Environmental Science & Technology

pubs.acs.org/est

Article

Occurrence of Current-Use Pesticides in Paired Indoor Dust, Drinking Water, and Urine Samples from the United States: Risk Prioritization and Health Implications

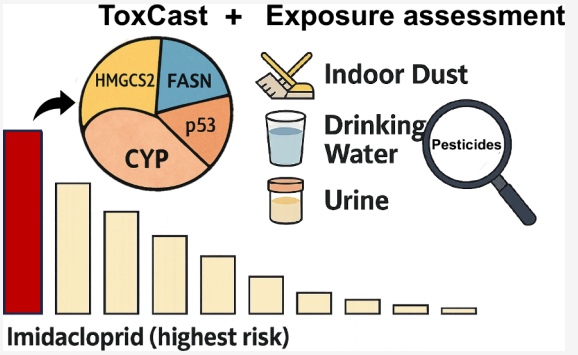
Yichun Xie, Juying Li, Amina Salamova,* and Guomao Zheng*

Cite This: *Environ. Sci. Technol.* 2025, 59, 12507−12519

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Despite being regarded as safer alternatives to legacy pesticides, current-use pesticides (CUPs) are now identified as emerging contaminants with growing evidence of their toxicity to wildlife and humans. In this study, we collected matched samples of indoor dust, drinking water, and urine from 81 households in Indiana, United States, and analyzed these samples for 82 CUPs, including 48 insecticides, 25 herbicides, and 9 fungicides. Of these, 47 CUPs were identified across samples of indoor dust, drinking water, and urine with median total CUP (∑CUP) concentrations of 18 300 ng/g, 101 ng/L, and 2.93 ng/mL, respectively. Notably, concentrations of neonicotinoids (NEOs) in indoor dust were higher than those reported in other studies. Herbicides were the most abundant CUPs detected in drinking water, constituting 55% of the ∑CUP concentrations. Insecticides were the most abundant CUP group detected in urine (median total insecticide concentration: 2.30 ng/mL), followed by herbicides (median: 0.409 ng/mL) and fungicides (median: 0.0531 ng/mL). The highest estimated daily intake (EDI) from drinking water and dust exposure was found for imidacloprid, with a median value of 1.00 ng/kg of body weight/day. Our results show that indoor dust is a significant exposure pathway for most insecticides and fungicides, while herbicides are mainly consumed through drinking water. In addition, the toxicity equivalent factor model, incorporated with data retrieved from the ToxCast database, indicated that imidacloprid poses the greatest health risk based on its high exposure levels and toxicity. This study underscores the importance of monitoring CUPs in indoor environments and sheds light on their potential health risks.



KEYWORDS: *current-use pesticides, ToxCast, indoor dust, drinking water, urine, risk prioritization*

INTRODUCTION

Pesticides, including insecticides, herbicides, and fungicides, are extensively used in agriculture to boost crop yields as well as in urban settings for landscape maintenance and household pest control.[1] Global pesticide use exceeded 4 million tons in 2019.[2] The adverse environmental and human health effects of pesticides have become a public health concern since the publication of Rachel Carson's book *Silent Spring*.[3,4] Due to their persistence, bioaccumulation, and toxicity, many pesticides, such as dichlorodiphenyltrichloroethane (DDT), have been restricted under the Stockholm Convention for persistent organic pollutants (POPs).[5−7] These regulatory actions have accelerated the shift toward the adoption of their replacements, current-use pesticides (CUPs), which are generally marketed as safer alternatives.[8]

However, a growing body of research shows that CUPs are emerging environmental contaminants that can be toxic to wildlife and humans.[9] Exposure to certain CUPs has been associated with various adverse health effects, including oxidative stress, alterations in DNA methylation, and changes in thyroid hormone levels.[10,11] For example, because of their endocrine disrupting properties and potential health effects such as developmental neurotoxicity and carcinogenicity, pyrethroid pesticides (PYPs) have been added to the list of priority chemicals for human biomonitoring.[12] Moreover, neonicotinoid pesticides (NEOs) have emerged as commonly used insecticides, yet their widespread use is alarming because of the severe toxicity to honeybees and possible adverse effects on mammalian nervous and reproductive systems.[12]

People spend most of their time indoors, thus, the indoor environment is important when considering exposure to environmental contaminants.[13,14] Indoor dust has long been recognized as a contaminant sink and intake through indoor dust is an important exposure pathway for many environmental

Received: January 20, 2025
Revised: June 2, 2025
Accepted: June 3, 2025
Published: June 13, 2025

pollutants, including CUPs.[15−17] In addition to indoor dust, CUPs have been found in drinking water and water consumption is considered as a significant exposure route for certain CUPs, given their higher hydrophilicity compared to legacy pesticides.[18−21] Thus, examining the occurrence of CUPs in indoor dust and drinking water is important for characterizing external human exposure.[22−24] Moreover, previous studies have identified various pesticides and their metabolites in human urine, including organophosphates (OPs), PYPs, and NEOs,[25,26] and provide evidence of the internal exposure dose of CUPs in humans. Multimedia exposure assessment is crucial for evaluating exposure pathways and estimating total exposure. This approach is particularly effective when environmental and biological samples are collected simultaneously from study participants. However, conducting multimedia exposure assessments is challenging, and studies evaluating CUPs in paired environmental and biological samples remain limited.[27]

Moreover, one of the main challenges in performing exposure assessment studies for CUPs lies in the difficulties of the analysis of CUPs in various matrices. CUPs are a diverse group of chemicals that includes over 1800 active compounds characterized by a wide range of physicochemical properties.[28] The octanol−water partitioning coefficients of CUPs range from < −3 to >7, and water solubility values span from 1 μg/L to 10 g/L.[18] These distinct characteristics of various CUPs significantly affect their detection in various biotic and abiotic samples.[29] Additionally, evaluating the toxicity of such a diverse group of chemicals is also challenging as conducting case-by-case toxicity assessments is not feasible.[28] The EPA's ToxCast database has conducted *in vitro* toxicity assays for over 700 end points of 1800 chemicals, including CUPs.[30] Recently, this high-throughput toxicity screening data has been successfully applied to risk assessment and prioritization of environmental contaminants in dust,[31] sediment and water,[32,33] providing an opportunity to evaluate the health risks posed by CUPs.

In this study, we utilized a multimedia exposure assessment approach, focusing on assessing the occurrence of CUPs in indoor dust, drinking water, and in urine. We collected paired samples of indoor dust, drinking water and urine from 81 participants residing in Indiana, United States, and analyzed them for 82 CUPs, including 48 insecticides, 25 herbicides, and 9 fungicides. The objectives of this study were to (1) characterize the occurrence and distribution pattern of CUPs in matched environmental and biological matrices collected from this population, (2) evaluate intakes of CUPs from indoor dust and drinking water, and (3) assess health risks and prioritize toxicity of CUPs based on actual exposure dose and the EPA's ToxCast model.

MATERIALS AND METHODS

Sample Collection and Analysis. A total of 81 participants were recruited in the State of Indiana, United States, from the Person-to-Person (P2P) Health Interview Study cohort (https://precisionhealth.iu.edu/get-involved/person-to-person.html). The study was approved by the Indiana University Institutional Review Board, and all participants signed an informed consent form before participating. Demographic, behavioral, and housing information were collected from each participant using questionnaires administered during sample collection. A summary of participants' demographic and housing characteristics (n = 81) is provided in Table S1. Indoor dust, drinking water, and urine samples were all paired and collected on the same day (one indoor dust, water, and urine sample per participant; total n = 243; 3 samples per participant) during August−December 2020. All samples were kept in cooler ice packs before being delivered to the laboratory at the end of each sampling day. Samples were stored at −20 °C before analysis.[34] Once the samples were thawed, they were processed as quickly as possible to minimize sample degradation and loss at room temperature. The pretreatment methods for processing indoor dust, drinking water, and urine followed the protocols established in previous studies with minor modifications.[8,35,36]

All dust samples were sieved using a 500 μm mesh size sieve. Approximately 100 mg of the sieved dust was spiked with surrogate standards and sonicated in 4 mL methanol for 1 h. The mixture was centrifuged at 3000 rpm for 5 min, the supernatant was transferred to a clean tube, and the extraction was repeated twice. The supernatants were combined, and the resulting extract was concentrated to 500 μL.

Samples of drinking water (300 mL each) were spiked with surrogate standards and loaded into 50 mL reservoirs coupled with Strata-X-AW cartridges (6 mL, 150 mg, 30 μm), preconditioned with 6 mL of methanol and then 6 mL of water. The columns were washed with 6 mL water and 6 mL 5% methanol in water, then allowed to dry completely under a vacuum and the targeted analytes were eluted with 6 mL of methanol (5% formic acid). The extracts were concentrated to dryness and reconstituted in 200 μL methanol.

Urine samples (1 mL each) were diluted with 1 mL phosphate buffer (0.1 M, pH 6.0) and then treated with 20 μL β-glucuronidase/aryl sulfatase enzyme solution [1000 units/mL in 1 M sodium acetate buffer (pH 5)] at 37 °C for 2 h. The samples were then fortified with surrogate standards and loaded onto Strata-X-AW cartridges (3 cm^3, 60 mg, 30 μm). The target analytes were eluted with 5 mL of 5% formic acid in methanol. The extract was then concentrated to dryness under a nitrogen gas blow down and reconstituted in 200 μL of methanol. The urine specific gravity was determined using a refractometer and urinary CUP concentrations were adjusted accordingly.

All extracts (indoor dust, water and urine) were filtered through 0.2 μm nylon syringe filters and spiked with a mixture of internal standards before instrumental analysis.

Instrumental Analysis. Eighty-two CUPs, including 48 insecticides, 25 herbicides, and 9 fungicides, were included in this analysis. The complete list of target analytes is provided in Table S2. An ultraperformance liquid chromatograph coupled with a triple-quadrupole mass spectrometer (Agilent 1290 Infinity II UPLC−6470 QQQ-MS) in the positive and negative electrospray ionization (ESI+ and ESI−) mode was used for the instrumental analysis. Chromatographic separation was achieved using an Acquity UPLC BEH C18 column (50 × 2.1 mm, 1.7 μm, Waters) at 40 °C. Mobile phases in negative mode consisted of 2 mM ammonium acetate in water (A) and 2 mM ammonium acetate in methanol (B), and the gradient was 10% B for 0.5 min initially, ramped to 40% B at 1 min, and then increased to 100% B at 17.5 min. For the positive mode, the mobile phase consisted of 0.1% formic acid in water (A) and 0.1% formic acid in methanol (B), and the gradient was 10% B for 0.5 min initially, ramped to 40% B at 1 min, and then increased to 100% B at 17.5 min. The instrument was equilibrated for 3.5 min after every run. The injection volume was 5 μL. The nebulizer, gas flow, capillary voltage, sheath gas

https://doi.org/10.1021/acs.est.5c00961
Environ. Sci. Technol. 2025, 59, 12507−12519

