JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

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A Comprehensive Review on Pesticide Residues in Human Urine

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Cite This: https://doi.org/10.1021/acs.jafc.4c02705 Read Online

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ABSTRACT: Numerous studies worldwide have evaluated pesticide residues detected in urine. This review serves as a contribution to this field by presenting an overview of scientific research studies published from 2001 to 2023, including details of study characteristics and research scope. Encompassing 72 papers, the review further delves into addressing key challenges in study design and method used such as sampling and analytical approaches, results adjustments, risk assessment, estimations, and results evaluation. The review explores urinary concentrations and detection frequency of metabolites of organophosphates and pyrethroids, as well as herbicides such as 2,4-D and glyphosate and their metabolites, across various studies. The association of the results with demographic and lifestyle variables were explored. While farmers generally have higher pesticide exposure, adopting organic farming practices can reduce the levels of pesticides detected in their urine. Residence close to agricultural areas has shown high exposure in some cases. Dietary exposure is especially high among people adopting a conventionally grown plant-rich dietary pattern. A higher detection level and frequency of detection are generally found in females and children compared to males. The implications of transitioning to organic and sustainable plant-rich diets for reducing pesticide exposure and potential health benefits for both adults and children require further investigation.

KEYWORDS: *urinary pesticides, environmental exposure, diet exposure, health issues, risk assessment*

1. INTRODUCTION

Exposure to pesticide residues is an environmental and public health concern worldwide due to potential harmful effects on ecosystems[1] and human health.[2,3] Human pesticide exposure can come from both environmental exposure, either through residence or work or through dietary intake. Previous research has consistently identified residential proximity to fields and pesticide application as significant determinants, highlighting the varied and complex influence of meteorological parameters on exposure patterns.[3,4] More recent studies have primarily focused on investigating consumer pesticide exposure through dietary intake.

Levels of pesticides or their metabolites are commonly used as biomarkers of human exposure to pesticides using a variety of biological samples, such as urine, blood, serum, and cerebrospinal fluid. Urine collection is generally preferred over, e.g., blood for short-term exposure monitoring as it is less invasive and can be collected by study participants themselves.[5] In recent years, an increasing number of reviews have been published specifically focusing on urinary pesticide levels of particular pesticides, metabolites, age groups, or geographic locations.[3,6−9] A review published in 2023, examining human exposure specifically to neonicotinoids (NEOs),[7] found a higher level of exposure to NEOs in Asian populations (ΣNEOs: 0.050−0.212 μg/kg bw/day) compared to US and Europe (ΣNEOs: 0.057−0.068 μg/kg bw/day). Hence, exposure to pesticides and the levels found may vary from one country to another. Another review published in 2022 addressed the exposure levels of, specifically, pyrethroids, chlorpyrifos, and glyphosate in EU,[6] while a review conducted in 2023 specifically targeted Spain in its examination of urinary pesticides.[8] The authors highlighted that the most frequently detected biomarkers were dialkyl phosphate (DAPs) metabolites, nonspecific metabolites of organophosphates, and 3,5,6-trichloro-2-pyridinol (TCPy), a specific biomarker of chlorpyrifos.[8] However, regulations may have changed since then, potentially leading to the detection of other pesticide levels. Finally, a recent review (2024) investigated dietary predictors of pyrethroid exposure through urinary biomarkers without geographical restrictions. The review revealed evidence of associations between the consumption of organic diets or food items and reduced concentrations of 3-phenobenzoic acid metabolites in urine, while less evidence was found for diet affecting other pyrethroid-specific biomarkers.[9] Likewise, a review published by Guzmann-Torres et al. based on frequency of urinary pesticides in children concludes that evidence supports that organic diets in children are successful interventions that can mainly decrease the urinary levels of pesticides, insecticides, and herbicides. They also concluded that although the amount of reported information regarding health damage is increasing, currently, no cause−effect fact has been reported between a specific pesticide and a specific disease.[2]

This review adds to the existing reviews, as it offers a more updated and comprehensive analysis of studies related to urinary pesticide analysis published between 2001 and 2023. While other studies have focused on specific chemical class of

Received: March 27, 2024
Revised: July 24, 2024
Accepted: July 24, 2024

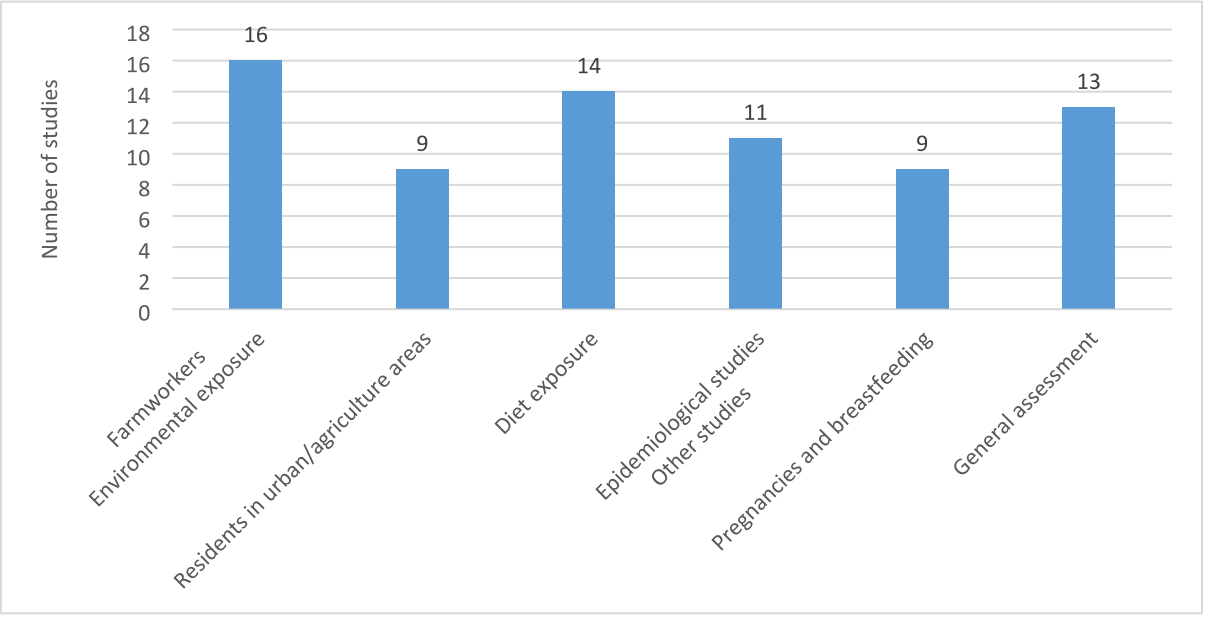

Figure 1. Research scope across studies on urinary pesticide investigations between 2001 and 2023 (n = 72).

pesticides, e.g., neonicotinoids, or specific countries, this review aims to provide a thorough evaluation and overview of various classes of detected pesticides and their metabolites, along with their respective levels across demographic variables such as age and gender, stage of life, including pregnancy and breastfeeding, and various geographical locations, both in Europe and outside. We examined the methodologies employed throughout the process, from sampling and analysis to reporting, considering factors such as the number of participants, targeted pesticides, and metabolites. We evaluated research findings and performed comparative analysis. Our focus extended to studies on residential proximity to agricultural fields, highlighting the environmental impact on pesticide exposure. We delved into papers exploring specific diets, particularly plant-based and organic diets, to showcase how such dietary choices influence pesticide levels. Additionally, we explored papers linking urinary pesticides to health risks and summarized methodologies for estimating exposure and conducting risk assessments. In short, the present review offers an updated overview of more recent studies on urinary pesticides as well as a broader perspective on the various research and objectives underlying published studies on urinary pesticides.

2. SEARCH AND SELECTION STRATEGY

Literature screening was done using the Reaxys platform. Research keywords used were "pesticide residues" and "urine samples". The search resulted in 206 citations in Reaxys, which were carefully filtered by reviewing and removing papers that are not relevant to the topic due to search bias that occurs in any database. Data spanning the past 22 years was gathered on urinary pesticides, and a total of 72 papers published since 2001 were incorporated into this review. The Supporting Information (SI), Table S1 displays a list of these papers, featuring information like date, country, number of participants, participant range, target group, spectrum of urinary investigation, sampling method, and whether single or multiple samples were collected. This information lays the groundwork for the results and discussion in this paper.

3. CHARACTERISTICS AND SCOPES OF URINARY PESTICIDES RESEARCH

3.1. Country and Date. Although there has been some interest in urinary pesticides since 2001, research papers have been relatively scarce. However, from 2020 onward, there has been a significant increase in research output, with a total of 38 research papers published during the period 2020−2023 (SI, Figure S1a). The majority of research papers on urinary pesticides originated from the United States (14 research papers), followed by a substantial contribution from Spain (7), China (7), and Thailand (6) (SI, Figure S1b). Studies on urinary pesticides have been conducted in various European countries, including Belgium, Czech Republic, Denmark, France, Germany, Ireland, Italy, Poland, Slovenia, Sweden, and the United Kingdom. In addition, research on urinary pesticides has also been carried out in Australia, Brazil, Chile, Costa Rica, Ghana, India, Iran, Japan, Mexico, Morocco, Sudan, and Turkey. The reason for the increased interest may vary by region and research priorities. According to the Food and Agriculture Organization of the United Nations (FAO),[10] Canada, the US, and Spain have the highest pesticide use per capita. According to data derived from Statista,[11] among the leading countries in agricultural consumption of pesticides were USA (457.30 thousand metric tons), China (233.88 thousand metric tons), and Spain (76.17 thousand metric tons). This explains the interest of these countries in conducting research on pesticide exposure to maintain a balance between agricultural needs and environmental and public health concerns.

3.2. Number of Participants and Target Age Groups. In the majority of the studies, urine samples were obtained from either 50−200 participants (22 studies) or 200−1000 participants (24 studies). There were 18 studies done on a small scale with a number of participants of less than 50. When the sample size is small, it can affect how reliably the study findings can be generalized. However, the study findings with a small sample size can still contribute to the field. Only 8 studies were of large scale, including more than 1000 participants. Studies involving more than 4000 participants

https://doi.org/10.1021/acs.jafc.4c02705
J. Agric. Food Chem. XXXX, XXX, XXX−XXX

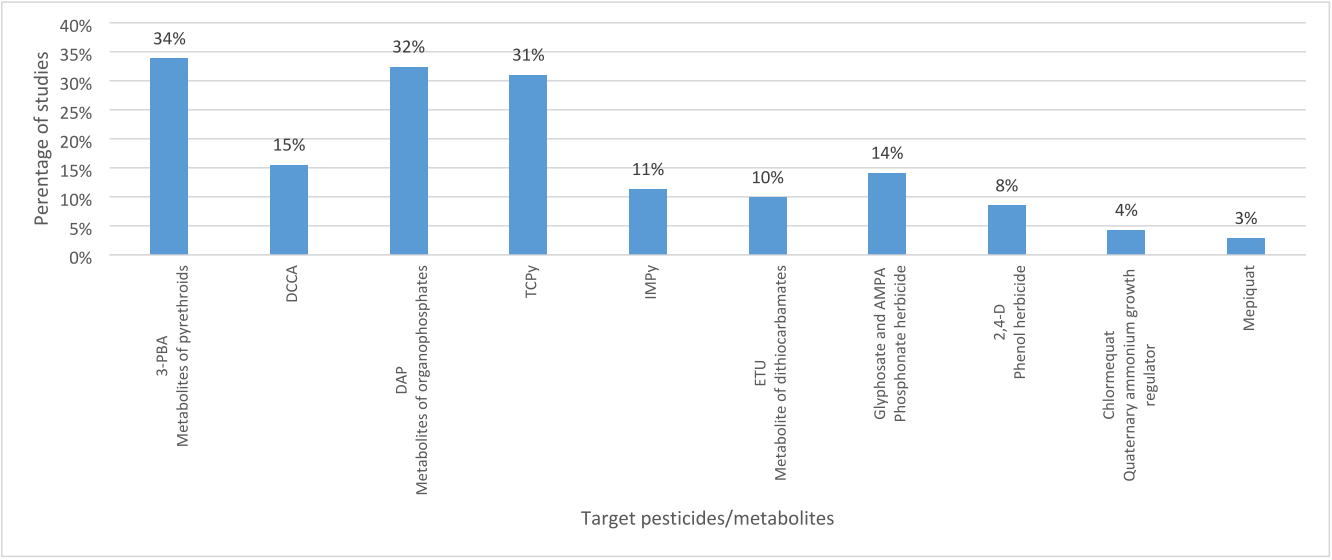

Figure 2. Target pesticides and metabolites in research papers on urinary pesticides.

are those from the US, where samples collected from the National Health and Nutrition Examination Survey (NHANES), under the National Center for Health Statistics (NCHS) program, were investigated.[12−14]

A total of 17 studies targeted only children, 33 studies targeted adults including adolescents, and 22 studies targeted both adults and children. Some of the generated data are classified according to gender and then subjected to separate investigations. Adults were the primary focus in some research studies due to factors such as occupational exposure. Among the 33 studies exclusively targeting adults, 11 primarily concentrated on farmworkers. Around half of the studies included children. Children may be more susceptible to the potential health risks associated with pesticide exposure, which may explain the focus on this age group. Comparative findings concerning children and adults are presented in section 6.3.

