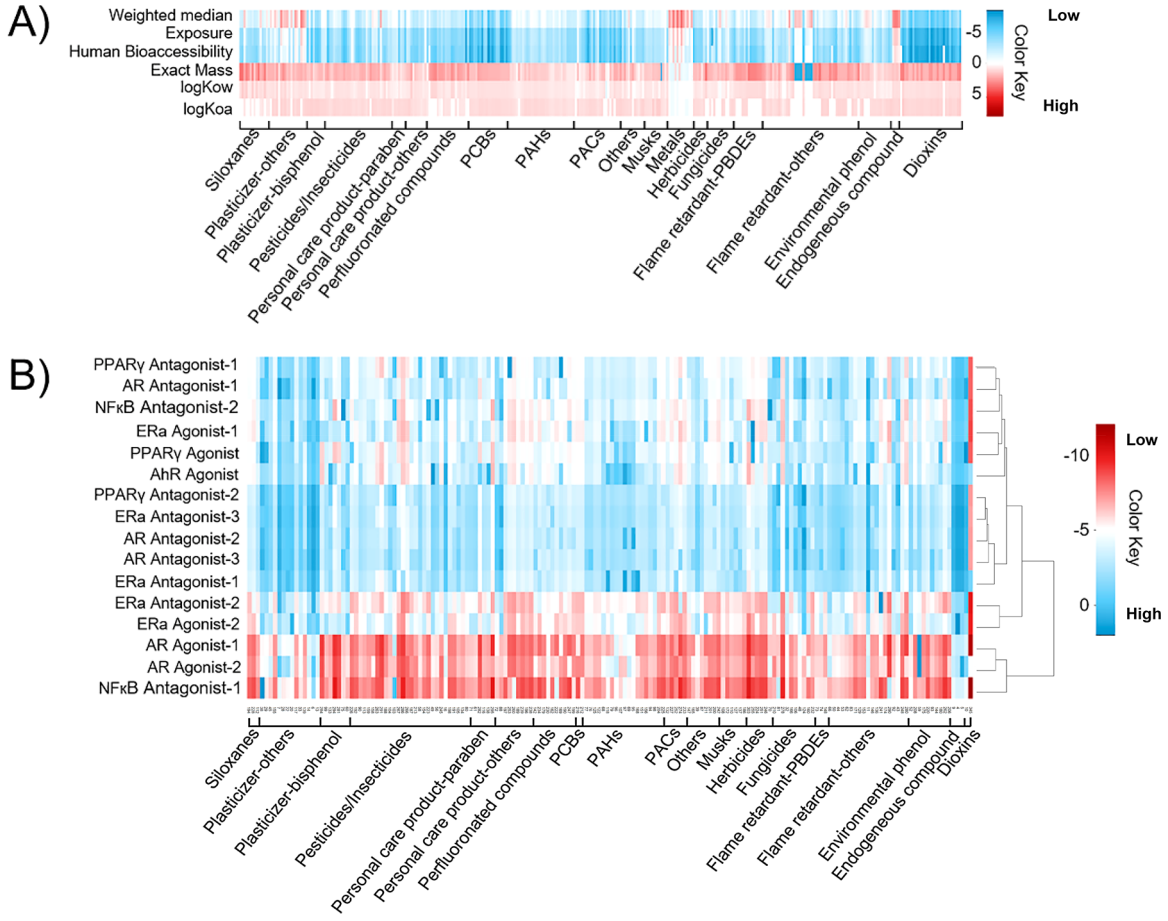


Figure 5. Heatmap of the documented chemicals in this study (all data are shown in log scale). (A) Heatmap of the chemical weighted median concentrations in dust, exposure levels, human bioaccessibility, exact mass, log K_{ow} and log K_{oa}. (B) Heatmap and hierarchical clustering of chemical contributions in 16 Tox21 assays.

antagonist activity in the ERα antagonist-1 assay due to their relatively low AC_{50} values (0.025−0.124 μM). It was reported that eight PAHs (including BA, BkF, DB(a,h)A, chrysene, benzo[b]fluoranthene, benzo[e]pyrene, B(a)P, and indeno-[1,2,3-cd]pyrene) were significantly antiestrogenic when tested in the MCF-7 focus assay, which was consistent with our results.[29] These three PAHs were not significant in the other two ERα antagonist assays due to their high AC_{50} values (1000 μM). HBB, a relatively less studied brominated flame retardant (BFR), contributed 91.4% to ERα antagonist activity in the ERα antagonist-2 assay owing to its low AC_{50} (1.56×10^{-6} μM). However, it was reported that even high concentrations of HBB (3.6 μM) were not able to trigger β-galactosidase production in the yeast cultures in the ERα activity assay.[30] These different results may be due to different cell lines or reporter systems. Interestingly, PA, which played a critical ERα agonist activity, showed significant ERα antagonist activity in the ERα antagonist-3 assay, suggesting that PA is an allosteric modulator, which has both ERα agonist and antagonist potency.