Table 1. Detection Frequencies (DF, %) and Minimum (Min), Maximum (Max) and Median Concentrations of Current-Use Pesticides (CUPs) Detected in Indoor Dust (ng/g), Drinking Water (ng/L) and Urine (ng/mL) [Only Concentrations above the MDLs Are Included in the Analysis]

		indoor dust				drinking water				urine[a]			
	group	DF	min	max	median	DF	min	max	median	DF	min	max	median
Insecticides													
acetamiprid	NEOs	100	2.36	30300	46.1	0				0			
clothianidin	NEOs	70	ND	263000	151	43	ND	18.8	4.84	0			
dinotefuran	NEOs	96	ND	336000	1300	11	ND	19.9	5.58	6.2	ND	15.0	2.03
imidacloprid	NEOs	100	5.41	833000	1390	75	ND	30.5	6.70	42	ND	26.9	1.91
thiacloprid	NEOs	16	ND	24.4	12.8	0				0			
thiacloprid-amide	NEOs	0								28	ND	7.01	0.811
thiamethoxam	NEOs	11	ND	303	51.0	38	ND	4.55	0.748	28	ND	7.41	2.29
NDMA	NEOs	14	ND	151	32.0	18	ND	0.142	0.0277	54	ND	6.57	0.161
6-CNA	NEOs	91	ND	4230	1110	0				0			
diazinon	OPs	23	ND	63.8	5.97	4.2	ND	0.541	0.0105	0			
ethoprophos	OPs	0				25	ND	0.0807	0.0415	59	ND	0.368	0.0228
malathion	OPs	28	ND	889000	202	13	ND	2.94	2.74	0			
IMPY	OPs	98	ND	3000	243	97	ND	463	31.1	32	ND	4.49	0.421
PNP	OPs	99	ND	1710	152	90	ND	268	3.49	0			
TCPγ	OPs	47	ND	23400	365	28	ND	289	57.2	0			
fipronil	PPs	88	ND	14900	111	0				0			
desulfinyl fipronil	PPs	44	ND	762	7.58	0				0			
fipronil sulfone	PPs	98	ND	8080	77.5	0				0			
3-PBA	PYPs	53	ND	16900	720	0				0			
4-F-3-BA	PYPs	22	ND	1790	57.0	0				0			
fenpropathrin	PYPs	27	ND	19600	8020	0				0			
carbaryl	others	58	ND	409000	149	0				0			
∑insecticides		100	70.7	905000	13400	100	1.71	472	45.6	86	ND	27.9	2.30
Herbicides													
atrazine	triazines	63	ND	266	9.77	76	ND	977	10.5	0			
OIET	triazines	25	ND	45.2	13.7	79	ND	559	20.3	0			
OIAT	triazines	0				99	ND	55.2	4.69	0			
CIAT	triazines	0				81	ND	413	6.66	0			
prometon	triazines	65	ND	698	7.43	71	ND	37.1	1.87	0			
simazine	triazines	8.6	ND	102	3.13	56	ND	189	1.45	0			
acetochlor	α-CAM	14	ND	312	31.4	50	ND	27.6	0.414	28	ND	0.198	0.0279
alachlor	α-CAM	46	ND	103	9.44	42	ND	2.67	0.471	91	ND	2.62	0.327
metolachlor	α-CAM	81	ND	315	16.7	68	ND	795	6.68	60	ND	0.0438	0.0165
acetochlor OA	α-CAM	0				22	ND	46.0	7.42	0			
metolachlor OA	α-CAM	0				81	ND	301	14.1	0			
2,4-D	others	98	ND	29500	976	56	ND	495	16.4	0			
diuron	others	83	ND	18400	70.8	39	ND	11.3	0.265	33	ND	0.339	0.0639
flumetsulam	others	0				53	ND	19.6	0.902	0			
pendimethalin	others	4.9	ND	302	73	0				0			
mesotrione	others	0				22	ND	8.45	0.361	9.9	ND	1.06	0.637
∑herbicides		100	10.3	30100	1160	100	1.27	2700	51.3	93	ND	2.70	0.409
Fungicides													
myclobutanil	azole	51	ND	719	7.21	35	ND	3.89	0.599	25	ND	0.0814	0.0223
metconazole	azole	0				0				1.2	ND	0.0106	0.0106
propiconazole	azole	65	ND	665	24.2	35	ND	1.24	0.157	0			
tebuconazole	azole	100	1.21	5000	156	61	ND	15.4	2.07	0			
azoxystrobin	strobilurin	95	ND	2650	114	38	ND	15.0	1.60	16	ND	0.242	0.0212
pyraclostrobin	strobilurin	4.9	ND	1110	344	18	ND	0.0901	0.0356	3.7	ND	0.0518	0.0146
boscalid	amide	75	ND	3560	325	26	ND	11.2	1.59	12	ND	2.67	1.20
metalaxyl	amide	0				44	ND	7.50	0.285	38	ND	0.414	0.0427
carbendazim	others	60	ND	5480	234	0				0			
∑fungicides		100	4.34	7170	995	75	ND	42.8	2.06	63	ND	2.79	0.0531
∑CUPs		100	85.4	906000	18300	100	3.70	3110	101	95	ND	28.3	2.93

[a]Urine concentrations were adjusted for specific gravity.

temperature, and sheath gas flow for the negative mode, were set to 20 psi, 10 L/min, 3000 V, 200 °C, and 10 L/min, respectively; and were set to 30 psi, 12 L/min, 2500 V, 250 °C, and 10 L/min, respectively, for the positive mode. Data acquisition was conducted in a multiple reaction monitoring (MRM) mode. The optimized MRM transitions, fragmentors,

https://doi.org/10.1021/acs.est.5c00961
Environ. Sci. Technol. 2025, 59, 12507−12519

and collision energies for target analytes, surrogate, and internal standards are obtained using the MassHunter Optimizer (Table S4).

Quality Assurance and Control. Procedural blank and matrix spike samples were analyzed along with each batch of 12 samples. The spike amounts and recoveries for each analyte are provided in Table S3. The results for procedural blanks, field blanks, and MDLs are included in Table S5. MDLs ranged from 0.01 to 2.49 ng/g in indoor dust, from 0.01 to 0.06 ng/L in drinking water, and from 0.01 to 1.75 ng/mL in urine, respectively. The highest MDL was found for IMPY across all matrices due to its relatively high procedural blank contamination. The absolute recoveries for all analytes in matrix spike samples ranged from 47 to 140%. Recoveries for surrogate standards ranged from 76 ± 5.3 to 124 ± 2.4% in indoor dust; 69 ± 1.5 to 78 ± 3.8% in water; and 45 ± 3.6 to 96 ± 3.1% in urine (Table S6). Quantification of the target analytes and surrogate standards was performed by isotope dilution of the internal standards using calibration curves with concentration ranges of 0.1−500 ng/mL. Correlation coefficients in linearity tests were all >0.99, and samples with concentrations exceeding the linearity ranges were diluted to achieve the levels within the concentration ranges of the calibration curves. Identification and quantitation of target analytes were performed on Agilent's MassHunter Quantitative Analysis Software (version B.08.00), with a retention time tolerance of ±0.1 min.

Estimated Daily Intake Calculation. Estimated daily intake (EDI) was calculated for dust intake (ingestion + dermal absorption), and drinking water intake using eq 1.[23,37]

$$\mathrm{EDI} = (C_{\mathrm{dust}} \times Q_{\mathrm{dust}} \times F_{\mathrm{uptake}} + C_{\mathrm{dust}} \times \mathrm{BSA} \times \mathrm{DAS} \times F_{\mathrm{skin}} + C_{\mathrm{water}} \times \mathrm{DWI})/\mathrm{BW} \quad (1)$$

C_{water} and C_{dust} are the median concentrations of a CUP detected in drinking water (ng/L) and indoor dust (ng/g), respectively, DWI is the daily drinking water intake: 0.028 L/kg/day, Q_{dust} is the dust ingestion rate: 30 mg/day.[38] F_{uptake} is the uptake fraction of a CUP through dust ingestion: 0.8 (unitless), BSA is the exposed body surface area: 4615 cm^2 and DAS is the amount of dust that adhered to skin: 0.01 mg/cm^2 and F_{skin} is the fraction of CUP absorbed by the skin: 0.48 (unitless),[39] BW is the body weight (kg).

Toxic Equivalency Calculation. The toxic equivalency (TEQ) model has been successfully adopted to prioritize the toxicity of different environmental contaminants.[31,40] Due to potential significant interspecies differences, human cell line assays and reporter constructs from the ToxCast program were employed in this study to assess the effects of chemical exposures on toxicity pathways relevant to human diseases.[41,42] Since biological activity data are not available for all CUPs targeted in this study and for each assay, we focused on the 66 assays retrieved from the ToxCast database that included our CUP analytes to assess their bioactivities. The details of assay selection are provided in the Supporting Information [ToxCast assay description (Excel)].

A toxicity potential for each CUP was estimated as a TEQ value, which was calculated by multiplying the weighted median EDI of a CUP analyte by its toxic equivalency factor (TEF). In each assay from the ToxCast dashboard, the concentration at 50% of maximum activity (AC_{50}) was extracted. The TEF was calculated on the basis of AC_{50} in relation to the most potent positive control that was retrieved from the EPA iCSS ToxCast Dashboard. Within a specific assay, CUP with the minimal AC_{50} was considered as a positive control, and its TEF was referred to as 1. The TEQ of each CUP and its share in the total TEQ were then calculated. TEF and TEQ_i data were provided in the Supporting Information [Detailed information on TEF and TEQ_i (Excel)]. The TEF and TEQ_i were determined by using eqs 2 and 3.

$$\mathrm{TEF} = \frac{AC_{50\,\mathrm{min}}}{AC_{50i}} \quad (2)$$

$$TEQ_i\,(\%) = \frac{TEF_i \times EDI_i}{TEQ_{\mathrm{Total}}} \times 100\% \quad (3)$$

Initially, 45 of the 47 detected CUPs were included in EDI calculations, excluding thiacloprid-amide and metconazole, which were only detected in urine, a matrix not incorporated into our EDI model based on dust and water exposure. Subsequently, TEFs were assigned to 33 out of the 45 CUPs based on their availability in the ToxCast's data set. Finally, TEQs were calculated for 22 out of these 33 CUPs, for which median EDIs were above zero.

Data Analysis. The reported concentrations were blank-corrected by subtracting the average blank levels from sample levels. For the descriptive statistics, only levels above MDL were used. For the correlation analysis, nondetects were replaced with 1/2 MDL.[43] CUP concentrations were in skewed distribution and therefore were logarithmically transformed for downstream analyses. Correlations between the concentrations of CUPs detected in more than 50% of the samples and demographic or housing characteristics were examined using Spearman correlation coefficients. A Mann−Whitney test was used for the comparison between the logarithmically transformed CUP concentrations in indoor dust from homes with different vacuuming frequencies, as well as in different drinking water sources. All statistical analyses were conducted using IBM SPSS Statistics 24 and Sigma Plot 13.

RESULTS AND DISCUSSION

Concentrations. Overall, 47 out of the 82 targeted CUPs were detected across indoor dust, drinking water, and urine samples (Table 1). The rest of the targeted CUPs (35 compounds) were not detected and are not discussed further.

Indoor Dust. Thirty-seven CUPs were detected in indoor dust with the ∑CUPs concentrations ranging from 85.4 to 906 000 ng/g (median: 18 300 ng/g). Among the detected CUPs, 20 were insecticides, 10 were herbicides, and 7 were fungicides with corresponding median total concentrations of 13 400, 1160, and 995 ng/g, respectively.