3.3. Research Scope. Studies conducted on urinary pesticides have different research scopes and perspectives. Some studies attributed their findings to environmental exposure. These studies analyzed occupational exposure in farmworkers, farmworkers and their families, spray applicants, and florists' exposure to pesticides (16 studies).[15−29] Additionally, some studies analyzed exposure due to residence close to agricultural areas and/or urban areas (9 studies).[20,30−37] Other studies linked the exposure of pesticide residues to the diet (14 studies).[31,38−47] Some other studies focused on exposure to pesticides on pregnant women[48−53] and lactating mothers,[54−56] to understand the transfer of pesticides to children (9 studies). Other studies linked the exposure to urinary pesticides to health issues by targeting a specific group (11 studies), and others were simply generally assessing the levels and frequency of detection of targeted pesticides and metabolites for a given number of participants (total of 13 studies),[37,57−68] without specifically linking it to the exposure route or to the health issues. Figure 1 shows the research scope of the urinary pesticide investigation.

Most of the studies were done by targeting farmworkers who were considered a vulnerable group due to their direct contact and their routine respiratory exposure to pesticides. Farmworkers family's exposure to pesticides can, to a certain extent, result from farmers inadvertently carrying pesticide residues home after working in the fields during the spraying season. Residents living in agricultural areas were also exposed to pesticides by breathing or drinking water. However, a study conducted in the Czech Republic revealed that pesticide exposure was primarily influenced by dietary intake, with environmental exposure having a less significant effect,[69] thus the number of studies investigating the link between urinary pesticides and dietary intake (14), among which four studies investigated the effect of organic diet intervention on urinary pesticides.[39,43,70,71]

3.4. Target Pesticides and Metabolites. Pesticides in urine can be detected as parent compounds, specific metabolites corresponding to a specific pesticide, and nonspecific metabolites corresponding to pesticides chemical class, e.g., organophosphates. Nonspecific metabolites are often targeted, as the aim in some cases is not solely to check exposure to a single pesticide but rather a range of pesticides. Parent pesticides may not always be observed due to metabolization. However, in some instances, it is possible to detect parent compounds, as not all pesticides undergo metabolization in the body and may be excreted intact. This underscores the importance of including both target compounds and metabolites in such studies to ensure an accurate evaluation of exposure to pesticides.

Figure 2 shows the target metabolites that were most frequently included and detected in urinary studies. 3-Phenoxybenzoid acid (3-PBA) was the primary metabolite of focus in urine and was included in 34% of the studies. It is a nonspecific metabolite of pyrethroids like deltamethrin, cypermethrin, and permethrin. Another specific metabolite of the pyrethroid cypermethrin, *cis*- and *trans*-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (DCCA), is also commonly analyzed. DAPs, including diethyl phosphate (DEs) and dimethyl phosphates (DMs), are nonspecific metabolites of organophosphates and are commonly analyzed in urine (32% of the studies). 3,5,6-Trichloro-2-pyridinol (TCPy), a specific metabolite of the organophosphate chlorpyrifos and chlorpyrifos-methyl, was monitored in 31% of the studies on urine. 2-Isopropyl-6-methyl-4-pyrimidol (IMPy), a specific metabolite of the organophosphate diazinon, was monitored in 11% of the studies. Ethylene thiourea (ETU), a nonspecific

https://doi.org/10.1021/acs.jafc.4c02705
J. Agric. Food Chem. XXXX, XXX, XXX−XXX

metabolite of dithiocarbamates, was monitored in 10% of the studies. Pyrethroids and organophosphates are extensively utilized, thus the interest in these chemical categories. Glyphosate and its metabolite aminomethylphosphonic acid (AMPA), and 2,4-D were also included in several studies on urinary pesticides. Additional targeted metabolites are the two pesticides (parent compounds), chlormequat, and mepiquat. Other pesticides and their metabolites, even if not explicitly mentioned, are certainly included in several studies, as multiresidue analyses are often used.

4. METHODS USED

4.1. Reliability of Sampling Methods. The sampling method plays a crucial role in every chemical analysis, including the analysis of pesticide residues in urine. The selection of a sampling method relies on the specific objectives and goal of the study, the nature of the exposure being investigated, practicalities, and pesticides of interest. Of the 54 studies, where sampling methods were detailed, 31 studies used first-morning void urine samples for analysis, 17 studies used random spot urine samples, and only 6 studies used 24 h pooled urine samples.[15,17,37,40,58,66]

Hyland et al. suggested taking a first morning void urine sample only when a 24 h urine sample collection is not feasible.[72] While the 24 h urine samples are considered most accurate for risk assessment, it is worth noting that in practical and clinical settings, spot urine samples are preferred due to their lower costs and convenience. Collecting urine samples from children, for instance, is challenging due to timing and psychological factors. In a study that compared the reliability of using first morning void urine samples and random spot samples to estimate exposure to pesticides, it was demonstrated that nonfirst morning void samples have a limited ability to predict 24 h dose and tend to underestimate daily organophosphorus exposure for risk assessment.[72] Therefore, if a spot sample must be used, then the first morning void sample is the better choice. When estimating exposure due to diet, it was demonstrated that mean concentrations of DAPs metabolites in first morning first urine samples were strongly correlated with concentrations of the same-day 24 h samples,[45] suggesting that first morning void samples are sufficient when investigating exposure to dietary intake. On the other hand, when assessing direct exposure of farmworkers to pesticides, It was demonstrated in a study published by Scher et al.[73] that the use of single voids can either over- or underestimate daily exposure. For instance, 2,4-D was detected at higher concentration in morning void than in 24 h urine samples. The opposite was observed for chlorpyrifos in some cases, suggesting an overestimation when 24 h samples were collected. Those results were highly dependent on the time of spraying, the frequency of spraying, the urine sampling time after spraying, and the excretion kinetics of a given pesticide. For instance, for chlorpyrifos, the excretion time is stable 24−48 h then starts to decrease.[73] Thus, to avoid bias, sampling should be carefully designed.

Among the studies that utilized first-morning urine or spot urine samples, a majority of them (80% of the studies) relied on a single sample for analysis. However, in a few cases, samples were collected over multiple days.[33,63] In certain cases, researchers pooled multiple spot urine or first-morning urine samples from each individual for analysis.[18,19,32,70,74] Some studies explored the reliability of a single urine sample. Intraclass coefficient (ICC) was suggested as a valuable statistical tool to assess the intraindividual variability, calculated as follows: $\mathrm{ICC} = \frac{\mathrm{BV}}{\mathrm{BV} + \mathrm{WV}}$ where BV is the between-individuals variability, and WV the within-individuals variability. ICC below 0.4 indicates poor reliability, ICC between 0.4 and 0.75 indicates fair to good reliability, and ICC above 0.75 as excellent reliability.[75] A study done for comparing urinary pesticides in samples collected at different times of the day (morning, afternoon, and evening) resulted in a high variability.[75] It was also demonstrated that the required number of samples is highly dependent on the measured urinary biomarker. If the biomarker level is consistent, fewer samples are needed. For instance, no difference was observed for diflufenican, fipronil, or fipronil sulfone, and monohydroxypropylheptyl-phthalate if urine samples were collected in the morning, afternoon, or evening, but for many others, e.g., MBzP, MEHP, oxo-MINCH, OH-MINCH, and cx-MINP, the morning sample yielded significantly higher results than the samples collected at other times.[75] Thus, sampling should be designed with consideration for the specific pesticides of interest. If the goal is to cover multiple pesticides with varying ICC, then opting for multiple urine samples should be considered. In another study conducted by Spaan et al., the reliability of a single urine sample was assessed. They analyzed six DAPs in urine collected from pregnant women at three different weeks of pregnancy. The study revealed a low ICC (<0.4) and a notable degree of variability in within-person reliability.[76]

Knowledge of urinary elimination kinetics can also help in the design of the sampling method. Some of the pesticides being half eliminated as early as 6.4 h (*trans*-DCCA) and as long as 49.5 h (sulfoxaflor) as shown in Table 1. Determination of urinary elimination kinetics can be described as $C(t) = c_{\max,xe}{}^{-kt}$; with elimination half-times $t_{1/2}$ calculated as $t_{1/2} = \ln^2/K$, with K being the kinetic constant of the exponential decline. Sampling should be designed taking into consideration the in vivo half-life of most pesticides. Table 1 shows the biological half-lives of some pesticides and metabolites in human urine, which can be used for the design of such studies.

Table 1. Biological Half-Life of Pesticides and Metabolites in Human Urine

pesticide	biological half-life	ref
glyphosate	10 h (*creatinine corrected concentration*)	77
tebuconazole	between 7.8 h and 16 h	78
trans-DCCA	6.4 h	79
3-PBA	8.7 h	79
DAP	15.5 h	80
acetamiprid	2.5 h	81
sulfoxaflor	49.5 h	81

Considerable attention was given to the design of storage, collection, and transportation procedures. In all of the studies, collected samples were promptly frozen or stored in cooling boxes or dry ice to maintain their chemical integrity during transportation to the laboratory for analysis. Upon arrival at the laboratory, the samples were maintained at temperatures of −20 °C or less until they underwent analysis. In summary, regarding sampling methods, while the 24 h urine samples are considered most accurate for risk assessment, first-morning void urine samples might be reliable when measuring dietary exposure, especially when multiple samples are collected.

4.2. Sample Preparation and Analysis. Numerous validated methods exist for the analysis of pesticide residues in urine. This section presents a comprehensive summary of the main steps used in the studies that involved the monitoring of pesticide residues in urine. Sample preparation methods differ depending on the specific analytes of interest. Various organic solvents, such as acetonitrile,[23,38,53,70,82] hexane,[36] methanol,[24] ethyl acetate,[15,62] or a mixture of organic solvents,[30,31,34,54] were utilized for effectively extracting pesticide residues from urine.

Both enzymatic hydrolysis and incubation at elevated temperatures under acidic conditions are suitable methods for deconjugation, enabling the disruption of chemical bonds between pesticides and conjugates, such as glucuronic acid, allowing the analytes to become available for subsequent analysis. Enzymatic deconjugation is commonly achieved through the use of β-glucuronidase,[62,63,65,68,83,84] and it is in some cases complemented by arylsulfatase.[57] Additionally, another approach involves subjecting the samples to high temperatures, reaching up to 100 °C, and incubating them for various durations, typically ranging from 30 min to 12 h.[28,34,56,62,66,68,85] This

https://doi.org/10.1021/acs.jafc.4c02705
J. Agric. Food Chem. XXXX, XXX, XXX−XXX

method was supported by several studies and serves as an alternative means of deconjugation in pesticide analysis.