In two NFκB agonist assays, plasticizers were found to play a critical role. In the NFκB agonist-1 assay, TOCP was responsible for the principle NFκB agonist activity owing to its low AC_{50} (1.29×10^{-5} μM). TOCP has been widely used as a plastic softener and a plasticizer in industry, and is reported to have a toxic effect on the male reproductive system in animals, in addition to neurotoxicity and immunotoxicity.[31] In the NFκB agonist-2 assay, BADGE accounted for 54.0% of NFκB agonist activity. BADGE is a newly described PPARγ antagonist in adipogenic cells, and overexpression of the coactivator p300 restored BADGE-suppressed promoter activity of the NFκB-luciferase reporter gene, suggesting that PPARγ may interfere with NFκB transcriptional activity via coactivator competition.[32] However, BADGE did not show significant PPARγ antagonist activity in our results due to its relatively high AC_{50}. It should be noted that endotoxin may outweigh the contribution from other chemicals due to its high potency in regulating NFκB activity; however, endotoxin is not included in our results.

In the PPARγ agonist assay, MA was the principle PPARγ agonist activity contributor, owing to its relatively high concentration (244.08 μg/g). Besides MA, the second main contributor was the plasticizer TOCP (16.0%) (Figure S2). In the PPARγ antagonist-2 assay, DBTC had the principle PPARγ antagonist activity contribution (32.2%) due to its relatively low AC_{50}; the PPARγ antagonist activity of DBTC was also observed in the PPARγ antagonist-1 assay, although at a lower percentage (1.6%). DBTC was reported to be a partial agonist to PPARγ.[33] This can be explained by the fact that a partial agonist actually acts as an antagonist when both a full agonist and a partial agonist are present. In the PPARγ antagonist-1 assay, the personal care product MP was the dominant contributor due to its relatively low AC_{50}. However, the concentration was reported in only one study, and PFHxA

DOI: 10.1021/acs.est.9b00280
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

became one of the main contributors (78.1%) when MP was excluded (Figure S2).

For the 16 assays with cluster analysis, it is interesting to observe that the AR agonist and NFκB agonist, PPARγ antagonist and ERα antagonist, and ERα agonist and PPARγ agonist were closely correlated (Figure 5B). It was reported that NFκB is part of a signaling network regulating AR expression in prostate cancer,[34] and signal cross talk existed bidirectionally between PPARγ and the ER in breast cancer cells,[35] which may explain the correlations between the assays shown in our study.

This study has several limitations. First, the EPA's ToxCast database could only cover ∼50% of the indoor chemicals summarized in this study, and some of the key chemicals that play critical roles in toxicity prioritization have very limited studies. Second, the TEF method is limited, as it is assumed to act through the same biological pathway, and dose-additivity is not applicable. Third, we cannot predict the effects of chemical mixtures using this model. Last, the toxicity contribution for some groups of compounds with many congeners might be underestimated. For example, existence of TCDD indicates the co-occurrence of other dioxin chemicals; likewise, the presence of PA also suggested the co-occurrence of many other endogenous metabolites. During the meta-analysis, only the levels of representative compounds in those chemical classes have been reported. Therefore, nonbiased targeted and nontargeted chemical screening in dust samples is still needed in the future to fully prioritize the chemicals.

In conclusion, we have established an indoor exposome database, and by using EPA's ToxCast database, we prioritized the chemicals in terms of their toxicity. The result showed the heavy metals still consist of the largest quantity compared with organic pollutants. However, the toxicity contribution of those metals cannot be figured out without metal speciation information. The result also showed that organic pollutants such as phthalates (e.g., DEHP and DINP), plasticizers (e.g., BADGE and TOCP), flame retardants (e.g., TBOEP), organotins (DBTC), and phenols (e.g., nitro-phenols) significantly contributed to the bioassays with endocrine disruption. Many of the primary contributors in some assays were also unexpected. For example, pesticide/insecticide (e.g., cypermethrin) use in indoor environment might incur health concerns; however, very limited monitoring data is available for those compounds and further studies should be conducted. Besides the synthesized molecules, the effect of metabolites and microbial products with biological origins such as endogenous fatty acids and LPS should also be considered in the dust exposome and risk prioritization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.9b00280.