Insecticides. The 20 insecticides identified in indoor dust can be classified into four distinct categories according to their mode of action,[44] including NEOs, OPs, phenyl-pyrazoles (PPs), and PYPs. The most abundant group found in indoor dust were NEOs and their degradation products, contributing more than 70% to the total insecticide concentrations. Most NEOs, including acetamiprid, clothianidin, dinotefuran, and imidacloprid, were detected in 70−100% of indoor dust samples at median concentrations ranging from 46.1 to 1390 ng/g, except for thiacloprid and thiamethoxam, which had lower detection frequencies (DFs: 16% and 11%, respectively). Imidacloprid is the most widely used NEO in the United States,[45] which may explain its prevalence in indoor dust

https://doi.org/10.1021/acs.est.5c00961
Environ. Sci. Technol. 2025, 59, 12507−12519

(median: 1390 ng/g). Interestingly, 6-chloronicotinic acid (6-CNA), a common NEO degradation product, was detected in 91% of the samples (median: 1110 ng/g), while *N*-desmethyl-acetamiprid (NDMA), a transformation product of acetamiprid, was detected less frequently (14%) and at much lower concentrations (median: 32.0 ng/g). One possible explanation could be that 6-CNA can be transformed from 4 common NEOs (including imidacloprid, acetamiprid, nitenpyram and thiacloprid) which were all detected at relatively high concentrations in indoor dust, whereas NDMA can only be formed from acetamiprid.[45]

Overall, the median total NEOs concentration in indoor dust was 4100 ng/g, approximately 3 orders of magnitude higher than that reported in urban settings.[46−48] It has been shown that NEOs can be released into the air and undergo long-range atmospheric transport to residential areas after they have been used in agricultural applications.[49,50] This phenomenon has been reported for the Midwestern region of the United States, that includes Indiana.[51] A study in Nebraska found elevated NEO concentrations in indoor air and dust in homes near agricultural fields,[52] suggesting that outdoor use of pesticides on agricultural fields may result in higher indoor levels in nearby homes. Another explanation for the high levels of NEOs found in indoor dust could be their widespread use in domestic pet deworming products.[53,54] For example, a recent study reported high concentrations of imidacloprid in dog and cat urine (medians: 1.06 and 15.1 ng/mL, respectively) from pets treated with flea control products.[55,56]

Five OPs and their transformation products were detected in indoor dust, including diazinon, malathion, 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMPY), *p*-nitrophenol (PNP), and 3,5,6-trichloro-2-pyridinol (TCPγ). TCPγ, the primary degradation product of chlorpyrifos, was the most abundant OP found in these samples at a median concentration of 365 ng/g. IMPY and PNP were detected in more than 90% of the samples at median concentrations of 243 and 152 ng/g, respectively. In contrast, diazinon, the parent compound of IMPY, was detected in only 24% of the indoor dust samples with a median concentration of 5.97 ng/g. These diazinon concentrations were generally lower than those in several previous studies (ND−63.8 ng/g vs 1−7170 ng/g).[57−59] As the United States Environmental Protection Agency restricted the use of OPs in residential applications in 2001, the frequent detection of diazinon, IMPY, PNP, and TCPγ may be related to agricultural drift from farmlands.[60] In contrast, malathion, the only OP that is used for residential lawn care,[57] was detected only in 13% of the samples, however its maximum concentrations reached 889 000 ng/g.[61] Malathion degrades rapidly, with approximately 90% of it breaking down within 24 h,[62] thus high levels of malathion in indoor dust may indicate recent application in the vicinity of these homes.

Three PYPs and their degradation products were detected in 27−53% of the samples. Among these, fenpropathrin, 3-phenoxybenzoic acid (3-PBA), and 4-fluoro-3-phenoxybenzoic acid (4-F-3-BA) were found at median concentrations of 8020, 720, and 57.0 ng/g, respectively. As PYPs are mainly used in the U.S. for home pest control,[63] the application of these insecticides can differ significantly in terms of individual choices. Consequently, PYP concentrations in these indoor dust samples ranged from nondetectable to several μg/g levels, and this distribution pattern is similar to what has been previously found for indoor dust from New Jersey and Brazil.[63,64] In addition, given the restrictions on residential use of OPs,[60] the use of PYPs for indoor pest control in the United States has increased.[65] In fact, PYP concentrations in indoor dust were over an order of magnitude higher than those previously found in the United States.[66,67]

Fipronil, commonly applied for urban pest control and lawn care,[68,69] was frequently detected in indoor dust (DF: 88%) and had a maximum concentration of 14 900 ng/g. Temperature plays a significant role in determining the environmental fate of fipronil. In warmer climates, desulfinyl fipronil is the main photodegradation product of fipronil.[70] We found desulfinyl fipronil in less than half of the indoor dust samples from Indiana and at relatively low concentrations (DF: 44%; median: 7.58 ng/g), while another fipronil degradation product, fipronil sulfone was found in 98% of the indoor dust samples and at a higher concentration (median 77.5 ng/g). This disparity was most probably because of the cooler temperatures in Indiana that affect degradation processes of fipronil in the environment. A similar finding was reported from Northern Italy,[71] a region with a similar climate to Indiana.

Herbicides. Herbicides were frequently detected in indoor dust samples at a median total concentration of 1170 ng/g. The detection frequencies and concentrations of certain herbicides in indoor dust were generally lower than those of insecticides. The most abundant herbicide detected in indoor dust was 2,4-dichorophenoxyacetic acid (2,4-D), which constituted more than 85% of the total herbicide concentrations. The levels of 2,4-D in indoor dust (median: 976 ng/g) from Indiana were much higher than those found in Ohio and North Carolina (156 and 47.5 ng/g, respectively).[72] 2,4-D has a short half-life of 1.5 days,[73] thus its widespread occurrence may indicate a recent application in the vicinity of the sampling area. Residential applications (e.g., gardens and lawns) of 2,4-D and diuron have been banned in the United States since 2001.[60] Thus, their prevalence in indoor dust could be indicative of a drift from agricultural applications in Indiana. Diuron was also frequently detected (DF: 83%) and measured at a median concentration of 70.8 ng/g. Metolachlor, prometon and atrazine were detected in 81, 65, and 63% of the samples, respectively, but at lower concentrations (medians: 16.7, 7.43, and 9.77 ng/g, respectively) compared to 2,4-D and diuron. Other herbicides were detected in less than half of the samples.

Fungicides. Azole, strobilurin and amide fungicides were found in all indoor dust samples at a median total concentration of 995 ng/g. Boscalid was the most abundant fungicide detected in indoor dust with a median concentration at 325 ng/g, followed by carbendazim (median: 234 ng/g), tebuconazole (156 ng/g), and azoxystrobin (114 ng/g). The boscalid level in Indiana was comparable to that reported in Washington.[74] The detection frequency of carbendazim was relatively lower compared to that reported in China, however, the concentration of carbendazim measured in the current study was much higher (medians: 234 ng/g vs 35.8 ng/g, respectively).[46] Tebuconazole was ubiquitous in indoor dust (median: 156 ng/g), which was orders of magnitude higher than those found in China (0.21−1.44 ng/g) and Washington (1−2 ng/g).[74,75] A higher concentration of azoxystrobin (median: 114 ng/g) was found in our study than that in Washington and North Carolina.[74,76]

Drinking Water. Thirty-three CUPs were detected in drinking water at a median $\sum$CUP concentration of 101 ng/L.

https://doi.org/10.1021/acs.est.5c00961
Environ. Sci. Technol. 2025, 59, 12507−12519

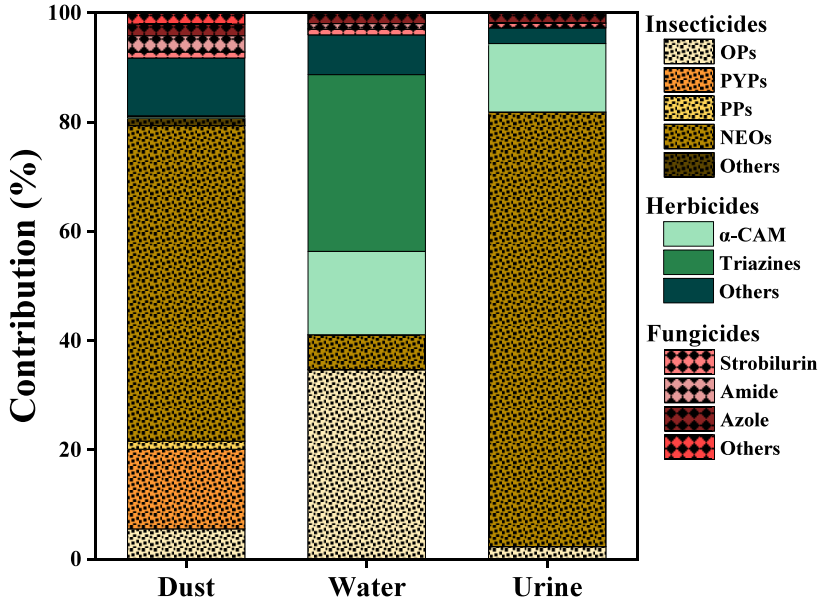


Figure 1. Percent contributions (%) of individual CUPs to the total CUP concentrations in indoor dust, drinking water, and urine (calculated based on median concentrations). Abbreviations: OPs, organophosphates; PYPs, pyrethroid pesticides; PPs, phenylpyrazoles; NEOs, neonicotinoids; and α-CAM, α-chloroacetamides.

Among these, 11 insecticides, 15 herbicides, and 7 fungicides were detected at median total concentrations of 45.6, 51.3, and 2.06 ng/L, respectively. About 10% of the drinking water samples analyzed here had ∑CUP concentrations above 0.5 μg/L, which is the maximum allowable total pesticide concentration established in the European Union.[77]

Insecticides. Five NEOs were identified in drinking water with median concentrations ranging from 0.0277 to 6.70 ng/L (median total NEOs concentration: 17.9 ng/L), which were comparable to those reported in other studies.[22,78−80] OPs were more frequently detected compared to NEOs and found at higher concentrations (median total OP concentration: 99.4 ng/L). IMPY and PNP were detected in more than 90% of the samples at median concentrations of 31.1 and 3.49 ng/L, respectively. While several water treatment processes, such as granular activated carbon filtration, powdered activated carbon contact, and bacteria degradation, have been shown to be effective in removing most of the pesticide residues from drinking water sources,[81,82] removal of some OPs has been reported to be less efficient compared to other pesticides.[83,84] Other OPs, including diazinon, ethoprophos, and malathion, were less frequently detected, whereas PPs and PYPs were not detected in any of the samples, probably due to their low solubility.[49]

Herbicides. Sixteen herbicides were found in drinking water samples. Herbicides were the predominant group of CUPs in drinking water samples and contributed 55% to the ∑CUP concentrations (Figure 1). Atrazine and its derivatives were the predominant herbicides detected in drinking water, constituting over 50% of the total herbicide concentrations. This finding aligns with previous studies that have reported atrazine and its derivatives in drinking water in North America.[85,86] The median concentrations of atrazine, 2-hydroxyatrazine (OIET), 2-hydroxy-4-isopropylamino-6-amino-*s*-triazine (OIAT), and desethyl-atrazine (CIAT), ranged from 4.69 to 20.3 ng/L. These levels were considerably higher than those of prometon and simazine, (medians: 1.87 and 1.45 ng/L, respectively). The elevated concentrations of atrazine and its derivatives can be attributed to their frequent use as well as their higher persistence compared to other *s*-triazine compounds.[87] Additionally, the detection frequencies of atrazine derivatives were higher than those of their parent compound (79, 99, and 81 vs 76%), a trend also noted in a previous Iowa study.[87] It should be noted that more than 13% of the drinking water samples had an atrazine level over 100 ng/L, a concentration potentially associated with an increased risk of small-for-gestational-age birth.[88]