Derivatization is a common technique used to improve the sensitivity and specificity of pesticide analysis. It involves chemical modification of the analytes to enhance their detectability and stability during analysis. Various derivatizing agents have been used, e.g., *N*-methyl-*N*-(*tert*-butyldimethylsilyl)trifluoroacetamide (MTBSTFA),[30,82] pentafluorobenzyl chloride (PFBBr),[31] trifluoroethanol and trifluoro- acetic anhydride,[64] pentafluorobenzyl bromide,[31] and others for the analysis of glyphosate, AMPA, DAPs, carbamates, and other pesticides and metabolites.

Solid-phase extraction (SPE) is the predominant purification technique in urine analysis. SPE was used in several studies for analyzing pesticide residues in urine, mainly employing HLB cartridges[68,70,83,85] and C18 cartridges.[35,56] Through SPE, impurities and undesired substances are eliminated from the extracted sample, ensuring that concentrated analytes are free from interfering compounds. While alternative methods may skip the cleanup step, they still achieve satisfactory outcomes with reduced analysis time.

While some studies involved solvent extraction, a deconjugation step, and SPE cleanup, others only used centrifugation in acidic conditions to ensure protein precipitation.[16,43,49,71]

The analysis methods employed in the majority of the studies (29) for assessing urinary pesticides involved the use of LC-MS/MS or isotope-dilution LC-MS. Additionally, 22 studies utilized GC-MS and GC-MS/MS, 4 studies incorporated GC coupled to a flame photometric detector, and 4 studies made use of high-resolution MS, such as LC-Orbitrap-MS and LC-Q-ToF-MS.[16,40,53,85] Pesticides exhibit diverse chemical properties, such as volatility and polarity, leading to variability in their analytical methods. Certain compounds are amenable to GC due to their volatility, while others are better suited for LC owing to their polarity (glyphosate, AMPA, 2,4-D). Additionally, some pesticides can be analyzed using both techniques, depending on their chemical compositions and properties (DAPs, TCPS, 3-PBA). All of the methods were designed as target methods, specifically focusing on the analysis of defined pesticides or metabolites. However, in two studies, different approaches were taken, where suspected and nontarget screening methods were initially employed,[53] and metabolomics tools were used to identify unknown biomarkers.[16]

Quality assessment is reported in most of the studies performed. Limit of detections (LOD) reported in the most recent studies varied from 0.0085 to 0.5 ng/mL for 3-PBA, 0.005 to 0.017 ng/mL for 4F-3-PBA, 0.025 to 0.06 ng/mL for DCCA, 0.005 to 2.25 ng/mL for DMP, 0.025 to 0.4 ng/mL for DMTP, 0.1−0.8 ng/mL for DMDTP, 0.025 to 0.06 ng/mL for DEP, 0.005 to 1 ng/mL for DETP, 0.0032 to 0.142 ng/mL for DEDTP, 0.01 to 2 ng/mL for TCPY, 0.01 to 0.32 ng/mL for 2,4D, 0.05 to 0.1 ng/mL for glyphosate, and 0.02 to 0.5 ng/mL for AMPA. Other quality measures reported in the studies include calculating the limit of quantitation (LOQ), injecting blanks, spiking blanks at different levels to check recovery, spiking pooled urine samples, and participating in proficiency testing.

4.3. Presentation of Analytical Results. Urinary pesticide concentrations are presented using various statistical measures, including the median, geometric mean (GM), and percentiles such as the 15th, 50th, 70th, and 95th. The 95th percentile indicates a value below which 95% of the data falls. Maximum and minimum levels are also reported in some studies.

The concentration of pesticide residues in the urine is dependent on how diluted the urine sample is and on the dietary intake of the individual. To enable comparison between concentrations between individuals at different times of the day and different days, it is important to adjust the concentration, taking into consideration the dilution effect. Urinary pesticide concentrations are either creatinine-adjusted or specific gravity-adjusted. The majority of the results were corrected for creatinine levels. Urinary concentration adjusted for creatinine (UEcrea) is calculated using the following equation:

$$\mathrm{UEcrea}\left(\frac{\mu g}{g\mathrm{crea}}\right) = \frac{\mathrm{UC}\left(\frac{\mu g}{l}\right) \times 1000\left(\frac{mg}{g}\right)}{\mathrm{UCcrea}\left(\frac{\mathrm{mmol}}{l}\right) \times \mathrm{MWcrea}\left(\frac{mg}{\mathrm{mmol}}\right)}$$

where UC is the measured urinary concentration, UCcrea is urinary concentration of creatinine, and MWcrea is molecular mass of creatinine (113.2 g/mol). Results are also commonly expressed in nanomoles per gram of creatinine (concentration in μg/L/compound molecular weight)

Urinary concentration adjusted for specific gravity UE(SG) is calculated using the following equation:

$$\mathrm{UE(SG)}\left(\frac{\mu g}{L}\right) = \mathrm{UC}\left(\frac{\mu g}{L}\right) \times \frac{(\mathrm{SG_{average}} - 1)}{\mathrm{SG} - 1}$$

where $\mathrm{SG_{average}}$ is the average of specific gravity of all individuals, and SG is the specific gravity of the respective urine sample.

SG is usually measured using a refractometer,[86] and creatinine is commonly measured by spectrophotometric[87] or LC-MS/MS.[88] In general, both creatinine and SG are valid correction methods.[48,89] However, some studies recommended correction with SG because creatinine levels can vary by age and sex.[90] However, most of the studies on urinary pesticides adjusted the levels by using creatinine.

4.4. Methodologies for Risk Assessment. The "Pesticide Residue Burden Score" and "Hazard Index" are two methods commonly used for assessing the risk associated with pesticide residues. The first method quantifies risk based on residue amount, type, toxicity, and frequency of application. The "hazard index method" measures the combined risk from multiple pesticides, considering toxicity and exposure routes.

4.4.1. Pesticide Residue Burden Score Method. The Pesticide Residue Burden Score (PRBS) is a tool that allows for the ranking of individuals in a population based on their exposure to pesticide residues. It is particularly useful in epidemiological studies aimed at evaluating the extent of pesticide residue exposure through the consumption of, e.g., fruits and vegetables.[12,91] In studies published by Hu et al.[12] and Chiu et al.,[44] food frequency questionnaires were used together with the PRBS to evaluate the exposure. PRBS uses three indexes to estimate overall pesticide residue profile for each fruit and vegetable: (1) the percentage of samples with any detected pesticides, (2) the percentage of samples tested with pesticides exceeding the tolerance level, and (3) the percentage of samples with three or more types of pesticides detectable.[92] The pesticide rank score is from 3 (least contaminated) to 9 (most contaminated). For a participant reporting consuming 3 apples/week and a PRBS for apple of 4, the pesticide residue burden score of the consumer PRBSc = number of serving by day*PRBS = 7/3*4. For the cumulative assessment, scores were summed up. Research has shown that urinary concentrations of pesticide biomarkers exhibit a positive correlation with a high intake of fruits and vegetables containing elevated pesticide levels. Conversely, there was an inverse relationship observed with fruits and vegetables having lower pesticide levels.[44] Overall, PRBS has the capability to assess and categorize individuals based on their exposure to pesticide residues on a population level.

4.4.2. Hazard Index Method. The risk of dietary exposure for a single pesticide can be estimated by the estimation of a hazard quotient (HQ) using the following equation:

$\mathrm{HQ} = \frac{\mathrm{UC} \times V24\mathrm{h} \times \mathrm{MWp}}{F_{\mathrm{UE}} \times \mathrm{BW}}$, where EDI is the estimated daily intake and ADI is the acceptable daily intake.

The EDI is calculated as follows: $\mathrm{EDI} = \frac{\mathrm{UC} \times V24\mathrm{h} \times \mathrm{MW}p}{F_{\mathrm{UE}} \times \mathrm{BW}}$, where UC is the molar concentration of the pesticide metabolite, *V*24h is the total urinary volume excreted within 24 h, MWp is the molecular weight of the selected parent pesticide (g/mol), and F_{UE} the urinary excretion factor of the parent pesticide, and BW the mean body weight of the target population.

The ADI is an estimate of the amount of a substance in food or drinking water that can be consumed over a lifetime without presenting an appreciable risk to health.[93]

https://doi.org/10.1021/acs.jafc.4c02705
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Table 2. Level and Detection Frequency of Nonspecific Metabolites of Pyrethroids Across Studies

year of publication	country	N	LOD (ng/mL)	LOQ (ng/mL)	reported result (unit)	concentration	DF%	ref
				3-PBA				
2004[a]	Sweden	197		0.005	median (ng/mL)	0.01	54%	
2004	Italy	69	0.5[b]		GM (ng/mL)	0.84[b]	54%	37
2009[a]	Sweden	154		0.009	median (ng/mL)	0.15	100%	57
2013[a]	Sweden	294		0.009	median (ng/mL)	0.15	100%	57
2013	US	135		0.4	GM (ng/mL)	0.33	64%	46
2015	Sweden	5		1.2−15	median (ng/mL)	24 000[c]	95%	70
2016	China	1884	0.008		GM (ng/mL)	80[c]	36%	82
2017	US	NHANES	0.1		GM (ng/mL)	0.3	75%	14
2017[a]	Sweden	195		0.009	median (ng/mL)	0.21	100%	57
2018	US	90	0.1		GM (ng/mL)	0.57	88%	44
2019	Australia	400	0.0009		GM (ng/mL)	2.3	100%	68
2019	US	16	0.02		median (ng/mL)	2.7	100%	94
2020[a]	Spain	568		0.5	GM (ng/mL)	1.51	79%	42
2020	Spain	116	0.5		GM (ng/mL)	1.7	65%	54
2020	Poland	14	0.1		GM (ng/mL)	0.27		66
2020	Belgium	258		0.09	P95 (ng/mL)	5.3	100%	67
2021	US	68	0.1				95%	63
2021	US	29	0.01		GM (ng/mL)	0.58	100%	24
2022	Spain	140	0.12		mean (ng/mL)	0.08		95
2022	Suriname	214	0.10		median (ng/mL)	0.65−1.3		48
2023	Turkey	186	0.03		GM (ng/g crea)	0.15	88% (M); 86% (F)	83
				4F-3-PBA				
2004[a]	Sweden	197		0.005	median (ng/mL)	0.01	54%	24
2009[a]	Sweden	254		0.005	median (ng/mL)	0.01	74%	24
2013[a]	Sweden	204		0.005	median (ng/mL)	<LOD	62%	24
2016	China	1884	0.02		GM (ng/mL)	40[c]	17%	82
2017[a]	Sweden	195		0.005	median (ng/mL)	<LOD	42%	57
2018	US	90	.		GM (ng/mL)	<LOD	9%	44
2019	Australia	400	0.01		GM (ng/mL)	0.09	70%	68
2020	Spain	568		0.125	GM (ng/mL)		4%	42
2020	Poland	14	0.1		range (ng/mL)	LOD−1.4	5%	66
2020	Belgium	258		0.11	(ng/mL)	<LOQ	2%	67
2021	US	29	0.005		GM (ng/mL)	0.01	57%	24
2021	US	68	0.1				8%	63
2023	Turkey	186	0.05		GM (ng/mL)	<LOD		83
				DCCA				
2017	Ghana	17	0.6		range (ng/mL)	0.11−9.7	17%	51
2018	US	90	0.6		GM (ng/mL)	<LOD	17%	44
2019	US	16	0.05 (t-DCCA) 0.1 (c-DCCA)		median (ng/mL)	2.5 (t-DBCA) 1.9 (c-DCCA)	96% (t-DCCA) 94% (c-DCCA)	94
2019	Australia	400	0.04 (t-DCCA) 1.3 (c-DCCA)		GM (ng/mL)	2.2 (t-DCCA)	100% (t-DCCA)	68
2020	Spain	116					>99%	54
2020	Spain	140		5	GM (ng/mL)	<LOQ	5%	95
2020	Poland	14	0.1		GM (ng/mL)	0.36 (t-DCCA) 0.22 (cDCCA)	94% (t-DCCA) 45% (c-DBCA)	66
2020	Belgium	258		0.15 (t-DCCA) 0.5 (c-DCCA)	P95 (ng/mL)	4.3 (t-DCCA) 2.01 (c-DCCA)	93% (t-DCCA) 40% (c-DCCA)	67
2021	US	68	0.6 (t-DCCA)				12% (t-DCCA)	63
2021	US	29	0.01		GM (ng/mL)	0.21−0.26	91−93%	24
2022	Spain	568	0.055		mean (ng/mL)	3.5	20%	42
2023	Turkey	186	0.025		GM (ng/mL)	<LOD		83

https://doi.org/10.1021/acs.jafc.4c02705
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Table 2. continued

[a]Year of the study. [b]Reported in nmol/mL in the study but converted in the table to ng/mL. [c]Reported in μg/g creatinine or ng/g creatinine and converted to ng/mL by considering creatinine concentration 1 g/mL to facilitate conversion. DF: detection frequency; M, males; F, females; t, trans; c, cis; P95, calculation at the 95th percentile.