Text S1, Chemical search; ; Text S2, Human dust exposure calculations; Text S3, In vitro and in vivo toxicity search; Text S4, Methods for figure generation; Text S5, In vitro and in vivo epidemiological toxicity of dust extract and causal chemical identification; Table S1, Nondietary ingestion and dermal dose equation; Table S2, Exposure factor mean (CV) values for dose calculations; Table S3, General model characteristics; Table S4, Chemical abbreviation used in this study; Figure S1, The variation of averaged median concentrations of indoor dust chemicals across studies (n≥4); Figure S2, Chemical contributions in every assay; Figure S3, Toxicity contribution from chemicals in dust in two ERα agonist assays (PDF)

Table S1, The documented chemicals with literature indoor dust levels; Table S2, Chemcials without documented concentration; Table S3, The documented volatile organic compounds; and Table S4, Tox21 assays used to assess bioactivities of potential chemicals in house dust (XLSX)

■ AUTHOR INFORMATION

Corresponding Authors

*Phone: +86 20-3733 6629; e-mail: dachen@jnu.edu.cn.
*Phone: +65 6790 5331; e-mail: mlfang@ntu.edu.sg.

ORCID

Da Chen: 0000-0001-5563-0091
Mingliang Fang: 0000-0002-2204-9783

Author Contributions

‖T.D. and Y.Z. contributed equally to this manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by the Singapore Ministry of Education Academic Research Fund Tier 1 (M4011732.030), NTU-Harvard SusNano (M4082370.030), a Start Up Grant of Nanyang Technological University (M4081915), the Singapore National Environment Agency (M4061617), and Singapore Ministry of Health's National Medical Research Council under its Clinician-Scientist Individual Research Grant (CS-IRG) (MOH-000141) and Open Fund−Individual Research Grant (OFIRG/0076/2018). Bei Wang, Mengjing Wang, Junjie Yang, and Bo Peng (Nanyang Technological University, Singapore) are gratefully acknowledged for assisting with the literature review and documentation.

■ REFERENCES

(1) Dai, D.; Prussin, A. J., 2nd; Marr, L. C.; Vikesland, P. J.; Edwards, M. A.; Pruden, A. Factors Shaping the Human Exposome in the Built Environment: Opportunities for Engineering Control. *Environ. Sci. Technol.* **2017**, *51* (14), 7759−7774.

(2) Butte, W.; Heinzow, B. Pollutants in house dust as indicators of indoor contamination. *Rev. Environ. Contam. T* **2002**, *175*, 1−46.

(3) Whitehead, T.; Metayer, C.; Buffler, P.; Rappaport, S. M. Estimating exposures to indoor contaminants using residential dust. *J. Exposure Sci. Environ. Epidemiol.* **2011**, *21* (6), 549−564.

(4) U.S. EPA *Child-Specific Exposure Factors Handbook (2008, Final Report)*; U.S. Environmental Protection Agency: Washington, DC, 2008.

(5) Johnson, P. I.; Stapleton, H. M.; Sjodin, A.; Meeker, J. D. Relationships between Polybrominated Diphenyl Ether Concentrations in House Dust and Serum. *Environ. Sci. Technol.* **2010**, *44* (14), 5627−5632.

(6) Stapleton, H. M.; Eagle, S.; Sjodin, A.; Webster, T. F. Serum PBDEs in a North Carolina toddler cohort: associations with handwipes, house dust, and socioeconomic variables. *Environ. Health Perspect.* **2012**, *120* (7), 1049−54.

(7) Schultz, I. R.; Cade, S.; Kuo, L. J. The Dust Exposome. In *Unraveling the Exposome*; Dagnino, S., Macherone, A., Eds; 2019, pp 247−254.