Five α-CAM (α-chloroacetamide) herbicides, including acetochlor, metolachlor, alachlor, acetochlor OA, and metolachlor OA, were detected in 22−81% of the drinking water samples. The median total concentration of α-CAM herbicides was 15.8 ng/L, with a maximum concentration reaching 1050 ng/L. The ubiquitous detection of α-CAM herbicides and their transformation products has been previously reported in drinking water samples collected from the Midwestern region of the United States.[89]

Fungicides. Seven fungicides across 3 different categories were detected in drinking water with a median total concentration of 2.06 ng/L. Tebuconazole was the only fungicide detected in over half of the samples, while other compounds were less frequently detected (<44%). These infrequent detections may be attributed to the effective water treatment removal, as research has shown that drinking water treatment plants can efficiently remove various types of fungicides, achieving removal efficiencies of 86% for propiconazole, 88% for tebuconazole, and 100% for azoxystrobin.[90]

Urine. Nineteen CUPs were detected in urine, with a median ∑CUP concentration of 2.93 ng/mL, similar to concentrations reported in previous studies.[91−94] The most abundant pesticides were insecticides with a median total concentration of 2.30 ng/mL, followed by herbicides (0.409 ng/mL) and fungicides (0.0531 ng/mL). A few NEOs and their transformation products, including clothianidin, dinotefuran, imidacloprid, thiacloprid-amide, thiamethoxam and NDMA, were found in urine with detection frequencies up

https://doi.org/10.1021/acs.est.5c00961
Environ. Sci. Technol. 2025, 59, 12507−12519

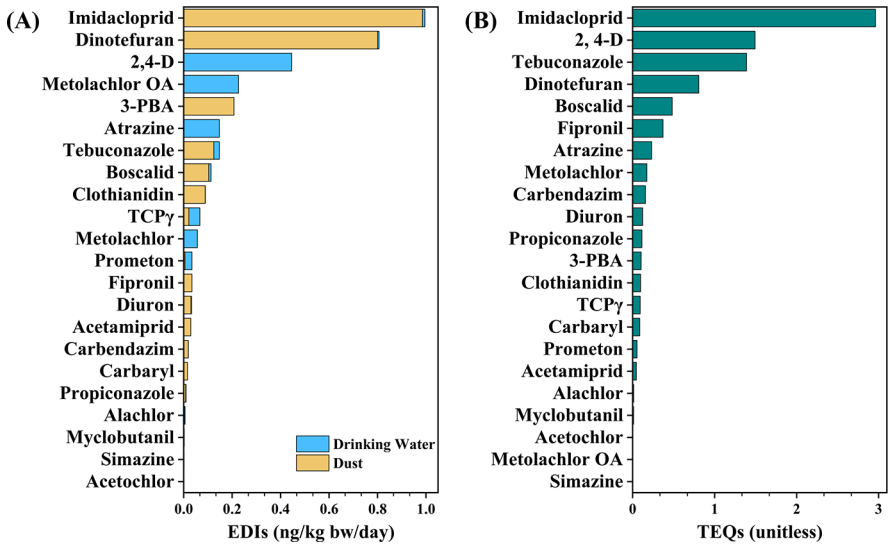


Figure 2. Estimated daily intakes (EDIs, ng/kg of bw/day) (A) and calculated toxic equivalency quotients (TEQs, unitless) (B), ranked in descending order. Only CUPs with available ToxCast data are included. Abbreviations: 2,4-D, 2,4-dichorophenoxyacetic acid; metolachlor OA, metolachlor oxanilic acid; 3-PBA, 3-phenoxybenzoic acid; and TCPγ, 3,5,6-trichloro-2-pyridinol.

to 54%. Two OPs, including ethoprophos and IMPY, were also detected but at relatively lower frequencies. This was different from the findings in a study from France where OPs were found in 100% of the analyzed urine samples.[95] No PYPs or PPs were detected in the current study.

Herbicides were detected in 93% of urine samples. Notably, each herbicide identified in urine samples was also found in drinking water samples, albeit generally at lower frequencies and concentrations, with the exception of alachlor. This herbicide had a significantly higher detection frequency in urine (91%) compared to drinking water (42%) and indoor dust (46%). The higher detection frequency of alachlor in urine suggests possible alternative exposure pathways other than indoor dust and drinking water through which humans are exposed to alachlor, such as food consumption.[96]

Individual fungicides were detected in less than 50% of the samples. Only a few studies have monitored fungicides in human samples. One study from North China found that azole fungicides were detected in human cerebrospinal fluid samples,[36] however, none of these fungicides were found in urine samples.

Comparison of Distribution Patterns. The distribution profile of CUPs in environmental and biological samples is presented in Figure 1. Overall, insecticides contributed 80% to the $\sum$CUP concentrations in indoor dust, followed by herbicides and fungicides (11 and 9%, respectively), similar to the profile in urine (82, 15, and 3.0% for insecticides, herbicides and fungicides, respectively). In contrast, herbicides were the most abundant group in drinking water, contributing 55% of the $\sum$CUP concentrations, followed by insecticides (41%) and fungicides (4.0%). The latter pattern corresponds to the pesticide usage trend in Indiana (data based on the 1995−2015 state census), which is heavily dominated by herbicides (Figure S1),[50] suggesting that agricultural pesticide use may have an effect on the occurrence of pesticides in drinking water. However, the application of household pesticides is likely to have a greater impact on indoor dust, largely influenced by individual preferences.[24,97] This assumption is further supported by a significantly higher variability in concentrations found in indoor dust compared to water samples (Figure S2; p = 0.027), with dust pesticide concentrations ranging from nondetectable to several micrograms per gram. Additionally, the differences in CUPs distribution in indoor dust, water, and urine can be explained by the inherent physicochemical characteristics of pesticides. For example, PPs and PYPs comprised up to 19% of the $\sum$CUP concentrations in indoor dust, while they were not detected in drinking water at all. This is likely due to the low water solubility of these compounds (log K_{oa} of ∼10),[98] and their higher binding affinity to dust particles.[49,99] In contrast, the abundance of NEOs in drinking water and urine is likely related to their higher water solubility compared to other CUP groups. In addition, correlation analysis of the concentrations of insecticides, herbicides, and fungicides in indoor dust revealed a significant association between insecticides and herbicides (p < 0.05). Similarly, significant correlations were observed among all three pesticide groups in drinking water (p < 0.05). These findings suggest that specific groups of pesticides may share a common source of contamination within certain environmental matrices.

Effect of Demographic and Housing Characteristics on CUP Concentrations. Households with frequent vacuuming had significantly lower $\sum$CUP concentrations in indoor dust compared to homes that were vacuumed less frequently (medians: 20 100 vs 13 900 ng/g; p = 0.04; Figure S3), indicating that more frequent vacuuming may lower indoor exposure to CUPs. This observation aligns with prior studies demonstrating that cleaning carpets and windowsills in farmworker homes reduces OP residues in indoor dust by ∼67%.[84]

Notably, the $\sum$CUP concentrations in private well water were significantly lower than those in municipal water (medians: 40.6 and 105 ng/L; p = 0.003; Figure S4). These differences may be related to the local municipal water infrastructure.[100,101] No significant associations were observed between pesticide concentrations and other demographic parameters or housing characteristics.

Exposure Assessment and Toxicity Prioritization of CUPs. EDIs of CUPs via consumption of drinking water, indoor dust (ingestion + dermal absorption) were evaluated

https://doi.org/10.1021/acs.est.5c00961
Environ. Sci. Technol. 2025, 59, 12507−12519

based on the median CUP concentrations in drinking water and indoor dust (Figure 2A). Overall, our results show that exposure through dust is more significant for insecticides and fungicides, while drinking water consumption is more important for herbicides (Figure 2A). The highest EDI was found for imidacloprid (1.00 ng/kg of bw/day), followed by IMPY (0.919 ng/kg of bw/day), dinotefuran (0.806 ng/kg of bw/day), 6-CNA (0.557 ng/kg of bw/day) and 2,4-D (0.446 ng/kg of bw/day). The EDIs of individual CUPs were below the tolerable daily intake thresholds established by the U.S. EPA (Table S7).[102]

To evaluate the toxicity of the targeted CUPs at the exposure levels determined here, we used a TEF model to determine the health risks of these exposures (Figure 2B).[31] The TEQ values for insecticides, herbicides, and fungicides were estimated as 4.56, 2.09, and 2.15, respectively. The TEQ ranking of insecticides, herbicides, and fungicides was different from the EDI (Figure S5). It is worth noting that although intake of fungicides based on water and dust exposure was lower compared to that of insecticides and herbicides, the results of the TEQ model demonstrate that fungicide toxicity is similar to that of herbicides. This funding concurs with the well-recognized aggravated risk concern of fungicides.[103]

Among individual CUPs, imidacloprid had the highest TEQ of 2.97. This TEQ value was a result of two factors: high exposure levels of imidacloprid and its ability to activate various adverse outcome pathways (AOPs), including the CYP (cytochrome P450 proteins), p53, and FASN (fatty acid synthase) pathways. According to the ToxCast database, the activation of the CYP pathway is involved in inducing most of the toxic end points. Multiple studies have shown that activation of the P450 genetic pathway is associated with an increased risk of cancer.[104,105] The tumor-suppressor gene p53 also plays a role in responses to imidacloprid exposure. As a critical regulator of DNA replication and cell division, dysfunction of p53 is known to lead to various cancers.[106] Additionally, the FASN pathway, essential for lipid metabolism and energy supply, has been linked to various malignancies, such as colorectal cancer.[107,108] In fact, evidence on the carcinogenicity of imidacloprid had been reported in *in vitro* and human health studies[109,110] Given these findings, there is a compelling need to explore the health risks posed by imidacloprid in humans, especially considering the high indoor exposure.