An HQ below 1 indicates that there is no appreciable risk of adverse health effects following dietary exposure to a specific pesticide. HQ can also be expressed in percentage.

For cumulative dietary exposure, the hazard index (HI), is calculated as the sum of the HQs for the individual pesticides detected in the food. Fernández et al.[42] suggests to calculate the accumulated exposure for pesticides having the same mode of action.

Another approach suggested by Fernández et al.[42] is based on a cumulative assessment groups (CAG) that assumes that pesticides grouped in the same CAG may collectively contribute to toxicity, even if they have distinct modes of action.

The individual margin of exposure (MOEi) to each CAG is calculated as follow:$MOE_{I,CAG=NOAEL_{i,CAG}/EDI_i}$, where NOAEL is the no observed adverse effect level (NOAEL) of acute exposure to each CAGi.

The cumulative risk was assessed using the total margin of exposure (MOET) is calculated as follow:$\frac{1}{MOET_{CAG}} = \sum \frac{1}{MOE_{i,CAG}}$

A MOET above 100 is not considered to be a risk for humans.

The PBRS is typically associated with the consumption of fruits and vegetables. It provides a measure of the potential pesticide burden based on the types and amounts of fruits and vegetables consumed. The PBRS aims to estimate the cumulative risk from pesticide residues in the diet, particularly focusing on how much and what types of produce an individual consumes. Therefore, extensive information on the consumed foods is necessary, making the process complex. While the HI is associated with the exposure to the pesticides themselves. It evaluates the risk based on exposure to specific pesticides, considering their toxicological properties, which provides a more accurate assessment of health risk.

5. DETECTION LEVELS AND FREQUENCIES

Table 2 shows the level and detection frequency of nonspecific metabolites of pyrethroids across studies, 3-PBA, 4F-3-PBA, and DCCA. 3-PBA is found in 50−100% of the study participants, followed by DCCA, detected in 17−100% of participants, and then by 4-F-3-PBA detected in 2−70% of the participants. The highest concentrations, in studies encompassing more than 100 participants, were observed for 3-PBA, with levels between 0.01 and 80 ng/mL, followed by 4-F-3-PBA, with levels up to 40 ng/mL, and then by DCCA, with levels up to 4.2 ng/mL (the highest level observed was for *trans*-DCCA).

3-PBA was the most frequently detected metabolite (100%) in participants from studies conducted in Sweden (2013−2019), Belgium (2020), Australia (2019), and the US (2017). The highest levels of 3-PBA, in studies encompassing more than 100 participants, were detected in China (80 ng/mL), Belgium (5.33 ng/mL), Australia (2.3 ng/mL), and Spain (1.7 ng/mL).

4F-3-PBA was detected in more than 90% of participants from studies conducted in Sweden and Australia, but the highest concentrations were observed in China (40 ng/mL). DCCA was detected in more than 90% of the studies in Ghana (up to 9 ng/mL), Belgium (4.29 ng/mL), and Spain (3.45 ng/mL). 3-PBA is not only one of the most frequently detected pyrethroid metabolites in urine samples but also exhibits the highest concentrations. Therefore, prioritizing the monitoring of 3-PBA in human urine is imperative for future investigations.

Table 3 shows the level and detection frequency of the nonspecific metabolites of organophosphates and the specific metabolite of chlorpyrifos (TCPy). Diethyl (DEs) phosphates are the most frequently detected, followed by dimethyl (DMs) phosphates. The DEs are the sum of the diethylphosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP). The DMs are the sum of dimethylphosate (DMP), dimethyldiphosphate (DMDP), and dimethyldithiophsophate (DMDTP). The DAPs are the sum of DEs and DMs. The highest concentration of DMP, DMTP, DMDTP, DEP, DETP, and DETP is observed in studies conducted in Japan, with concentrations ranging from 1000 to 13100 ng/mL. High concentrations of DEP and DMP were observed in studies conducted in China with concentrations of 177 ng/mL and 122 ng/mL, respectively. In Spain, the concentration of DMP in urine is 310 ng/mL, while DEP is measured at 130 ng/mL, DETP at 110 ng/mL, and DEDTP at 60 ng/mL. For the specific metabolite of organophosphates, concentrations ranged from 0.82 to 12.12 ng/mL, except for the highest concentration recorded in China, which reached 920 ng/mL.

Table 4 displays the levels and detection frequencies of the two herbicides 2,4-D and glyphosate, along with its specific metabolite, AMPA. Both 2,4-D and glyphosate were frequently monitored in the papers. The detection frequency exceeded 50% in most of the studies. Concentrations ranged between 0.12 and 190 ng/mL for 2,4-D, 0.1 and 1.19 ng/mL for glyphosate, and 0.1 and 70 ng/mL for AMPA.

The data provided above are intended to offer an overview rather than comparison. Comparing urinary pesticide levels between countries poses several challenges due to variations in the available data. Not all countries measured the same pesticides and metabolites, and the discrepancy in study years adds complexity to cross-country comparisons, as figures may have shifted in some regions. The disparity was also due to the targeted groups, with some studies targeting adults, pregnant women in particular, lactating mothers, children, farmworkers and their families, or people residing in agricultural areas. For instance, the study in Japan targeted children living close to agricultural areas, thus the high levels obtained. Furthermore, the diverse reporting methods, such as GM, median, and adjustments using creatinine or specific gravity, introduce additional complexities, making it challenging to draw direct comparisons. In certain cases, it was feasible to standardize units, while in others, additional information was necessary for conversion. Frequency of detection serves as a valuable tool for comparison. Making a direct comparison study is also challenging due to the different targeted analytes. Because certain studies exclusively focused on organophosphate nonspecific metabolites while others solely examined pyrethroid metabolites, it becomes challenging to make assumptions about the absence of nontargeted pesticides, those not included in the analysis.

Making direct comparisons for studies conducted in different years also makes it challenging. The profile of urinary pesticides is prone to variation over time, influenced by shifts in pesticide usage patterns, updates to regulations governing

https://doi.org/10.1021/acs.jafc.4c02705
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Table 3. Level and Detection Frequency of Nonspecific Metabolites and Specific Metabolites of Organophosphates Across Studies

nonspecific metabolites of organophosphates								
year of publication	country	*N*	LOD (ng/mL)	LOQ (ng/mL)	reported result (unit)	concentration	DF%	ref
				DMP				
2001	US	27	0.7[b]		mean (ng/mL)	8.2	37%	20
2004	Italy	69	1.1[b]		GM (ng/mL)	10[b]	90%	37
2017	US	NHANES	1.1[b]		GM (ng/mL)	11[b]	45%	14
2018	India	377		0.07	P95 (ng/mL)	0.95		45
2019	Spain	222		0.5	GM (ng/mL)	310[c]		35
2019	Australia	400	0.23		GM (ng/mL)	6.1	100%	68
2019	US	16	0.2				100%	94
2020	Thailand	161		12	GM (ng/mL)	1.8 (AR); 1.3 (UR)	3% (AR); 0% (UR)	96
2020	China	522	0.18		GM (ng/mL)	122	69%	97
2020	Spain	116		0.5	GM (ng/mL)	0.9	65%	54
2022	Thailand	395	2.3	20	GM (ng/mL)	5.9−24	3−16%	38
2020	Spain	568		0.5	GM (ng/mL)	0.95	65%	42
2022	Japan	73		0.4	GM (ng/mL)	13 100[c]		41
2022	Suriname	214	0.1		median (ng/mL)	1.3−0.8		48
2023	Turkey	186	0.005		GM (ng/mL)	<LOD		83
				DMTP				
2001	US	27	7.5		mean (ng/mL)	13	30%	20
2004	Italy	69	0.8[b]		GM (ng/mL)	11[b]	83%	37
2017	US	NHANES			GM (ng/mL)	1.6[b]	66%	14
2017	Ghana	17	0.1		range (ng/mL)	0.15−8.5	27%	51
2018	India	377		0.04	P95 (ng/mL)	6.6		45
2019	Australia	400	0.02		GM (ng/mL)	5.3		68
2019	Australia	400	0.02		GM (ng/mL)	5.3	100%	68
2019	US	16	0.4				100%	94
2020	Spain	568		0.5	GM (ng/mL)	<LOQ	33%	42
2020	Spain	116		0.5	GM (ng/mL)	<LOQ	47%	54
2020	Thailand	161		0.5−12.5	GM (ng/mL)	0.17(AR); 0.12 (UR)	12% (AR); 8% (UR)	96
2020	China	522	0.3		GM (ng/mL)	12	84%	97
2020	Belgium	258	0.5		P95 (ng/mL)	13	65%	67
2020	Spain	116		0.5	GM (ng/mL)	<LOQ	47%	54
2022	Suriname	214	0.1		median (ng/mL)	1.3−1.7		48
2022	Thailand	395	0.2	5.5	GM (ng/mL)	1.3−4.5	32−48%	38
2022	Japan	73		0.45	GM (ng/mL)	11 900[c]		41
2023	Turkey	186	0.05		GM (ng/mL)	<LOD		83
				DMDTP				
2001	US	27	7.5		mean (ng/mL)	ND		20
2004	Italy	69	0.79[b]		GM (nM)	3.1[b]	61%	37
2017	US	NHANES			GM (nM)	0.36[b]	27%	14
2017	Ghana	17	0.1		range (ng/mL)	0.11−5.2	18%	51
2018	India	377		0.03	P95 (ng/mL)	0.80	0.93	45
2019	Australia	400	0.11		GM (ng/mL)	0.39	95%	68
2019	US	16	0.07				100%	94
2020	Spain	568		0.5	GM (ng/mL)	<LOQ	27%	42
2020	Thailand	161		0.5−12.5	GM (ng/mL)	0.17 (AR); 0.13 (UR)	1%(AR); 0% (UR)	96
2020	China	522	0.3		GM (ng/mL)	0.76	14%	97
2020	Belgium	258		0.5	P95 (ng/mL)	1.3	28%	67
2022	Thailand	395	0.1	3	GM (ng/mL)	0.4−0.7	46%	38
2022	Japan	73		0.18	GM (ng/mL)	1000[c]		41
				DEP				
2001	US	27	6.3		mean (ng/mL)		7%	20
2004	Italy	69	1.4[b]		GM (ng/mL)	5.11[b]	81%	37
2017	US	NHANES			GM (ng/mL)	0.6[b]	44%	14
2017	Ghana	17	0.1		range (ng/mL)	0.58−15	14%	51
2018	India	377		0.03	P95 (ng/mL)	6.9	98%	45
2019	Spain	222		0.5	GM (ng/mL)	130[c]		35
2019	Australia	400	0.02		GM (ng/mL)	1.5	100%	68
2019	US	16	0.25				100%	94