(8) Mitro, S. D.; Dodson, R. E.; Singla, V.; Adamkiewicz, G.; Elmi, A. F.; Tilly, M. K.; Zota, A. R. Consumer Product Chemicals in

DOI: 10.1021/acs.est.9b00280
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

Indoor Dust: A Quantitative Meta-Analysis of U.S. Studies (vol 50, pg 10661, 2016). *Environ. Sci. Technol.* **2016**, *50* (24), 13611−13611.
(9) Kleinstreuer, N. C.; Yang, J.; Berg, E. L.; Knudsen, T. B.; Richard, A. M.; Martin, M. T.; Reif, D. M.; Judson, R. S.; Polokoff, M.; Dix, D. J.; Kavlock, R. J.; Houck, K. A. Phenotypic screening of the ToxCast chemical library to classify toxic and therapeutic mechanisms. *Nat. Biotechnol.* **2014**, *32* (6), 583−591.
(10) Wambaugh, J. F.; Setzer, R. W.; Reif, D. M.; Gangwal, S.; Mitchell-Blackwood, J.; Arnot, J. A.; Joliet, O.; Frame, A.; Rabinowitz, J.; Knudsen, T. B.; Judson, R. S.; Egeghy, P.; Vallero, D.; Cohen Hubal, E. A. High-throughput models for exposure-based chemical prioritization in the ExpoCast project. *Environ. Sci. Technol.* **2013**, *47* (15), 8479−8488.
(11) Jablonowski, M. Using probabilistic risk analysis to improve risk management. *Risk Management* **1996**, *43* (3), 23.
(12) U. S. EPA. *Exposure Factors Handbook*, 2011 Edition; (Final Report).
(13) Thompson, K. M.; Graham, J. D. Going beyond the single number: using probabilistic risk assessment to improve risk management. *Hum. Ecol. Risk Assess.* **1996**, *2* (4), 1008−1034.
(14) Sugano, K.; Hamada, H.; Machida, M.; Ushio, H. High throughput prediction of oral absorption: improvement of the composition of the lipid solution used in parallel artificial membrane permeation assay. *J. Biomol. Screening* **2001**, *6* (3), 189−196.
(15) Sugano, K.; Hamada, H.; Machida, M.; Ushio, H.; Saitoh, K.; Terada, K. Optimized conditions of bio-mimetic artificial membrane permeation assay. *Int. J. Pharm.* **2001**, *228* (1−2), 181−188.
(16) Hou, T.; Zhang, W.; Xia, K.; Qiao, X.; Xu, X. ADME evaluation in drug discovery. 5. Correlation of Caco-2 permeation with simple molecular properties. *Journal of chemical information and computer sciences* **2004**, *44* (5), 1585−1600.
(17) Fang, M.; Stapleton, H. M. Evaluating the bioaccessibility of flame retardants in house dust using an in vitro Tenax bead-assisted sorptive physiologically based method. *Environ. Sci. Technol.* **2014**, *48* (22), 13323−30.
(18) Turner, A.; Ip, K.-H. Bioaccessibility of Metals in Dust from the Indoor Environment: Application of a Physiologically Based Extraction Test. *Environ. Sci. Technol.* **2007**, *41* (22), 7851−7856.
(19) Huang, M.; Wang, W.; Chan, C. Y.; Cheung, K. C.; Man, Y. B.; Wang, X.; Wong, M. H. Contamination and risk assessment (based on bioaccessibility via ingestion and inhalation) of metal (loid) s in outdoor and indoor particles from urban centers of Guangzhou, China. *Sci. Total Environ.* **2014**, *479*, 117−124.
(20) Rager, J. E.; Strynar, M. J.; Liang, S.; McMahen, R. L.; Richard, A. M.; Grulke, C. M.; Wambaugh, J. F.; Isaacs, K. K.; Judson, R.; Williams, A. J.; et al. Linking high resolution mass spectrometry data with exposure and toxicity forecasts to advance high-throughput environmental monitoring. *Environ. Int.* **2016**, *88*, 269−280.
(21) Destaillats, H.; Maddalena, R. L.; Singer, B. C.; Hodgson, A. T.; McKone, T. E. Indoor pollutants emitted by office equipment: A review of reported data and information needs. *Atmos. Environ.* **2008**, *42* (7), 1371−1388.