2,4-D was identified as the second highest risk pesticide with a TEQ value of 1.49. 2,4-D activates the peroxisome proliferators-activated receptor γ (PPARγ), p53, and hypoxia inducible factor 1 (HIF1A) pathways (Figures 2B and 3). It has been demonstrated that exposure to 2,4-D induces reproductive toxicity via PPAR activation in mice and disrupts glucose metabolism by activating PPARβ in HepG2 cells.[111,112] Furthermore, exposure to 2,4-D has been associated with various adverse health outcomes, including cancer, reproductive toxicity, genotoxicity, and neurotoxicity.[113]

Dinotefuran was ranked as the third high-risk compound based on our results. According to the data from the ToxCast database, dinotefuran is a potent activator of the liver X receptor (LXR), which plays a crucial role in regulating systemic cholesterol metabolism.[114−116] Studies have shown that exposure to dinotefuran can disrupt lipid metabolism in animals, reflecting its capacity to interfere with essential metabolic processes.[117,118] Furthermore, exposure to dinotefuran has been associated with childhood adiposity.[119]

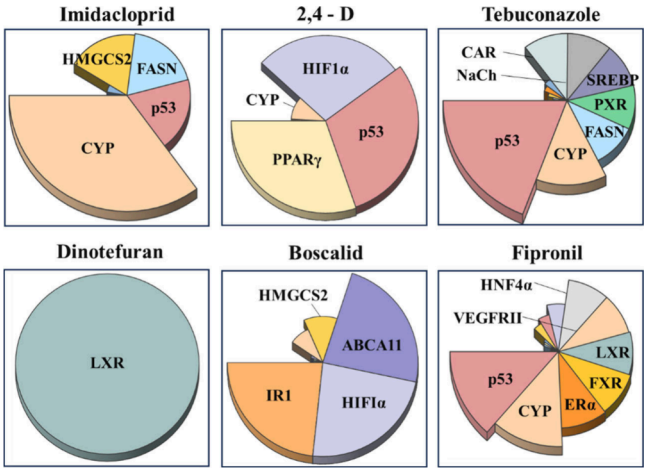


Figure 3. Bioactivity hits for the selected CUPs based on the ToxCast database. Abbreviations: ABCA11, members of the ATP-binding cassette subfamily A; CAR, constitutive and rostane receptor; CYP, cytochrome P450; ERα, estrogen receptor α; FASN, fatty acid synthase; FXR, farnesoid X receptor; HIF1α, hypoxia inducible factor 1 subunit α; HMGCS2, HMG-CoA synthase 2; HNF4α, human hepatocyte nuclear factor α; IR1, imidazoline 1 receptor; LXR, liver X receptor; NaCh, nicotinic acetylcholine receptor; PPARγ, peroxisome proliferator-activated receptor γ; PXR, pregnane X receptor; SREBP, sterol regulatory element-binding protein; and VEGFRII, vascular endothelial growth factor receptor II.

Interestingly, the TEQ model demonstrates some inconsistencies regarding the evaluation of risks based solely on the EDIs. For example, based on the EDIs calculated in this study, risks based on the intake of certain CUPs, such as tebuconazole, fipronil and boscalid, are minimal (<0.2 ng/kg of bw/day). However, when considering toxicity pathways based on the TEF model, it is clear that tebuconazole can activate several AOs (adverse outcomes), including CYP, p53, and FASN (Figure 3). In fact, tebuconazole is reported to cause cognitive disorders, liver toxicity, reproductive toxicity, and colitis in several animal models.[120−123] In addition, fipronil exposure, as modeled in the TEQ, is linked to the activation of several pathways (e.g., CYP, ERα, and FXR), potentially triggering multiple adverse effects. Both *in vitro* and *in vivo* toxicological studies have shown that fipronil exposure could induce hepatotoxic, nephrotoxic, neurotoxic, and altered reproductive development and endocrine systems in humans and animals.[124] These findings suggest that the TEQ model can provide valuable insights into health risks by integrating real-world exposure scenarios.

Limitations. This study has several limitations. First, a single spike pretreatment method was employed in the current study. The implementation of multiconcentration designs for validating pretreatment methods should be prioritized to ensure the effective detection of CUPs in future large-scale biomonitoring projects. Additionally, our study had a small sample size collected from a limited geographic area. Geographical factors, seasonal variations, and other exposure pathways (such as food consumption and inhalation) are important elements influencing the occurrence patterns of CUPs.[125,126] These factors should be considered in future research. Furthermore, the limited number of CUPs and their transformation products included in the ToxCast database restricted our ability to evaluate health risks for all the CUPs targeted in this study.

https://doi.org/10.1021/acs.est.5c00961
Environ. Sci. Technol. 2025, 59, 12507−12519

Environmental Implications. This study reports a comprehensive multimedia assessment of exposure to CUPs in an agricultural region of the United States and sheds light on the potential health risks of these exposures when considering both exposure levels and toxicity of individual chemicals. Our study demonstrates that imidacloprid represents the highest risk due to both high intake through multiple exposure routes as well as the ability to activate several adverse outcome pathways. Notably, current regulatory frameworks lack mitigation strategies for the health risks of imidacloprid, thus continuous monitoring and toxicity evaluation are crucial for effective risk management and ensuring public health safety. In addition, the high levels of NEOs in indoor dust with relatively lower concentrations found in drinking water indicate that residential indoor use of NEOs may be an important source of exposure. The TEQ model demonstrated that risk evaluation based solely on EDIs can underestimate the health risks of CUPs. However, the health effects of CUPs with high TEQs, with data based on the *in vitro* ToxCast database warrant further validation through *in vivo* and epidemiological studies.[127] Moreover, humans are exposed to a cocktail of environmental contaminants at low doses that may result in more complex synergistic or antagonistic effects,[128] and a more comprehensive approach involving both mixture effects and cumulative toxicity evaluations is needed to fully understand the overall health effects of these pesticides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.5c00961.

Detailed information on chemicals and reagents, population characteristics, MRM transitions, surrogate and matrix spike recoveries, MDLs and blank concentrations, of targeted CUPs, reference doses, pesticide use in Indiana, and variation coefficients (PDF)

Description of the ToxCast assay end points and details of the TEF, TEQ, and EDI calculations provided in the ToxCast assay description (XLSX)

Detailed information of TEF and TEQ_i (XLSX)

Detailed information of EDI (XLSX)

■ AUTHOR INFORMATION

Corresponding Authors

Guomao Zheng − *Shenzhen Key Laboratory of Precision Measurement and Early Warning Technology for Urban Environmental Health Risks, School of Environmental Science and Engineering, Southern University of Science and Technology, Shenzhen 518055, China;* orcid.org/0000-0002-5235-9950; Email: zhenggm@sustech.edu.cn

Amina Salamova − *Gangarosa Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, Georgia 30322, United States;* orcid.org/0000-0003-2174-030X; Email: amina.salamova@emory.edu

Authors

Yichun Xie − *Shenzhen Key Laboratory of Precision Measurement and Early Warning Technology for Urban Environmental Health Risks, School of Environmental Science and Engineering, Southern University of Science and Technology, Shenzhen 518055, China*

Juying Li − *College of Chemistry and Environmental Engineering, Shenzhen University, Shenzhen 518060, China;* orcid.org/0000-0003-1294-241X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.est.5c00961

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Indiana University, the Indiana Clinical and Translational Sciences Institute, the Shenzhen Science and Technology Program (KQTD20240729102048052), the National Natural Science Foundation of China (22206071), the Shenzhen Key Laboratory of Precision Measurement and Early Warning Technology for Urban Environmental Health Risks (ZDSYS20220606100604008), and High Level of Special Funds (G03050K001) for funding this project. The authors also appreciate the tremendous effort in the recruitment and sample collection by the Indiana University Center for Survey Research and the Person-to-Person Health Interview Study. The authors sincerely thank Dr. Li Juan for her assistance with ArcGIS and extend their gratitude to Haoran Xia, Zihao Zhang, Xinrui Leng, Xi He, Jia Zhao, and Xiaozhen Zhang for their valuable contributions in collecting the ToxCast data. The authors are also grateful to the study participants for donating their time and samples. The authors also thank Dr. Marta Venier for the overall support of the study.

■ REFERENCES

(1) Begum, A., Alam, S. N., Jalal Uddin, M. Management of pesticides: Purposes, uses, and concerns. *Pesticide Residue in Foods: Sources, Management, and Control*; Khan, M. S., Rahman, M. S., Eds.; Springer International Publishing: Cham, Switzerland, 2017; pp 53−86.

(2) Mohafrash, S. M.; Mossa, A.-T. H. Disposal of expired empty containers and waste from pesticides. *Egyptian J. Chem.* **2023**, *67* (4), 65−85.

(3) Heckel, D. G. Insecticide resistance after Silent Spring. *Science.* **2012**, *337* (6102), 1612−4.

(4) Epstein, L. Fifty years since Silent Spring. *Annu. Rev. Phytopathol.* **2014**, *52*, 377−402.

(5) Pućko, M.; Stern, G. A.; Burt, A. E.; Jantunen, L. M.; Bidleman, T. F.; Macdonald, R. W.; Barber, D. G.; Geilfus, N. X.; Rysgaard, S. Current use pesticide and legacy organochlorine pesticide dynamics at the ocean-sea ice-atmosphere interface in resolute passage, Canadian Arctic, during winter-summer transition. *Sci. Total Environ.* **2017**, *580*, 1460−9.

(6) Mohamed, A. H.; Noorhisham, N. A.; Yahaya, N.; Mohamad, S.; Kamaruzzaman, S.; Osman, H.; Aboul-Enein, H. Y. Sampling and sample preparation techniques for the analysis of organophosphorus pesticides in soil matrices. *Crit. Rev. Anal. Chem.* **2023**, *53* (4), 906−27.

(7) Hertz-Picciotto, I.; Sass, J. B.; Engel, S.; Bennett, D. H.; Bradman, A.; Eskenazi, B.; Lanphear, B.; Whyatt, R. Organophosphate exposures during pregnancy and child neurodevelopment: Recommendations for essential policy reforms. *PLoS. Med.* **2018**, *15* (10), No. e1002671.

(8) Wang, S.; Salamova, A.; Hites, R. A.; Venier, M. Spatial and seasonal distributions of current usepesticides (CUPs) in the atmospheric particulate phase in the Great Lakes region. *Environ. Sci. Technol.* **2018**, *52* (11), 6177−86.

(9) Kalyabina, V. P.; Esimbekova, E. N.; Kopylova, K. V.; Kratasyuk, V. A. Pesticides: Formulants, distribution pathways and effects on human health - a review. *Toxicol. Rep.* **2021**, *8*, 1179−92.