https://doi.org/10.1021/acs.jafc.4c02705
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Table 3. continued

nonspecific metabolites of organophosphates								
year of publication	country	*N*	LOD (ng/mL)	LOQ (ng/mL)	reported result (unit)	concentration	DF%	ref
				DEP				
2020	Spain	568		0.5	GM (ng/mL)	1.5	92%	42
2020	Thailand	161		0.5−12	GM (ng/mL)	2.7 (AR); 1.9 (UR)	87% (AR); 86% (UR)	96
2020	China	522	0.06		GM (ng/mL)	177	85%	97
2020	Belgium	258		0.5	P95 (ng/mL)	30	73%	67
2020	Spain	116		0.5	GM (ng/mL)	1.9	91%	54
2022	Thailand	395	0.05	2	GM (ng/mL)	1.3−2.4	17−79%	38
2022	Japan	73		0.4	GM (ng/mL)	9700[c]		41
2022	Suriname	214	0.1		median (ng/mL)	0.35−1.5		48
2023	Turkey	186	0.03		GM (ng/mL)	<LOD		83
				DETP				
2001	US	27	4.8		mean (ng/mL)	6.8	7%	20
2004	Italy	69	0.08*		GM (ng/mL)	3.2[b]	28%	37
2017	US	NHANES			GM (ng/mL)	0.2[b]	8%	14
2017	Ghana	17	1		range (ng/mL)	1.05−3.06	12%	51
2018	India	377		0.49	P95 (ng/mL)	4.39	87%	45
2019	Spain	222	0.5		GM (ng/mL)	110[c]		35
2019	Australia	400	0.31		GM (ng/mL)	1.8	95%	68
2019	US	16	0.09				100%	94
2020	Spain	568		0.5	GM (ng/mL)	<LOQ	21%	42
2020	Thailand	161		0.5	GM (ng/mL)	0.21 (AR); 0.10 (UR)	12% (AR); 0% (UR)*	96
2020	China	522	0.06		GM (ng/mL)	<LOD	19%	97
2020	Belgium	258		0.5	P95 (ng/mL)	3.5	49%	67
2020	Poland	14	0.5		median (ng/mL)	3.5	49%	66
2020	Spain	116		0.5	GM (ng/mL)	0.6	51%	54
2022	Thailand	395	0.1	2	GM (ng/mL)	0.4−628	8−95%	38
2022	Japan	73		0.2	GM (ng/mL)	1000[c]		41
2022	Suriname	214	0.1		median (ng/mL)	0.27−0.57		48
2023	Turkey	186	0.005		GM (ng/mL)	<LOD		83
				DEDTP				
2001	US	27	6		mean (ng/mL)	ND		20
2004	Italy	69	1[b]		GM (nM)	1.8[b]	62%	37
2017	US	NHANES			GM (nM)	0.5[b]	42%	14
2017	Ghana	17	0.1		range (ng/mL)	0.51−0.56	18%	51
2018	India	377		0.07	P95 (ng/mL)	0.61	51%	45
2019	Spain	222	0.5		GM (ng/mL)	60[c]		35
2019	Australia	400	0.003		GM (ng/mL)	<LOD	35%	68
2019	US	16		0.06	P95 (ng/mL)	0.608	51%	94
2020	Spain	568		0.5	GM (ng/mL)		3%	42
2020	Thailand	161		0.5−12	GM (ng/mL)	0.15 (UR); 0.48 (AR)	74%(AR); 50% (UR)	96
2020	China	522	0.09		GM (ng/mL)	15	92%	97
2020	Belgium	258		0.5	P95 (ng/mL)	0.59	6%	67
2020	Poland	14	0.5		median (ng/mL)	0.59	6%	66
2022	Suriname	214		0.1	median (ng/mL)	0.27−0.55	1%	48
2022	Thailand	395	0.1	3	GM (ng/mL)	0.8−1.5	81−95%	38
2022	Japan	73		1.6	GM (ng/mL)	300[c]		41
2022	Spain	568	0.14		mean (ng/mL)	0.74		42
				∑DEs				
2019	US	16			median (ng/mL)	31.4	100%	94
2020	Spain	116			GM (ng/mL)	21.5		54
2020	Thailand	161			GM (ng/mL)	4.1 (AR); 2.4 (UR)	88% (AR); 86% (UR)	96
2020	Spain	568			GM (ng/mL)	13		42
2020	Spain	116			GM (ng/mL)	21		54
2022	Thailand	395			GM (ng/mL)	1.9−3.6	49−99%	38
2022	Japan	73			nmol/g crea	12.2		41
				∑DMs				
2019	US	16			median (ng/mL)	101.42	100%	94
2020	Spain	116			GM (ng/mL)	13.6		54

https://doi.org/10.1021/acs.jafc.4c02705
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Table 3. continued

nonspecific metabolites of organophosphates								
year of publication	country	*N*	LOD (ng/mL)	LOQ (ng/mL)	reported result (unit)	concentration	DF%	ref
					∑DMs			
2020	Thailand	161			GM (ng/mL)	2.2 (AR); 1.6 (UR)	13% (AR) 8% (UR)	96
2020	Spain	568			GM (ng/mL)	16		42
2020	Spain	116			GM (ng/mL)	14		54
2022	Thailand	395			GM (ng/mL)	2.6−12	18−52%	38
2022	Japan	73			nmol/g creatinine	30		41
					∑DAPs			
2019	Spain	222			GM (ng/g crea)	7560		35
2019	US	16			median (ng/mL)	138	100%	94
2020	Spain	116			GM (ng/mL)	40		54
2020	Thailand	161			GM (ng/mL)	7.8 (AR); 4.8 (UR)	88% (AR) 86% (UR)	96
2020	Spain	568			GM (ng/mL)	37		42
2020	Spain	116			GM (ng/mL)	40		54
2022	Thailand	395			GM (ng/mL)	2.8−9.2	3−98%	38
2022	Japan	73			nmol/g creatinine	47		41
Specific Metabolite of the Organophosphate of Chlorpyrifos TCPy								
2000[1]	Sweden	209		0.06	median (ng/mL)	0.82	99%	57
2004[a]	Sweden	197		0.06	Mmedian (ng/mL)	0.84	99%	57
2004	Italy	69	1.7[b]		GM (ng/mL)	6.8−7.8[b]	78%	37
2009[a]	Sweden	254		0.06	median (ng/mL)	1.4	100%	57
2013[a]	Sweden	204		0.06	median (ng/mL)	1.1	100%	57
2013	US	135	2		GM (ng/mL)	5	99%	46
2016	Spain	30	0.8−3.2		average (ng/mL)	3.8−5.9	17−71%	53
2016	China	1884	0.2		median (ng/mL)	920[c]	44%	82
2017	Ghana	17	0.1		range (ng/mL)	0.11−11.18	78%	51
2017[a]	Sweden	195		0.06	median (ng/mL)	0.92	99%	57
2018	US	90	0.1		GM (ng/mL)	0.69	77%	44
2019	Australia	400	0.02		GM (ng/mL)	9.7		68
2019	US	16	0.2		median (ng/mL)	2.8	98%	94
2020	Spain	116	0.25		GM (ng/mL)	1.5	85%	54
2020	Spain	568		0.50	GM (ng/mL)	1.2	74%	42
2020	Poland	14	0.2		GM (ng/mL)	2.1	97%	66
2020	Belgium	258		0.08	P95 (ng/mL)	12	100%	67
2021	US	29	0.01		GM (ng/mL)	0.28	91%	24
2022	Spain	140			average (ng/mL)	0.08	54%	95
2022	Suriname	214	0.1		median (ng/mL)	0.44−1.3		48
2023	Turkey	186	0.01		GM (ng/mL)	0.1[c]	61% (M); 63% (F)	83

[a]Year of the study; [b]Reported in nmol/mL in the study, but converted in the table to ng/mL. [c]Reported in μg/g creatinine or ng/g creatinine and converted to ng/mL by considering creatinine concentration 1 g/mL to facilitate conversion. DF, detection frequency; M, males; F, females; t, trans; c, cis; P95, calculation at the 95th percentile.

pesticide use, and the prohibition of certain pesticides. Fluctuations in the export of food commodities between countries may contribute to variations in the level of exposure to pesticide residues. Studies done on urinary pesticides in Sweden showed an increase trend (3.7% year) of 3-PBA from 0.11 μg/L (median value) in 2000, to 0.15 μg/L in 2013, and 0.21 μg/L in 2017. The same was observed for TCPy with an increase trend of 1.7% year. On the other hand, a decrease trend was observed for chlormequat (−5.5%) and ETU (−3.9%).[57] This could not be explained with the pesticide use per capita, which was reduced from 2000 (0.19 kg/pc) to 2017 (0.15 kg/pc) in Sweden.[10] This was likely attributed to changes in pesticide usage patterns, characterized by a rise in the application of pyrethroids and a concurrent reduction in carbamate usage, with the latter known for its higher toxicity.

6. DEMOGRAPHIC AND LIFESTYLE VARIABLES

Exposure to pesticide residues is influenced by a variety of demographic factors, including occupation, agricultural practices, seasonal variations, residence, diet, age, and gender.

6.1. Association of Urinary Pesticides with Occupation, Agriculture Practices, And Season. Table 5 presents a collection of studies showing disparities between worker families and nonworker families, as well as more detailed practices, such as differences between pome farmworkers and

https://doi.org/10.1021/acs.jafc.4c02705
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Table 4. Level and Detection Frequency of the 2 Herbicides 2,4-D and Glyphosate and Its Specific Metabolite, AMPA[a]

year of publication	country	N	LOD (ng/mL)	LOQ (ng/mL)	reported result (unit)	concentration	DF%	ref
				2,4-D				
2000[a]	Sweden	209		0.11	median (ng/mL)	0.12	65%	57
2004[a]	Sweden	197		0.11	median (ng/mL)	0.12	58%	57
2009[a]	Sweden	254		0.11	median (ng/mL)	<LOD	58%	57
2013[a]	Sweden	204		0.11	median (ng/mL)	0.13	69%	57
2013	US	135		0.4	GM (ng/mL)	5.04		46
2017[a]	Sweden	195		0.11	median (ng/mL)	<LOD	39%	57
2017	Ghana	17	0.15		range (ng/mL)	0.15−166	71%	51
2018	US	90	0.15		GM (ng/mL)	0.31	78%	44
2019	Australia	400	0.32		GM (ng/mL)	<LOD	45%	68
2020	Spain	568	0.25		GM (ng/mL)	<LOQ	25%	42
2021	US	29	0.01		GM (ng/mL)	0.35	100%	24
2022	Suriname	214	0.15		median (ng/mL)	106−190	65%	48
				Glyphosate				
2021	Germany	2144		0.1	GM (ng/mL)	0.11	52%	64
2021	Spain	97		0.1	GM (ng/mL)	0.12	54%	55
2021	France	6484	0.05	0.05	median (ng/mL)	1.2	100%	61
2023	Morocco	48	0.1	0.7	median (ng/mL)	0.97	73%	32
				AMPA				
2021	Germany	2144		0.1	GM (ng/mL)	0.1	46%	64
2021	Spain	97		0.1	GM (ng/mL)	0.13	60%	55
2022	France	121	0.02	0.05	GM (ng/mL)	70	83%	61
2023	Morocco	48	0.5	1	median (ng/mL)	0.79	75%	32

[a]Year of the study. Reported in nmol/mL in the study, but converted in the table to ng/mL. Reported in μg/g creatinine or ng/g creatinine and converted to ng/mL by considering creatinine concentration 1 g/mL to facilitate conversion. DF, detection frequency; M, males; F, females; t, trans; c, cis; P95, calculation at the 95th percentile.

nonpome farmworkers and between conventional and organic farmers. The detection frequencies for workers families workers and nonworkers families are quite similar; however, higher levels are observed among workers families.[21] This is attributed to the dust they bring home from the workplace. This disparity is found to depend on the pesticide used in agriculture. In another study targeting glyphosate and AMPA, no significant differences was found between levels detected in farm family workers and nonfarm family workers,[23] which could suggest that exposure to glyphosate is more associated with diet. Farmworkers who worked in the pome fruits had significantly higher concentrations, and higher detection frequency of dimethyl pesticide metabolites in their urine than those who did not work in these crops due to the highest pesticide application for pome fruits.[18]

Exposure to pesticides is also associated with variations in agricultural practices. In a study conducted in Thailand,[22] it was found that farmworkers practicing organic farming exhibited significantly low detection levels of cypermethrin and its metabolites ($p = 0.089$) compared to those practicing conventional farming.[22] As indicated in Table 5, GM levels of urinary pesticides for farmworkers were measured at 6.0 nmol/g creatinine for 3-PBA, 30 for DCCA, and 37 for total cypermethrin. In contrast, those practicing organic farming displayed lower GM levels of 5.1 nmol/g creatinine for 3-PBA at, 26 for DCCA, and 32 for cypermethrin. Organic farming has the potential to enhance the quality of life for numerous farmers in an environmentally sustainable manner.