(22) Mercier, F.; Glorennec, P.; Thomas, O.; Bot, B. L. Organic contamination of settled house dust, a review for exposure assessment purposes. *Environ. Sci. Technol.* **2011**, *45* (16), 6716−6727.
(23) Ghisari, M.; Long, M.; Tabbo, A.; Bonefeld-Jorgensen, E. C. Effects of currently used pesticides and their mixtures on the function of thyroid hormone and aryl hydrocarbon receptor in cell culture. *Toxicol. Appl. Pharmacol.* **2015**, *284* (3), 292−303.
(24) Jaensson, A.; Scott, A. P.; Moore, A.; Kylin, H.; Olsen, K. H. Effects of a pyrethroid pesticide on endocrine responses to female odours and reproductive behaviour in male parr of brown trout (Salmo trutta L.). *Aquat. Toxicol.* **2007**, *81* (1), 1−9.
(25) McDaniel, K. L.; Moser, V. C. Utility of a neurobehavioral screening battery for differentiating the effects of two pyrethroids, permethrin and cypermethrin. *Neurotoxicol. Teratol.* **1993**, *15* (2), 71−83.
(26) Shen, O. X.; Du, G. Z.; Sun, H.; Wu, W.; Jiang, Y.; Song, L.; Wang, X. R. Comparison of in vitro hormone activities of selected phthalates using reporter gene assays. *Toxicol. Lett.* **2009**, *191* (1), 9−14.
(27) Gray, L. E.; Ostby, J.; Furr, J.; Price, M.; Veeramachaneni, D. N. R.; Parks, L. Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. *Toxicol. Sci.* **2000**, *58* (2), 350−365.
(28) Fang, M.; Webster, T. F.; Stapleton, H. M. Effect-Directed Analysis of Human Peroxisome Proliferator-Activated Nuclear Receptors (PPARgamma1) Ligands in Indoor Dust. *Environ. Sci. Technol.* **2015**, *49* (16), 10065−73.
(29) Arcaro, K. F.; O'Keefe, P. W.; Yang, Y.; Clayton, W.; Gierthy, J. F. Antiestrogenicity of environmental polycyclic aromatic hydrocarbons in human breast cancer cells. *Toxicology* **1999**, *133* (2−3), 115−127.
(30) Ezechias, M.; Svobodova, K.; Cajthaml, T. Hormonal activities of new brominated flame retardants. *Chemosphere* **2012**, *87* (7), 820−824.
(31) Somkuti, S. G.; Lapadula, D. M.; Chapin, R. E.; Lamb, J. C. t.; Abou-Donia, M. B. Reproductive tract lesions resulting from subchronic administration (63 days) of tri-*o*-cresyl phosphate in male rats. *Toxicol. Appl. Pharmacol.* **1987**, *89* (1), 49−63.
(32) Nakamuta, M.; Enjoji, M.; Uchimura, K.; Ohta, S.; Sugimoto, R.; Kotoh, K.; Kato, M.; Irie, T.; Muta, T.; Nawata, H. Bisphenol a diglycidyl ether (BADGE) suppresses tumor necrosis factor-alpha production as a PPAR gamma agonist in the murine macrophage-like cell line, raw 264.7. *Cell Biol. Int.* **2002**, *26* (3), 235−241.
(33) Milton, F. A.; Lacerda, M. G.; Sinoti, S. B. P.; Mesquita, P. G.; Prakasan, D.; Coelho, M. S.; de Lima, C. L.; Martini, A. G.; Pazzine, G. T.; Borin, M. D.; Amato, A. A.; Neves, F. D. R. Dibutyltin Compounds Effects on PPAR γ/RXR α-Activity, Adipogenesis, and Inflammation in Mammalians Cells. *Front. Pharmacol.* **2017**, *8*. DOI: 10.3389/fphar.2017.00507
(34) Zhang, L.; Altuwaijri, S.; Deng, F.; Chen, L.; Lal, P.; Bhanot, U. K.; Korets, R.; Wenske, S.; Lilja, H. G.; Chang, C.; Scher, H. I.; Gerald, W. L. NF-kappaB regulates androgen receptor expression and prostate cancer growth. *Am. J. Pathol.* **2009**, *175* (2), 489−99.
(35) Wang, X.; Kilgore, M. W. Signal cross-talk between estrogen receptor alpha and beta and the peroxisome proliferator-activated receptor gamma1 in MDA-MB-231 and MCF-7 breast cancer cells. *Mol. Cell. Endocrinol.* **2002**, *194* (1−2), 123−33.

DOI: 10.1021/acs.est.9b00280
Environ. Sci. Technol. XXXX, XXX, XXX−XXX