(10) Janoš, T.; Ottenbros, I.; Bláhová, L.; Šenk, P.; Šulc, L.; Pálešová, N.; Sheardová, J.; Vlaanderen, J.; Čupr, P. Effects of pesticide exposure on oxidative stress and DNA methylation urinary biomarkers in Czech adults and children from the CELSPAC-SPECIMEn cohort. *Environ. Res.* **2023**, *222*, 115368.
(11) Kongtip, P.; Nankongnab, N.; Pundee, R.; Kallayanatham, N.; Pengpumkiat, S.; Chungcharoen, J.; Phommalachai, C.; Konthonbut, P.; Choochouy, N.; Sowanthip, P.; Khangkhun, P.; Yimsabai, J.; Woskie, S. Acute changes in thyroid hormone levels among Thai pesticide sprayers. *Toxics* **2021**, *9* (1), 16.
(12) Gao, B.; Poma, G.; Malarvannan, G.; Dumitrascu, C.; Bastiaensen, M.; Wang, M.; Covaci, A. Development of an analytical method based on solid-phase extraction and LC-MS/MS for the monitoring of current-use pesticides and their metabolites in human urine. *J. Environ. Sci. (China).* **2022**, *111*, 153−63.
(13) Zheng, G.; Eick, S. M.; Salamova, A. Elevated levels of ultrashort- and short-chain perfluoroalkyl acids in US homes and people. *Environ. Sci. Technol.* **2023**, *57* (42), 15782−93.
(14) Zheng, G.; Filippelli, G. M.; Salamova, A. Increased indoor exposure to commonly used disinfectants during the COVID-19 pandemic. *Environ. Sci. Technol. Lett.* **2020**, *7* (10), 760−5.
(15) Simcox, N. J.; Fenske, R. A.; Wolz, S. A.; Lee, I. C.; Kalman, D. A. Pesticides in household dust and soil: Exposure pathways for children of agricultural families. *Environ. Health. Perspect.* **1995**, *103* (12), 1126−34.
(16) Gaspar, F. W.; Chevrier, J.; Bornman, R.; Crause, M.; Obida, M.; Barr, D. B.; Bradman, A.; Bouwman, H.; Eskenazi, B. Undisturbed dust as a metric of long-term indoor insecticide exposure: Residential DDT contamination from indoor residual spraying and its association with serum levels in the VHEMBE cohort. *Environ. Int.* **2015**, *85*, 163−7.
(17) Gunier, R. B.; Ward, M. H.; Airola, M.; Bell, E. M.; Colt, J.; Nishioka, M.; Buffler, P. A.; Reynolds, P.; Rull, R. P.; Hertz, A.; Metayer, C.; Nuckols, J. R. Determinants of agricultural pesticide concentrations in carpet dust. *Environ. Health. Perspect.* **2011**, *119* (7), 970−6.
(18) Guo, J.; Li, A. Trends in sample preparation and analysis of current use pesticides in abiotic environmental matrices. *TrAC* **2024**, *172*, 117605.
(19) Sjerps, R. M. A.; Kooij, P. J. F.; van Loon, A.; Van Wezel, A. P. Occurrence of pesticides in Dutch drinking water sources. *Chemosphere.* **2019**, *235*, 510−8.
(20) Aparicio, V.; De Gerónimo, E. Pesticide pollution in argentine drinking water: A call to ensure safe access. *Environ. Challenges.* **2024**, *14*, 100808.
(21) Cosgrove, S.; Jefferson, B.; Jarvis, P. Pesticide removal from drinking water sources by adsorption: A review. *Environ. Technol. Rev.* **2019**, *8* (1), 1−24.
(22) Xiong, Z.; Wu, Y.; Zhou, Y.; He, S.; Huang, D.; Zhang, M.; Jiang, Y.; Cheng, L.; Zhao, Z.; Zhao, H.; Lin, H. Rapid determination and health risk assessment of neonicotinoids in source water and tap water of the tropical Hainan Island, China. *Environ. Sci. Pollut. Res. Int.* **2023**, 1−12.
(23) Mahai, G.; Wan, Y.; Xia, W.; Wang, A.; Shi, L.; Qian, X.; He, Z.; Xu, S. A nationwide study of occurrence and exposure assessment of neonicotinoid insecticides and their metabolites in drinking water of China. *Water. Res.* **2021**, *189*, 116630.
(24) Deziel, N. C.; Friesen, M. C.; Hoppin, J. A.; Hines, C. J.; Thomas, K.; Freeman, L. E. A review of nonoccupational pathways for pesticide exposure in women living in agricultural areas. *Environ. Health. Perspect.* **2015**, *123* (6), 515−24.
(25) Castorina, R.; Bradman, A.; Fenster, L.; Barr, D. B.; Bravo, R.; Vedar, M. G.; Harnly, M. E.; McKone, T. E.; Eisen, E. A.; Eskenazi, B. Comparison of current-use pesticide and other toxicant urinary metabolite levels among pregnant women in the CHAMACOS cohort and NHANES. *Environ. Health. Perspect.* **2010**, *118* (6), 856−63.
(26) Pirard, C.; Remy, S.; Giusti, A.; Champon, L.; Charlier, C. Assessment of children's exposure to currently used pesticides in Wallonia, Belgium. *Toxicol. Lett.* **2020**, *329*, 1−11.
(27) Arbuckle, T. E.; Bruce, D.; Ritter, L.; Hall, J. C. Indirect sources of herbicide exposure for families on Ontario farms. *J. Expo. Sci. Environ. Epidemiol.* **2006**, *16* (1), 98−104.
(28) Chio, E. H.; Li, Q. X. Pesticide research and development: General discussion and spinosad case. *J. Agric. Food. Chem.* **2022**, *70* (29), 8913−9.
(29) Xie, S.; Hofmann, J. N.; Sampson, J. N.; Josse, P. R.; Andreotti, G.; Madrigal, J. M.; Ward, M. H.; Beane Freeman, L. E.; Friesen, M. C. Elevated 2,4-dichlorophenoxyacetic acid (2,4-D) herbicide concentrations in the household dust of farmers with recent occupational use. *J. Occup. Environ. Hyg.* **2023**, *20* (5−6), 207−18.
(30) 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.
(31) Dong, T.; Zhang, Y.; Jia, S.; Shang, H.; Fang, W.; Chen, D.; Fang, M. Human indoor exposome of chemicals in dust and risk prioritization using EPA's ToxCast database. *Environ. Sci. Technol.* **2019**, *53* (12), 7045−54.
(32) Baldwin, A. K.; Corsi, S. R.; Stefaniak, O. M.; Loken, L. C.; Villeneuve, D. L.; Ankley, G. T.; Blackwell, B. R.; Lenaker, P. L.; Nott, M. A.; Mills, M. A. Risk-based prioritization of organic chemicals and locations of ecological concern in sediment from Great Lakes tributaries. *Environ. Toxicol. Chem.* **2022**, *41* (4), 1016−41.
(33) Pronschinske, M. A.; Corsi, S. R.; DeCicco, L. A.; Furlong, E. T.; Ankley, G. T.; Blackwell, B. R.; Villeneuve, D. L.; Lenaker, P. L.; Nott, M. A. Prioritizing pharmaceutical contaminants in Great Lakes tributaries using risk-based screening techniques. *Environ. Toxicol. Chem.* **2022**, *41* (9), 2221−39.
(34) Schaafsma, A. W.; Limay-Rios, V.; Forero, L. G. The role of field dust in pesticide drift when pesticide-treated maize seeds are planted with vacuum-type planters. *Pest Manag Sci.* **2018**, *74* (2), 323−31.
(35) Xiang, J.; Fu, C. Z.; Xu, R. Q.; Lu, Q. Y.; Tang, B.; Xing, Q.; Wang, L. C.; Hao, Q. W.; Mo, L.; Zheng, J. Occurrence and risk assessment of current-use pesticides in a tropical drinking water source reservoir in Hainan Province, China. *Environ. Sci. Process. Impacts.* **2025**, *27* (4), 1063−73.
(36) Zhao, K. X.; Zhang, M. Y.; Yang, D.; Zhu, R. S.; Zhang, Z. F.; Hu, Y. H.; Kannan, K. Screening of pesticides in serum, urine and cerebrospinal fluid collected from an urban population in China. *J. Hazard. Mater.* **2023**, *449*, 131002.
(37) Zhang, H.; Shen, K.; Wu, R.; Li, Z.; Wang, X.; Wang, D.; Zhan, M.; Xu, W.; Gao, Y.; Lu, L. Occurrence and distribution of neonicotinoids and characteristic metabolites in paired urine and indoor dust from young adults: Implications for human exposure. *Environ. Res.* **2021**, *199*, 111175.
(38) United States Environmental Protection Agency (U.S. EPA). *Exposure Factors Handbook*; U.S. EPA: Washington, D.C., 2011; EPA/600/R-09/052F.
(39) Stubbings, W. A.; Schreder, E. D.; Thomas, M. B.; Romanak, K.; Venier, M.; Salamova, A. Exposure to brominated and organophosphate ester flame retardants in U.S. childcare environments: Effect of removal of flame-retarded nap mats on indoor levels. *Environ. Pollut.* **2018**, *238*, 1056−68.
(40) Qiao, L.; Gao, L.; Huang, D.; Liu, Y.; Xu, C.; Li, D.; Zheng, M. Screening of ToxCast chemicals responsible for human adverse outcomes with exposure to ambient air. *Environ. Sci. Technol.* **2022**, *56* (11), 7288−97.
(41) Phillips, M. B.; Leonard, J. A.; Grulke, C. M.; Chang, D. T.; Edwards, S. W.; Brooks, R.; Goldsmith, M. R.; El-Masri, H.; Tan, Y. M. A workflow to investigate exposure and pharmacokinetic influences on high-throughput *in vitro* chemical screening based on adverse outcome pathways. *Environ. Health. Perspect.* **2016**, *124* (1), 53−60.
(42) Aguayo-Orozco, A.; Audouze, K.; Siggaard, T.; Barouki, R.; Brunak, S.; Taboureau, O. sAOP: Linking chemical stressors to