Urinary pesticides are highly dependent on season. In a study conducted on Japanese farmworkers, higher DAPs, DMP, DMTP, and DETP concentrations were detected in summer than in winter.[28] It was reasonable to expect increased environmental exposure to pesticides in the summer season as it was linked with increased agricultural activities. Moreover, during summer, when temperatures are higher, pesticides sprayed are expected to evaporate at a higher rate compared to the cooler winter conditions, and thus, higher respiratory exposure is expected. This mainly revolves around how pesticides are applied, and their chemical and physical properties, including whether they tend to evaporate or adhere to plants. No significant differences were found between some biomarker levels in samples collected during the nonspray and spray seasons in a study conducted on farmworkers in South Western Idaho and Czech Republic.[24,69] Stable exposure during seasons suggests that exposure was mainly driven by diet and that the effect of environmental exposure was less significant.

In such studies aiming to find a link between agriculture practices and pesticide exposure, it is common to analyze and evaluate together with urine sampling, environmental samples (air, soil, and water).[21,98]

6.2. Association of Urinary Pesticides with Residence.

For the assessment of environmental exposure, residence is also an important factor. Numerous studies have investigated urinary pesticide levels across various regions within a country, with a primary focus on comparing biomarker concentrations in both rural and urban settings. High urinary concentrations of DAPs were found in children living in farmworker houses than those living in nonfarmworker houses in the USA.[21] Samples collected from participants residing in agricultural areas showed higher detection frequencies and higher levels compared to those from urban areas, particularly for DAPs metabolites, according to a study conducted in Thailand,[96] as shown in Table 2. In the study done in the Czech Republic, during the summer, adults living in rural areas also had significantly higher levels in comparison to adults living in

https://doi.org/10.1021/acs.jafc.4c02705
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Table 5. Concentration and Frequency of Detection of Urinary Pesticides/Metabolites by Occupation and Agriculture Practices[a]

year	country	chemical class	pesticide/ metabolite	*N*	LOD (ng/mL)	concentration unit	concentration conventional farmers	concentration organic farmers	DF (%) conventional farmers	DF (%) organic farmers	ref
2023	Thailand	pyrethroid insecticide	total cypermethrin	433	0.5	GM (nmol/g creatinine)	37	32			22
2023	Thailand	nonspecific metabolite of pyrethroids	3-PBA	433	0.5	GM (nmol/g creatinine)	6	5.1			22
2023	Thailand	specific metabolite of cypermethrin	*cis*-DCCA	433	0.5	GM (nmol/g creatinine)	18	15			22
2023	Thailand	specific metabolite of cypermethrin	*trans*-DCCA	433	0.5	GM (nmol/g creatinine)	11	10			22

year	country	chemical class	pesticide/ metabolite	*N*	LOD (ng/mL)	concentration unit	concentration NPFW	concentration PFW	DF (%) NPFW	DF (%) PFW	ref
2006	US	nonspecific metabolite of organophosphates	DMP	218		GM (ng/mL)	0.71	1.72	8.80%	20.4%	18
2006	US	nonspecific metabolite of organophosphates	DMTP	218		GM (ng/mL)	4.4	15.34	86%	96.6%	18
2006	US	nonspecific metabolite of organophosphates	DMDTP	218		GM (ng/mL)	1.3	3.53	36.80%	61.2%	18

year	country	chemical class	pesticide/ metabolite	*N*	LOD (ng/mL)	concentration unit	concentration FW	concentration NFW	DF (%) FW	DF (%) NFW	ref
2018	US	nonspecific metabolite of organophosphates	DMP	200	0.6	GM (nmol/ mL)	0.05	0.03	96%	98%	21
2018	US	nonspecific metabolite of organophosphates	DMTP	200	0.2	GM (nmol/mL)	0.12	0.05	100%	100%	21
2018	US	nonspecific metabolite of organophosphates	DMDTP	200	0.1	GM (nmol/ mL)	0.02	0.005	85%	85%	21
2018	US	nonspecific metabolite of organophosphates	DEP	200	0.2	GM (nmol/ mL)	0.01	0.01	94%	98%	21
2018	US	nonspecific metabolite of organophosphates	DETP	200	0.1	GM (nmol/ mL)	0.004	0.004	98%	96%	21
2018	US	nonspecific metabolite of organophosphates	DEDTP	200	0.1	GM (nmol/ mL)	0.001	0.001	79%	92%	21

year	country	chemical class	pesticide/ metabolite	*N*	LOQ (ng/ mL)	concentration unit	concentration FW	concentration NFW	DF (%) FW	DF (%) NFW	ref
2022	Ireland	phosphonate herbicide	glyphosate	225	0.05	median (μg/ L)	<LOQ	<LOQ	20%	43%	23
2022	Ireland	specific metabolite of glyphosate	AMPA	225	0.05	median (μg/ L)	0.06	0.07	59%	57%	23

year	country	chemical class	pesticide/ metabolite	*N*	LOD (ng/ mL)	concentration unit	concentration nonspray season	concentration spray season	DF (%) nonspray season	DF (%) spray season	ref
2021	US	metabolite of organophosphates	IMPy	29		geometric mean (ng/mL)	0.02	0.013			24
2021	US	metabolite of organophosphates	MDA	29		geometric mean (ng/mL)	0.7	0.52			24
2021	US	metabolite of organophosphates	PNP	29		geometric mean (ng/mL)	0.52	0.75			24
2021	US	metabolite of organophosphates	TCPY	29		geometric mean (ng/mL)	0.56	0.16			24
2021	US	metabolite of pyrethroids	3-PBA	29		geometric mean (ng/mL)	0.58	0.62			24
2021	US	metabolite of pyrethroids	4-F-3-PBA	29		geometric mean (ng/mL)	0.02	0.01			24
2021	US	metabolite of pyrethroids	*trans*-DCCA	29		geometric mean (ng/mL)	0.29	0.25			24
2021	US	metabolite of pyrethroids	*cis*-DCCA	29		geometric mean (ng/mL)	0.13	0.24			24
2021	US	metabolite of pyrethroids	*cis*-DBCA	29		geometric mean (ng/mL)	<LOD	<LOD			24
2021	US	herbcides	2,4-D	29		geometric mean (ng/mL)	0.36	0.37			24
2021	US	herbcides	2,4,5-T	29		geometric mean (ng/mL)	<LOD	0.06			24

https://doi.org/10.1021/acs.jafc.4c02705
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Table 5. continued

year	country	chemical class	pesticide/ metabolite	N	LOD (ng/mL)	concentration unit	concentrationSummer	concentration winter	DF (%) summer	DF (%) winter	ref
2012	Japan	metabolite of organophosphates	DMP	678	0.15	GM (ng/mL)	22.3	6.3	100%	98%	28
2012	Japan	metabolite of organophosphates	DMTP	678	0.07	GM (ng/mL)	6.8	3.4	100%	100%	28
2012	Japan	metabolite of organophosphates	DEP	678	0.05	GM (ng/mL)	2.8	2.7	100%	100%	28
2012	Japan	metabolite of organophosphates	DETP	678	0.05	GM (ng/mL)	1.1	0.4	99%	100%	28
2012	Japan	metabolite of organophosphates	∑DAP	678		GM (ng/mL)	297	115			28
2023	Czech Republic	metabolite of pyrethroids	3-PBA		0.04	GM (ng/mL)	0.123	0.121	52%	52%	74
2023	Czech Republic	metabolite of pyrethroids	DCCA		0.04	GM (ng/mL)	0.195	0.3	50%	61%	74
2023	Czech Republic	metabolite of pyrethroids	TCPY		0.03	GM (ng/mL)	0.243	2.29	41%	87%	74
2023	Czech Republic	metabolite of pyrethroids	tebuconazole		0.02	GM (ng/mL)	0.494	0.459	9%	98%	74

[a]N, number of participants; DF, detection frequency; FM, family worker; NFW, nonfamily worker; PFW, prone fruit worker; NPFW, nonprone fruit worker.

urban areas. Additionally, during the summer, the evaporation of sprayed pesticides can lead to increased exposure of adults living in rural areas. However, in this same study, Sulc et al.[69] found no correlation between the levels of some urinary pesticides (e.g., tebuconazole) and the proximity to agricultural areas. Similar exposure of adults living in agricultural and urban areas for some metabolites also reinforces the fact that exposure to pesticides was mainly driven by diet and that the environmental exposure was secondary.

6.3. Association of Urinary Pesticides with the Dietary Intake. *6.3.1. Challenges.* One of the challenges of studies assessing the relationship between dietary intake and urinary pesticides is the ability to track the dietary intake of participants. In most of the studies, urine sampling was accompanied by surveys and questionnaires conducted on participants. Information was collected about lifestyle, food intake, organic food consumption, frequency of shopping, and overall dietary habits.[40,42−47,70,71] In a limited number of studies, food samples consumed by participants, such as fruits, vegetables, water, and beverages, were analyzed to identify sources of contamination.[38,41,47] Investigating the correlation between urinary pesticides and diet is achievable, especially when focusing on a well-recognized dietary source. For instance, studying the connection between vegetables served in a school canteen and the exposure of children to these pesticides provides a feasible approach that was performed in a study in Thailand,[38] showing that there was a consistent relationship between organophosphates in vegetables and DAPs (organophosphates metabolites) in urine samples.

It is also challenging to attribute urinary pesticides to solely dietary intake. To establish a direct link between urinary exposure and dietary intake, researchers in a Chilean study analyzed pesticide residues not only in fruits and vegetables but also in drinking water and soil samples.[47] The analysis yielded no significant levels of organophosphate metabolites in the environmental samples. Consequently, researchers could attribute the urinary concentration of DAP solely to dietary factors.[47]

Some studies[40,41] demonstrated that some metabolites including chlorpyrifos-methyl metabolites (TCPy, chlorpyrifos-methyl-desmethyl) and organophosphate metabolites (DAP), can already be present in the food, as some pesticides are metabolized in the plant, which can results in over estimation of exposure to the parent compound based on metabolites measurements in urine, making it challenging to associate the dietary intake to the urinary metabolite levels. Thus, the presence of metabolites in urine can be due to exposure to the parent pesticides and the metabolites themselves via food.