adverse outcomes pathway networks. *Bioinformatics.* **2019**, *35* (24), 5391−2.
(43) Jiang, W.; Conkle, J. L.; Luo, Y.; Li, J.; Xu, K.; Gan, J. Occurrence, distribution, and accumulation of pesticides in exterior residential areas. *Environ. Sci. Technol.* **2016**, *50* (23), 12592−601.
(44) Insecticide Resistance Action Committee (IRAC). *The IRAC Mode of Action Classification Online*, 2024; https://irac-online.org/mode-of-action/classification-online/ (accessed May 28, 2024).
(45) Simon-Delso, N.; Amaral-Rogers, V.; Belzunces, L. P.; Bonmatin, J. M.; Chagnon, M.; Downs, C.; Furlan, L.; Gibbons, D. W.; Giorio, C.; Girolami, V.; Goulson, D.; Kreutzweiser, D. P.; Krupke, C. H.; Liess, M.; Long, E.; McField, M.; Mineau, P.; Mitchell, E. A.; Morrissey, C. A.; Noome, D. A.; Pisa, L.; Settele, J.; Stark, J. D.; Tapparo, A.; Van Dyck, H.; Van Praagh, J.; Van der Sluijs, J. P.; Whitehorn, P. R.; Wiemers, M. Systemic insecticides (neonicotinoids and fipronil): Trends, uses, mode of action and metabolites. *Environ. Sci. Pollut. Res. Int.* **2015**, *22* (1), 5−34.
(46) Wang, A.; Mahai, G.; Wan, Y.; Jiang, Y.; Meng, Q.; Xia, W.; He, Z.; Xu, S. Neonicotinoids and carbendazim in indoor dust from three cities in China: Spatial and temporal variations. *Sci. Total Environ.* **2019**, *695*, 133790.
(47) Chen, Q.; Zhang, Y.; Su, G. Comparative study of neonicotinoid insecticides (NNIs) and NNI-related substances (r-NNIs) in foodstuffs and indoor dust. *Environ. Int.* **2022**, *166*, 107368.
(48) Huang, Y.; Zhang, B.; Xue, J.; Lan, B.; Guo, Y.; Xu, L.; Zhang, T. A pilot nationwide survey on the concentrations of neonicotinoids and their metabolites in indoor dust from China: Application for human exposure. *Bull. Environ. Contam. Toxicol.* **2022**, *109* (5), 900−9.
(49) Bonmatin, J. M.; Giorio, C.; Girolami, V.; Goulson, D.; Kreutzweiser, D. P.; Krupke, C.; Liess, M.; Long, E.; Marzaro, M.; Mitchell, E. A.; Noome, D. A.; Simon-Delso, N.; Tapparo, A. Environmental fate and exposure; neonicotinoids and fipronil. *Environ. Sci. Pollut. Res. Int.* **2015**, *22* (1), 35−67.
(50) National Agricultural Statistics Service (NASS), United States Department of Agriculture (USDA). *Census of Agriculture—State Data*, 2017; https://www.nass.usda.gov/Publications/AgCensus/2017/Full_Report/Volume_1,_Chapter_1_State_Level/Indiana/st18_1_0001_0001.pdf (accessed Dec 20, 2024).
(51) Thompson, D. A.; Hruby, C. E.; Vargo, J. D.; Field, R. W. Occurrence of neonicotinoids and sulfoxaflor in major aquifer groups in Iowa. *Chemosphere.* **2021**, *281*, 130856.
(52) Taiba, J.; Rogan, E. G.; Snow, D. D.; Achutan, C.; Zahid, M. Characterization of environmental levels of pesticide residues in household air and dust samples near a bioenergy plant using treated seed as feedstock. *Int. J. Environ. Res. Public. Health.* **2023**, *20* (21), 6967.
(53) Forrester, M. B. Neonicotinoid insecticide exposures reported to six poison centers in Texas. *Hum. Exp. Toxicol.* **2014**, *33* (6), 568−73.
(54) Casida, J. E. Neonicotinoids and other insect nicotinic receptor competitive modulators: Progress and prospects. *Annu. Rev. Entomol.* **2018**, *63*, 125−44.
(55) Li, Z. M.; Robinson, M.; Kannan, K. An assessment of exposure to several classes of pesticides in pet dogs and cats from New York, United States. *Environ. Int.* **2022**, *169*, 107526.
(56) Kilduff, S.; Steinman, B.; Xie, Y.; Kiss-Farengo, T.; Foca, M.; Hayde, N. Pet safety guidelines for pediatric transplant recipients. *Pediatr. Transplant.* **2024**, *28* (1), No. e14527.
(57) Harnly, M. E.; Bradman, A.; Nishioka, M.; McKone, T. E.; Smith, D.; McLaughlin, R.; Kavanagh-Baird, G.; Castorina, R.; Eskenazi, B. Pesticides in dust from homes in an agricultural area. *Environ. Sci. Technol.* **2009**, *43* (23), 8767−74.
(58) Gunier, R. B.; Nuckols, J. R.; Whitehead, T. P.; Colt, J. S.; Deziel, N. C.; Metayer, C.; Reynolds, P.; Ward, M. H. Temporal trends of insecticide concentrations in carpet dust in California from 2001 to 2006. *Environ. Sci. Technol.* **2016**, *50* (14), 7761−9.
(59) Madrigal, J. M.; Jones, R. R.; Gunier, R. B.; Whitehead, T. P.; Reynolds, P.; Metayer, C.; Ward, M. H. Residential exposure to carbamate, organophosphate, and pyrethroid insecticides in house dust and risk of childhood acute lymphoblastic leukemia. *Environ. Res.* **2021**, *201*, 111501.
(60) Wilson, N. K.; Strauss, W. J.; Iroz-Elardo, N.; Chuang, J. C. Exposures of preschool children to chlorpyrifos, diazinon, pentachlorophenol, and 2,4-dichlorophenoxyacetic acid over 3 years from 2003 to 2005: A longitudinal model. *J. Expo. Sci. Environ. Epidemiol.* **2010**, *20* (6), 546−58.
(61) Colt, J. S.; Cyr, M. J.; Zahm, S. H.; Tobias, G. S.; Hartge, P. Inferring past pesticide exposures: A matrix of individual active ingredients in home and garden pesticides used in past decades. *Environ. Health. Perspect.* **2007**, *115* (2), 248−54.
(62) Menzie, C. M. Fate of pesticides in the environment. *Annu. Rev. Entomol.* **1972**, *17*, 199−222.
(63) Nakagawa, L. E.; Costa, A. R.; Polatto, R.; Nascimento, C. M. D.; Papini, S. Pyrethroid concentrations and persistence following indoor application. *Environ. Toxicol. Chem.* **2017**, *36* (11), 2895−8.
(64) Zhou, J.; Mainelis, G.; Weisel, C. P. Pyrethroid levels in toddlers' breathing zone following a simulated indoor pesticide spray. *J. Expo. Sci. Environ. Epidemiol.* **2019**, *29* (3), 389−96.
(65) Wang, N.; Huang, M.; Guo, X.; Lin, P. Urinary metabolites of organophosphate and pyrethroid pesticides and neurobehavioral effects in Chinese children. *Environ. Sci. Technol.* **2016**, *50* (17), 9627−35.
(66) Richards, J.; Reif, R.; Luo, Y.; Gan, J. Distribution of pesticides in dust particles in urban environments. *Environ. Pollut.* **2016**, *214*, 290−8.
(67) Starr, J.; Graham, S.; Stout, D., 2nd; Andrews, K.; Nishioka, M. Pyrethroid pesticides and their metabolites in vacuum cleaner dust collected from homes and day-care centers. *Environ. Res.* **2008**, *108* (3), 271−9.
(68) Sadaria, A. M.; Sutton, R.; Moran, K. D.; Teerlink, J.; Brown, J. V.; Halden, R. U. Passage of fiproles and imidacloprid from urban pest control uses through wastewater treatment plants in northern California, USA. *Environ. Toxicol. Chem.* **2016**, *36* (6), 1473−82.
(69) Perkins, R.; Whitehead, M.; Civil, W.; Goulson, D. Potential role of veterinary flea products in widespread pesticide contamination of English rivers. *Sci. Total Environ.* **2021**, *755*, 143560.
(70) Tingle, C. C.; Rother, J. A.; Dewhurst, C. F.; Lauer, S.; King, W. J. Fipronil: Environmental fate, ecotoxicology, and human health concerns. *Rev. Environ. Contam. Toxicol.* **2003**, *176*, 1−66.
(71) Testa, C.; Salis, S.; Rubattu, N.; Roncada, P.; Miniero, R.; Brambilla, G. Occurrence of Fipronil in residential house dust in the presence and absence of pets: A hint for a comprehensive toxicological assessment. *J. Environ. Sci. Health, Part B* **2019**, *54* (6), 441−8.
(72) Morgan, M. K.; Sheldon, L. S.; Thomas, K. W.; Egeghy, P. P.; Croghan, C. W.; Jones, P. A.; Chuang, J. C.; Wilson, N. K. Adult and children's exposure to 2,4-D from multiple sources and pathways. *J. Expo. Sci. Environ. Epidemiol.* **2008**, *18* (5), 486−94.
(73) Fu, F.; Xiao, L.; Wang, W.; Xu, X.; Xu, L.; Qi, G.; Chen, G. Study on the degradation of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2-methyl-4-chloro-phenoxyacetic sodium (MCPA sodium) in natural agriculture-soils of Fuzhou, China using capillary electrophoresis. *Sci. Total Environ.* **2009**, *407* (6), 1998−2003.
(74) Bennett, B.; Workman, T.; Smith, M. N.; Griffith, W. C.; Thompson, B.; Faustman, E. M. Longitudinal, seasonal, and occupational trends of multiple pesticides in house dust. *Environ. Health. Perspect.* **2019**, *127* (1), 17003.
(75) Liu, J.; Wan, Y.; Jiang, Y.; Xia, W.; He, Z.; Xu, S. Occurrence of azole and strobilurin fungicides in indoor dust from three cities of China. *Environ. Pollut.* **2022**, *304*, 119168.
(76) Cooper, E. M.; Rushing, R.; Hoffman, K.; Phillips, A. L.; Hammel, S. C.; Zylka, M. J.; Stapleton, H. M. Strobilurin fungicides in house dust: Is wallboard a source? *J. Expo. Sci. Environ. Epidemiol.* **2020**, *30* (2), 247−52.
(77) Council of the European Union.. On the quality of water intended for human consumption. *Off. J. Eur. Communitiee* **1998**, *330*, 32−54.