6.3.2. Vegetarian versus Nonvegetarian Diets. The majority of the observed associations between urinary pesticide concentrations was primarily accounted for by the intake of pesticide residues from fruits and vegetables. However, there is a limited number of studies that directly compare the impact of vegetarian and nonvegetarian diets on urinary pesticide levels. In a conducted study within the US, distinct intake groups were established.[46] These groups were not necessarily categorized as vegetarian or nonvegetarian but were distinguished based on higher fruit consumption or increased intake of chicken. The findings revealed a notable association between the urinary pesticide TCP and the consumption of apples and fruit juices. Additionally, a correlation was observed between 3-PBA and the consumption of chicken/turkey. However, no discernible association was identified between the consumption of any specific food item and 2,4-D concentrations in urine.[46] A comparative study examining the impact of Western and Mediterranean diets on urinary excretion revealed that transitioning to a Mediterranean diet led to an increase in the excretion of insecticides, organophosphates, and pyrethroid residues.[39] However, another study in Germany found no clear association between exposure to glyphosate or AMPA and a vegetarian diet, as well as the consumption of cereals, pulses, or vegetables.[64] In some other studies, urinary pesticides were demonstrated to be associated with the consumption of specific fruits such as bananas and oranges in China[49] and other citrus fruits, apple juice, sweet peppers, tomatoes, beans and dry peas, soy and rice beverages, whole grain bread, white wine, and green and herbal teas in Canada.[52] Exposure levels were highly contingent upon the profiles of pesticide residues present in the food available in these countries' markets.

https://doi.org/10.1021/acs.jafc.4c02705
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6.3.3. Organic versus Conventional Diet. Table 6 shows the concentrations of urinary pesticides and metabolites in conventional and organic diets. A noticeable decrease in concentration is observed for phenols and phosphonate herbicides, with a 41−100% decrease, pyrethroid metabolites (16−100%), organophosphate metabolites (41−75%), and quaternary ammonium growth regulators (74−93%). Considering the initial relative high concentrations, a noticeable decrease in the levels was observed for DAPs, the nonspecific metabolites of organophosphates, as shown in Table 6. A significant decrease in the levels of chlormequat chloride was also noted, with the median value dropping from 41 μg/g creatinine to below the detection limit 7 days after switching to an organic diet.[70] The consumption of organic products notably reduces the level of pesticide residues in urine. Likewise, detection frequencies of pesticides/metabolites significantly dropped from 10−100% to 0−50% when switching to an organic diet.

In the studies presented in Table 6, samples were analyzed 5 days,[43] 6 days,[43] 7 days,[70] and up to 3 weeks[39] after switching to an organic diet. While some pesticides were sufficiently eliminated from the body within the observed time frame, others were only partially eliminated. Some pesticides can accumulate in the body and remain nonexcreted for extended periods, with traces lingering for months. Therefore, examination of urine levels after a longer period following the switch to an organic diet is necessary to precisely determine when the total urinary excretion of pesticides occurs. Collecting more data is also necessary for a better understanding of the elimination process, particularly in cases with varying initial exposure levels.

The detection of pesticide residues even when switching to organic diet might also be due to the fact that some organic products do contain pesticide residues, e.g., TCP and mepiquat in wine and coffee.[70] Besides, some commodities in EU (1064 samples) flagged as organic contain pesticide residues below or above the MRL level (18%) or above the MRL (1.5%) as reported by EFSA.[99] The most frequently detected pesticide in organic products are copper compounds primarily in cereals, bromide ion in rye and carrots, spinosad in bananas and tomatoes, chlorates mainly present in cucurbits with edible peel, lettuce, and spinach, fosetyl in wine grapes and ginger roots, and chlorpyrifos in teas.[99] Thus, the importance of these studies lies in analyzing the food consumed and directly linking it to the urinary pesticide levels for a comprehensive assessment of pesticide exposure.

Collection of demographic information such as age helps researchers understanding exposure patterns. Numerous studies evaluated the exposure of adults and children separately or only targeted children. Table 7 shows the concentration and frequency of detection of urinary pesticides and metabolites in adults and children, as specified by studies that specifically examined these age groups separately. In studies targeting pyrethroids, children exhibited notably higher concentrations (up to 1.5 ng/mL) than adults (up to 0.56 ng/mL) with a p-value of 0.008 and detection frequencies (ranging from 30% to 88%) compared to adults (16% to 67%), with a p-value of 0.13. In most studies, higher concentrations of organophosphate metabolites were observed in children compared to adults (p = 0.04). However, in studies focusing on occupational and residential exposure, adults exhibited higher concentrations, primarily due to occupational exposure, while children were exposed indirectly through their working families.

There is a positive correlation observed between age and the PRBS.[12] Higher concentrations in children are linked to a relatively higher food and water intake relative to their body weight in children than adults.[31,85] Dietary habits and preferences between children and adults vary, potentially leading to variable levels of exposure to pesticides. Children exhibit distinct metabolic, detoxification, and elimination processes for chemicals compared to adults. In certain instances, children may even possess a greater metabolic capacity for certain toxicants than adults.[100] Thus, the highest detected levels of metabolites were detected in children urine rather than parent compounds. In a study published by Zhao et al.,[101] it was demonstrated that the total pesticide concentrations in serum increased significantly with age ($p < 0.05$). Contrary to the trend shown in the serum, it was also demonstrated that the total pesticide levels in urine decreased significantly ($p < 0.05$) with age. This suggests that the decrease in pesticide concentrations in urine with age may be due to a decrease in the body's ability to metabolize and excrete these substances.

Limited research has explored the various changes that occur when transitioning from a conventional to an organic diet by comparing adults and children. As shown in Table 6, switching to an organic diet led to a relatively greater reduction in the chemical load of AMPA, 2,4-D, DCCA, and 3-PBA for adults (41−81%) compared to children (16−47%).[43,70] For DAPs, higher percent change was observed with children (73%) compared to adults (58%).[71] While for glyphosate, similar reduction rate (64−65%) was observed for both adult and children.[43] More extensive studies are needed, encompassing a broader range of chemical substances and involving a larger number of participants, to draw a conclusive assessment on the reduction rate of urinary pesticides in adults versus children when switching to an organic diet.

Aside from dietary exposure, environmental exposure, primarily due to differences in residence or occupancy, also contributed to the varying results observed between adults and children. Higher concentrations in adults are observed when adults work on farms and children are exposed indirectly. Higher concentrations and detection frequency in children could be linked to the respiratory rate, or the number of breaths taken per minute, which tends to be higher in children than in adults, which explains the higher exposure to pesticides for children, especially for those living close to agricultural areas.

There is a limited number of studies that specifically focus on investigating the disparities in pesticide exposure between males and females. While most studies design include the specific number of male and female participants to encompass sociodemographic diversity, the analysis involves evaluating the results combined. Most of the studies encompassed approximately similar numbers of males and females. However, due to possible disparity in urinary concentrations by gender, some studies adjusted statistically their results based on gender[46,82] or analytically by correcting for creatinine.

It was demonstrated that women have a higher PRBS than men.[12] Table 8 shows the concentration and frequency of detection of urinary pesticides/metabolites in male and female. Pesticide detection is significantly more common in females (p = 0.01). In 60% of the studies included in Table 8, the concentration of pesticides in urine is higher in women. Higher levels, exceeding 30% more, were reported for 3-PBA,[83] DAPs,[45] and TCPY[42] in females. Slightly higher values for

https://doi.org/10.1021/acs.jafc.4c02705
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Table 6. Concentration and Frequency of Detection of Urinary Pesticides/Metabolites in Conventional and Organic Diets[a]

year	country	chemical class	pesticide/ metabolite	N	target group	LOD (ng/mL)	concentration unit	concentration conventional diet	concentration organic diet	DF (%) conventional diet	DF (%) organic diet	percent changes%	ref
2019	US	phenol herbicide	2,4-D	7	adult	0.2	median (ng/ mL)	0.56	0.33			41%	71
2019	US	phenol herbicide	2,4-D	9	children	0.2	median (ng/ mL)	0.67	0.43			36%	71
2015	Sweden	phenol herbicide	2,4-D	5	adult and children	0.25−3*	median (μg/g creatinine)	2		65%	0%	100%	70
2020	US	phosphonate herbicide	glyphosate	7	adult	0.023−0.02	GM (ng/g creatinine)	0.26	0.09			65%	43
2020	US	phosphonate herbicide	glyphosate	9	children	0.023−0.02	GM (ng/g creatinine)	1.27	0.46			64%	43
2020	US	specific metabolite of glyphosate	AMPA	7	adult	0.033−0.013	GM (ng/g creatinine)	0.32	0.06			81%	43
2020	US	specific metabolite of glyphosate	AMPA	9	children	0.033−0.013	GM (ng/g creatinine)	0.8	0.27			66%	43
2015	Sweden	nonspecific metabolite of chloroacetanilide herbicides	3,5-DCA	5	adult and children	0.5−5.6*	median (μg/g creatinine)	13		60%	0%	100%	70
2015	Sweden	nonspecific metabolite of pyrethroid	3-PBA	5	adult and children	0.02	median (μg/g creatinine)	24		95%	0%	100%	70
2019	US	nonspecific metabolite of pyrethroids	3-PBA	7	adult	0.02	median (ng/ mL)	3.71	0.71			81%	71
2019	US	nonspecific metabolite of pyrethroids	3-PBA	9	children	0.02	median (ng/ mL)	1.64	1.37			16%	71
2015	Sweden	nonspecific metabolite of pyrethroids	3-PBA	5	adult and children	1.2−15*	median (μg/g creatinine)	24		95%	0%	100%	70
2019	US	nonspecific metabolite of pyrethroids	4F-3-PBA	16	adult and children	0.01	median (ng/mL)	0.04	0.02			50%	71
2019	US	specific metabolite of cypermethrin	*cis*-DCCA	7	adult	0.05	median (ng/mL)	3.44	0.71			79%	71
2019	US	specific metabolite of cypermethrin	*cis*-DCCA	9	children	0.05	median (ng/ mL)	1.27	0.67			47%	71
2019	US	specific metabolite of cypermethrin	*trans*-DCCA	7	adult	0.05	median (ng/ mL)	3.35	0.97			71%	71
2019	US	specific metabolite of cypermethrin	*trans*-DCCA	9	children	0.05	median (ng/ mL)	2.35	1.45			38%	71
2022	UK	pyrethroids		13/14	adult	0.1−0.2	concentration (μg/day)	4.5	2.1			53%	39
2019	US	nonspecific metabolite of organophosphates	DAPs	7	adult	0.06−0.25	median (nmol/ L)	93.34	39.2			58%	71
2019	US	nonspecific metabolite of organophosphates	DAPs	9	children	0.06−0.25	median (nmol/ L)	212.98	57.64			73%	71
2019	US	specific metabolite of the organophosphate malathion	malathion dicarboxylic acid	16	adult and children	0.02	median (ng/ mL)	1.03	<LOD				71
2015	Sweden	specific metabolite of the organophosphate chlorpyrifos	TCPy	5	adult and children	1.3−17*	median (μg/g creatinine)	31	<LOD	100%	30%		70
2019	US	specific metabolite of the organophosphate chlorpyrifos	TCPy	7	adult	0.02−0.6	median (ng/ mL)	2.55	0.63			75%	71

https://doi.org/10.1021/acs.jafc.4c02705
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Table 6. continued

year	country	chemical class	pesticide/ metabolite	N	target group	LOD (ng/mL)	concentration unit	concentration conventional diet	concentration organic diet	DF (%) conventional diet	DF (%) organic diet	percent changes%	ref
2019	US	specific metabolite of the organophosphate chlorpyrifos	TCPy	9	children	0.02−0.6	median (ng/mL)	2.99	1.77			41%	71
2022	UK	organophosphates		13/14	adult	1	concentration (μg/day)	7.3	3.8			48%	39
2019	US	nenonicotinoid	clothianidin	16	adult	0.05	median (ng/mL)	0.24	<LOD				71
2015	Sweden	carbamate fungicide	propamocarb	5	adult and children	0.11−1.4*	median (μg/g creatinine)	<LOD	<LOD	35%	5%		70
2015	Sweden	metabolite of carbamates	ETU	5	adult and children	0.55−6.7*	median (μg/g creatinine)	<LOD		10%	0%		70
2015	Sweden	quaternary amonium growth regulator	mepiquat	5	adult and children	0.95−12*	median (μg/g creatinine)	14	3.6	100%	50%	74%	70
2015	Sweden	quaternary amonium growth regulator	chlormequat chloride	5	adult and children	1.2−15*	mMedian (μg/g creatinine)	41	<LOD	90%	10%		70
2022	UK	quaternary amonium growth regulator	chlormequat	13/14	adult	2.5	concentration (μg/day)	141	10			93%	39

[a]N, number of participants; DF, detection frequency; * μg/g creatinine6.4. Association of urinary pesticides with age.

specific pesticides, e.g., ETU[37] and glyphosate,[61,64] were observed in males. However, in some studies, no correlation was found between urinary levels and gender.[60,65] Studies focusing on individuals residing near agricultural areas, such as vineyards, also found no gender differences in urinary pesticide levels.[33,64]

The predominantly higher levels and frequencies observed in women was attributed to the possibility that women consume more fruits and vegetables than men as suggested by some studies,[76] or that the larger body size of men compared to women potentially resulted in lower urinary concentration in man.[76] This was also attributed to the fact that males have higher metabolic capabilities than females. In an interesting study, the concentration of DMDTP and PNP in pools from female children exhibited a more pronounced increase with age compared to male children, whereas the opposite trend was observed for DETP.[68] However, this was not further explained.