(78) Sultana, T.; Murray, C.; Kleywegt, S.; Metcalfe, C. D. Neonicotinoid pesticides in drinking water in agricultural regions of southern Ontario, Canada. *Chemosphere.* **2018**, *202*, 506−13.
(79) Wan, Y.; Wang, Y.; Xia, W.; He, Z.; Xu, S. Neonicotinoids in raw, finished, and tap water from Wuhan, Central China: Assessment of human exposure potential. *Sci. Total Environ.* **2019**, *675*, 513−9.
(80) Klarich, K. L.; Pflug, N. C.; DeWald, E. M.; Hladik, M. L.; Kolpin, D. W.; Cwiertny, D. M.; LeFevre, G. H. Occurrence of neonicotinoid insecticides in finished drinking water and fate during drinking water treatment. *Environ. Sci. Technol. Lett.* **2017**, *4* (5), 168−73.
(81) Taylor, A. C.; Mills, G. A.; Gravell, A.; Kerwick, M.; Fones, G. R. Pesticide fate during drinking water treatment determined through passive sampling combined with suspect screening and multivariate statistical analysis. *Water. Res.* **2022**, *222*, 118865.
(82) Schostag, M. D.; Gobbi, A.; Fini, M. N.; Ellegaard-Jensen, L.; Aamand, J.; Hansen, L. H.; Muff, J.; Albers, C. N. Combining reverse osmosis and microbial degradation for remediation of drinking water contaminated with recalcitrant pesticide residue. *Water. Res.* **2022**, *216*, 118352.
(83) Duirk, S. E.; Collette, T. W. Degradation of chlorpyrifos in aqueous chlorine solutions: pathways, kinetics, and modeling. *Environ. Sci. Technol.* **2006**, *40* (2), 546−51.
(84) McCaule, L. A.; Travers, R.; Lasarev, M.; Muniz, J.; Nailon, R. Effectiveness of cleaning practices in removing pesticides from home environments. *J. Agromedicine* **2006**, *11* (2), 81−88.
(85) Montiel-León, J. M.; Vo Duy, S.; Munoz, G.; Bouchard, M. F.; Amyot, M.; Sauvé, S. Quality survey and spatiotemporal variations of atrazine and desethylatrazine in drinking water in Quebec, Canada. *Sci. Total Environ.* **2019**, *671*, 578−85.
(86) Muller, G.; LeBaron, H.; McFarland, J.; Burnside, O. History of the discovery and development of triazine herbicides. *The Triazine Herbicides*; Elsevier: Amsterdam, Netherlands, 2008; Vol. *50*, Chapter 2, pp 13−29, DOI: 10.1016/B978-044451167-6.50005-2.
(87) Klementova, S.; Keltnerova, L. *Triazine Herbicides in the Environment*; IntechOpen: London, U.K., 2015; DOI: 10.5772/60858.
(88) Ochoa-Acuña, H.; Frankenberger, J.; Hahn, L.; Carbajo, C. Drinking-Water herbicide exposure in Indiana and prevalence of Small-for-Gestational-Age and preterm delivery. *Environ. Health. Perspect.* **2009**, *117* (10), 1619−24.
(89) Hladik, M. L.; Bouwer, E. J.; Roberts, A. L. Neutral degradates of chloroacetamide herbicides: Occurrence in drinking water and removal during conventional water treatment. *Water. Res.* **2008**, *42* (20), 4905−14.
(90) Elfikrie, N.; Ho, Y. B.; Zaidon, S. Z.; Juahir, H.; Tan, E. S. S. Occurrence of pesticides in surface water, pesticides removal efficiency in drinking water treatment plant and potential health risk to consumers in Tengi River Basin, Malaysia. *Sci. Total Environ.* **2020**, *712*, 136540.
(91) Wise, C. F.; Hammel, S. C.; Herkert, N. J.; Ospina, M.; Calafat, A. M.; Breen, M.; Stapleton, H. M. Comparative assessment of pesticide exposures in domestic dogs and their owners using silicone passive damplers and biomonitoring. *Environ. Sci. Technol.* **2022**, *56* (2), 1149−61.
(92) Tu, H.; Wei, X.; Pan, Y.; Tang, Z.; Yin, R.; Qin, J.; Li, H.; Li, A. J.; Qiu, R. Neonicotinoid insecticides and their metabolites: Specimens tested, analytical methods and exposure characteristics in humans. *J. Hazard. Mater.* **2023**, *457*, 131728.
(93) Li, A. J.; Kannan, K. Profiles of urinary neonicotinoids and dialkylphosphates in populations in nine countries. *Environ. Int.* **2020**, *145*, 106120.
(94) Tao, Y.; Dong, F.; Xu, J.; Phung, D.; Liu, Q.; Li, R.; Liu, X.; Wu, X.; He, M.; Zheng, Y. Characteristics of neonicotinoid imidacloprid in urine following exposure of humans to orchards in China. *Environ. Int.* **2019**, *132*, 105079.
(95) Hardy, E. M.; Dereumeaux, C.; Guldner, L.; Briand, O.; Vandentorren, S.; Oleko, A.; Zaros, C.; Appenzeller, B. M. R. Hair versus urine for the biomonitoring of pesticide exposure: Results from a pilot cohort study on pregnant women. *Environ. Int.* **2021**, *152*, 106481.
(96) Rahman, M. M.; Sharma, H. M.; Park, J. H.; Abd El-Aty, A. M.; Choi, J. H.; Nahar, N.; Shim, J. H. Determination of alachlor residues in pepper and pepper leaf using gas chromatography and confirmed via mass spectrometry with matrix protection. *Biomed. Chromatogr.* **2013**, *27* (7), 924−30.
(97) Matsushita, T.; Morimoto, A.; Kuriyama, T.; Matsumoto, E.; Matsui, Y.; Shirasaki, N.; Kondo, T.; Takanashi, H.; Kameya, T. Removals of pesticides and pesticide transformation products during drinking water treatment processes and their impact on mutagen formation potential after chlorination. *Water. Res.* **2018**, *138*, 67−76.
(98) United States Environmental Protection Agency (U.S. EPA). *EPI Suite*; U.S. EPA: Washington, D.C., 2024; https://www.epa.gov/tsca-screening-tools/download-epi-suitetm-estimation-program-interface-v411 (accessed Dec 20, 2024).
(99) Blanchard, O.; Glorennec, P.; Mercier, F.; Bonvallot, N.; Chevrier, C.; Ramalho, O.; Mandin, C.; Bot, B. L. Semivolatile organic compounds in indoor air and settled dust in 30 French dwellings. *Environ. Sci. Technol.* **2014**, *48* (7), 3959−69.
(100) Erban, L. E.; Walker, H. A. Beyond old pipes and ailing budgets: Systems thinking on twenty-first century water infrastructure in Chicago. *Front. Built. Environ.* **2019**, *5*, 1−124.
(101) Panis, C.; Candiotto, L. Z. P.; Gaboardi, S. C.; Gurzenda, S.; Cruz, J.; Castro, M.; Lemos, B. Widespread pesticide contamination of drinking water and impact on cancer risk in Brazil. *Environ. Int.* **2022**, *165*, 107321.
(102) United States Environmental Protection Agency (U.S. EPA). *Human Health Benchmarks for Pesticides*; U.S. EPA: Washington, D.C., 2021; https://www.epa.gov/sdwa/2021-human-health-benchmarks-pesticides (accessed May 15, 2024).
(103) Zubrod, J. P.; Bundschuh, M.; Arts, G.; Brühl, C. A.; Imfeld, G.; Knäbel, A.; Payraudeau, S.; Rasmussen, J. J.; Rohr, J.; Scharmüller, A.; Smalling, K.; Stehle, S.; Schulz, R.; Schäfer, R. B. Fungicides: An overlooked pesticide class? *Environ. Sci. Technol.* **2019**, *53* (7), 3347−65.
(104) Rodriguez-Antona, C.; Ingelman-Sundberg, M. Cytochrome P450 pharmacogenetics and cancer. *Oncogene.* **2006**, *25* (11), 1679−91.
(105) Hong, J.-Y.; Yang, C. S. Genetic polymorphism of cytochrome P450 as a biomarker of susceptibility to environmental toxicity. *Environ. Health. Perspect.* **1997**, *105*, 759−62.
(106) Vogelstein, B.; Lane, D.; Levine, A. J. Surfing the p53 network. *Nature.* **2000**, *408* (6810), 307−10.
(107) Xiao, Y.; Yang, Y.; Xiong, H.; Dong, G. The implications of FASN in immune cell biology and related diseases. *Cell. Death. Dis.* **2024**, *15* (1), 88.
(108) Wei, W.; Qin, B.; Wen, W.; Zhang, B.; Luo, H.; Wang, Y.; Xu, H.; Xie, X.; Liu, S.; Jiang, X.; Wang, M.; Tang, Q.; Zhang, J.; Yang, R.; Fan, Z.; Lyu, H.; Lin, J.; Li, K.; Lee, M.-H. FBXW7β loss-of-function enhances FASN-mediated lipogenesis and promotes colorectal cancer growth. *Signal. Transduct. Target. Ther.* **2023**, *8* (1), 187.
(109) Zhang, H.; Zhang, R.; Zeng, X.; Wang, X.; Wang, D.; Jia, H.; Xu, W.; Gao, Y. Exposure to neonicotinoid insecticides and their characteristic metabolites: Association with human liver cancer. *Environ. Res.* **2022**, *208*, 112703.
(110) Liu, H.; Wang, K.; Han, D.; Sun, W.; Xu, S. Co-exposure of avermectin and imidacloprid induces DNA damage, pyroptosis, and immune dysfunction in epithelioma papulosum cyprini cells via ROS-mediated Keap1/Nrf2/TXNIP axis. *Fish. Shellfish. Immunol.* **2023**, *140*, 108985.
(111) Harada, Y.; Tanaka, N.; Ichikawa, M.; Kamijo, Y.; Sugiyama, E.; Gonzalez, F. J.; Aoyama, T. PPARα-dependent cholesterol/testosterone disruption in Leydig cells mediates 2,4-dichlorophenoxyacetic acid-induced testicular toxicity in mice. *Arch. Toxicol.* **2016**, *90* (12), 3061−71.
(112) Sun, H.; Shao, W.; Liu, H.; Jiang, Z. Exposure to 2,4-dichlorophenoxyacetic acid induced PPARβ-dependent disruption of

glucose metabolism in HepG2 cells. *Environ. Sci. Pollut. Res. Int.* **2018**, *25* (17), 17050−7.
(113) Burns, C. J.; Swaen, G. M. Review of 2,4-dichlorophenoxyacetic acid (2,4-D) biomonitoring and epidemiology. *Crit. Rev. Toxicol.* **2012**, *42* (9), 768−86.
(114) Mullur, R.; Liu, Y. Y.; Brent, G. A. Thyroid hormone regulation of metabolism. *Physiol. Rev.* **2014**, *94* (2), 355−82.
(115) King, R. J.; Singh, P. K.; Mehla, K. The cholesterol pathway: Impact on immunity and cancer. *Trends. Immunol.* **2022**, *43* (1), 78−92.
(116) Du, D.; Liu, C.; Qin, M.; Zhang, X.; Xi, T.; Yuan, S.; Hao, H.; Xiong, J. Metabolic dysregulation and emerging therapeutical targets for hepatocellular carcinoma. *Acta Pharm. Sin B* **2022**, *12* (2), 558−80.
(117) Yan, S.; Meng, Z.; Tian, S.; Teng, M.; Yan, J.; Jia, M.; Li, R.; Zhou, Z.; Zhu, W. Neonicotinoid insecticides exposure cause amino acid metabolism disorders, lipid accumulation and oxidative stress in ICR mice. *Chemosphere.* **2020**, *246*, 125661.
(118) Liu, T.; Wang, X.; Xu, J.; You, X.; Chen, D.; Wang, F.; Li, Y. Biochemical and genetic toxicity of dinotefuran on earthworms (Eisenia fetida). *Chemosphere.* **2017**, *176*, 156−64.
(119) Lu, Z.; Hu, Y.; Tse, L. A.; Yu, J.; Xia, Z.; Lei, X.; Zhang, Y.; Shi, R.; Tian, Y.; Gao, Y. Urinary neonicotinoid insecticides and adiposity measures among 7-year-old children in northern China: A cross-sectional study. *Int. J. Hyg. Environ. Health.* **2023**, *251*, 114188.
(120) Qiao, K.; Liang, Z.; Wang, A.; Wu, Q.; Yang, S.; Ma, Y.; Li, S.; Schiwy, S.; Jiang, J.; Zhou, S.; Ye, Q.; Hollert, H.; Gui, W. Waterborne tebuconazole exposure induces male-biased sex differentiation in zebrafish (Danio rerio) larvae via aromatase inhibition. *Environ. Sci. Technol.* **2023**, *57* (44), 16764−78.
(121) Ku, T.; Zhou, M.; Hou, Y.; Xie, Y.; Li, G.; Sang, N. Tebuconazole induces liver injury coupled with ROS-mediated hepatic metabolism disorder. *Ecotoxicol. Environ. Saf.* **2021**, *220*, 112309.
(122) Ku, T.; Liu, Y.; Xie, Y.; Hu, J.; Hou, Y.; Tan, X.; Ning, X.; Li, G.; Sang, N. Tebuconazole mediates cognitive impairment via the microbe-gut-brain axis (MGBA) in mice. *Environ. Int.* **2023**, *173*, 107821.
(123) Meng, Z.; Sun, W.; Liu, W.; Wang, Y.; Jia, M.; Tian, S.; Chen, X.; Zhu, W.; Zhou, Z. A common fungicide tebuconazole promotes colitis in mice via regulating gut microbiota. *Environ. Pollut.* **2022**, *292*, 118477.
(124) Bhatt, P.; Gangola, S.; Ramola, S.; Bilal, M.; Bhatt, K.; Huang, Y.; Zhou, Z.; Chen, S. Insights into the toxicity and biodegradation of fipronil in contaminated environment. *Microbiol Res.* **2023**, *266*, 127247.
(125) Li, W.; Wang, B.; Yuan, Y.; Wang, S. Spatiotemporal distribution patterns and ecological risk of multi-pesticide residues in the surface water of a typical agriculture area in China. *Sci. Total Environ.* **2023**, *870*, 161872.
(126) Sereda, B.; Bouwman, H.; Kylin, H. Comparing water, bovine milk, and indoor residual spraying as possible sources of DDT and pyrethroid residues in breast milk. *J. Toxicol. Environ. Health A* **2009**, *72* (13), 842−51.
(127) Punt, A.; Firman, J.; Boobis, A.; Cronin, M.; Gosling, J. P.; Wilks, M. F.; Hepburn, P. A.; Thiel, A.; Fussell, K. C. Potential of ToxCast data in the safety assessment of food chemicals. *Toxicol. Sci.* **2020**, *174* (2), 326−40.
(128) Braun, G.; Herberth, G.; Krauss, M.; König, M.; Wojtysiak, N.; Zenclussen, A. C.; Escher, B. I. Neurotoxic mixture effects of chemicals extracted from blood of pregnant women. *Science.* **2024**, *386* (6719), 301−9.

https://doi.org/10.1021/acs.est.5c00961
Environ. Sci. Technol. 2025, 59, 12507−12519