7. URINARY BIOMARKERS AND ASSOCIATED HEALTH RISKS

Several studies solely aimed to determine the levels of pesticides in urine without linking them to health concerns; however, some studies have explored this connection. The health issues detailed below have been demonstrated based on findings in urine analysis. These studies do not require only the analysis of urinary pesticides but also careful selection of the target group. The studies have been performed on a large number of participants (more than 110).

7.1. Lactating Mothers. A Spanish study among breastfeeding women found that none of the detected pesticides, chloryprifos, dimethoate, parathion, deltamethrin,[54] glyphosate, and AMPA[55] exceeded the safety limit and therefore showed a relatively low health risks based on hazard quotient (HQ). Another study examining urinary pesticides in lactating women and their infants indicated that infants receive concentrated chlorpyrifos residues through breast milk.[56]

7.2. Relationship between Oxidative Stress and Pesticide Exposure. Four studies demonstrated the relationship between oxidative stress and pesticide exposure. In a recent study done in the US, a linear relationship was observed between elevated pyrethroid exposure, as indicated by the concentrations of 3-PBA in urine, and an increased prevalence of rheumatoid arthritis,[13] a chronic autoimmune disease that primarily affects the joints. In another recent study conducted in the Czech Republic, it was demonstrated that elevated levels of pyrethroid metabolites in urine, particularly t/c-DCCA and TCPy, have been linked to increased oxidative stress. Furthermore, these metabolites have been associated with higher cytosine methylation biomarkers, which implies a potential involvement of these pesticides in inhibiting DNA glycosylase and subsequently reducing the demethylation processes.[74] In a 2022 study conducted in Spain, findings were consistent with the latest research, demonstrating that elevated levels of pyrethroid metabolite 3-PBA, and other metabolites such as malathion diacid (MDA), and ETU were linked to increased DNA methylation percentages at multiple CpG sites.[95] The effect of pesticide residues on oxidative stress was also demonstrated by a study conducted in Thailand in 2020, where organophosphate metabolites (DAPs) were proved to cause oxidative stress.[96] Children living in agricultural communities were found to have lower levels of glutathione (GSH), a vital antioxidant responsible for

https://doi.org/10.1021/acs.jafc.4c02705
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Table 7. Concentration and Frequency of Detection of Urinary Pesticides/Metabolites in Adults and Children[a]

year	country	chemical class	pesticide/ metabolite	N	LOD (ng/mL)	LOQ (ng/mL)	concentration unit	concentration adult	concentration children	DF (%) adult	DF (%) children	ref
Diet Exposure or General Assessement												
2022	Czech republic	nonspecific metabolite of pyrethroids	3-PBA	220	0.04	0.14	median (μg/L)	0.16	0.56	52%	88%	69
2023	Czech republic	nonspecific metabolite of pyrethroids	3-PBA	110	0.04	0.14	GM (ng/mL)	0.21	0.46	52%	88%	74
2020	Slovenia	nonspecific metabolite of pyrethroids	3-PBA	168	0.02		GM (ng/mL)	0.16*	0.31	67%	80%	65
2020	Slovenia	nonspecific metabolite of pyrethroids	4F-3-PBA	168	0.02		GM (ng/mL)	0.03*	<LOD	16%	30%	65
2022	Czech republic	specific metabolite of the pyrethroid cypermethrin	DCCA	220	0.03	0.11	median (μg/L)	0.56	1.5	61%	84%	69
2023	Czech republic	specific metabolite of the pyrethroid cypermethrin	DCCA	110	0.03	0.11	GM (ng/mL)	0.3	1.08	61%	86%	74
2004	US	nonspecific metabolite of organophosphates	DEP	213	2.9					46−64%	36−56%	19
201[a]	Denmark	nonspecific metabolite of organophosphates	DEP	289	0.3		GM (μg/L)	3.8*	4.5	97%	96%	31
2011[a]	Denmark	nonspecific metabolite of organophosphates	DMP	289	1.5		GM (μg/L)	2.7*	4	54%	69%	31
2011[a]	Denmark	nonspecific metabolite of organophosphates	DETP	289	0.3		GM (μg/L)	0.52*	0.59	34%	40%	31
2011[a]	Denmark	nonspecific metabolite of organophosphates	DEDTP	289	0.3		GM (μg/L)				0%	31
2004	US	nonspecific metabolite of organophosphates	DMAP	213						12−24%	14−24%	19
2004	US	nonspecific metabolite of organophosphates	DMDTP	213	0.65					90−96%	84−92%	19
2011[a]	Denmark	nonspecific metabolite of organophosphates	DMDTP	289	0.3		GM (μg/L)			2.1%	1.4%	31
2011[a]	Denmark	nonspecific metabolite of organophosphates	DMTP	289	0.3		GM (μg/L)	2.2*	2.4	73%	76%	31
2011	Thailand	nonspecific metabolite of organophosphates	∑DAPs	48	64**		GM (mg/g crea)	13	7.6			29
2022	Czech republic	specific metabolite of the organophosphate chlorpyrifos	TCPY	220	0.03	0.09	median (μg/L)	3.27	4.6	87%	84%	69
2023	Czech republic	specific metabolite of the organophosphate chlorpyrifos	TCPY	110	0.03	0.09	GM (ng/mL)	2.29	2.53	87%	84%	74
2019	Iran	specific metabolite of the organophosphate chlorpyrifos	TCPY	61	0		median (μg/L)	1.3*	1.4	20%	34%	56
2020	Slovenia	specific metabolite of the organophosphate chlorpyrifos	TCPY	168	0.02		GM (ng/mL)	0.02*	0.02	88%	84%	65
2019	US	specific metabolite of the organophosphate chlorpyrifos	TCPY	16	0.2		median (ng/mL)	2.6	3			71
2022	Czech republic	triazole fungicide	tebuconazole	220	0.02	0.05	median (μg/L)	0.47	0.44	98%	91%	69
2023	Czech republic	triazole fungicide	tebuconazole	110	0.02	0.05	GM (ng/mL)	0.46	0.46	92%	99%	74
2020	US	phosphonate herbicide	glyphosate	16			median (ng/mL)	1.2	1.0			43
2020	US	specific metabolite of glyphosate	AMPA	16			median (ng/mL)	0.27	0.79			43
Occupation and Residency												
2016	China	nonspecific metabolite of pyrethroids	3-PBA	40	0.008	0.025	median (μg/L)	0.35	0.43	30%	35%	30
2016	China	nonspecific metabolite of pyrethroids	4FPBA	40	0.02	0.05	median (μg/L)	0.02	0.03	25%	20%	30
2016	China	nonspecific metabolite of organophosphates	TCPY	40	0.2	0.6	median (μg/L)	1.57	2.9	40%	50%	30
2001	US	nonspecific metabolite of organophosphates	DMP	27	5.9		mean (ppb)	8.11	8.4	33%	44%	20
2004	US	nonspecific metabolite of organophosphates	DMP	213						12−24%	14−24%	19

https://doi.org/10.1021/acs.jafc.4c02705
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Table 7. continued

year	country	chemical class	pesticide/ metabolite	N	LOD (ng/mL)	LOQ (ng/mL)	concentration unit	concentration adult	concentration children	DF (%) adult	DF (%) children	ref
Occupation and Residency												
2006	US	nonspecific metabolite of organophosphates	DMP	218	1.1		GM (μg/L)	0.71−1.7	1.3−3.5			18
2006	US	nonspecific metabolite of organophosphates	DMTP	218	0.65		GM (μg/L)	4.4−15	3.5−6.2			18
2001	US	nonspecific metabolite of organophosphates	DMTP	27	7.5		mean (ppb)	13	14	28%	33%	20
2004	US	nonspecific metabolite of organophosphates	DMTP	213						90−96%	84−92%	19
2016	China	nonspecific metabolite of organophosphates	DMTP	40	0.67	2	median (μg/L)	9	2.4	80%	40%	30
2004	US	nonspecific metabolite of organophosphates	DMDTP	213						46−64%	36−56%	19
2006	US	nonspecific metabolite of organophosphates	DMDTP	218	2.9		GM (μg/L)	0.47−1.37	0.65−0.98			18
2001	US	nonspecific metabolite of organophosphates	DEP	27	6.3		mean (ppb)	ND		11%	11%	20
2016	China	nonspecific metabolite of organophosphates	DEP	40	0.07	0.2	median (μg/L)	5.5	2.3	85%	70%	30
2001	US	nonspecific metabolite of organophosphates	DETP	27	4.8		mean (ppb)	8	5.7	6%	11%	20
2016	China	nonspecific metabolite of organophosphates	DETP	40	0.08	0.25	median (μg/L)	6.0	2	85%	60%	30

[a]N, number of participants; DF, detection frequency; ND, not detected; [1], year of the study; *adult (mothers), **concentration in ng/g creatinine6.5. Association of urinary pesticides with gender

maintaining the body's redox balance, compared to those residing in urban areas.[96]

7.3. Effects of Urinary Pesticides on the Neurological Systems of Children and Adolescent. Some studies highlighted the effects of urinary pesticides on the neurological systems of children. Higher concentrations of IMPy, TCPy, and ETU were significantly associated with a higher incidence of behavioral issues, such as social difficulties, thought-related problems, and rule-breaking symptoms. Furthermore, IMPy, MDA, DETP, and 1-naphthol were significantly correlated with reduced serum brain-derived neurotrophic factor levels.[95] These findings suggest a potential relationship between pesticide exposure and epigenetic changes, as well as behavioral and neurobiological impacts.[95] Findings of a study conducted in China indicate that children's working memory and verbal comprehension could be notably influenced by exposure to organophosphate and pyrethroid pesticides.[82] Neurodevelopment impact was also suspected due to carbamate exposure in utero and at a young age.[102] DAPs were linked to low verbal IQ scores in 3−4 year old boys, but this effect was not observed with girls.[84] This suggests that gender differences exist in the effects, leading some studies to segregate urine samples based on the gender of participants. Additional research on urinary pesticides encompassing nonoccupationally exposed adults and children is necessary to gain insight into the possible mechanisms and causative factors behind certain diseases.

7.4. Other Associations to Health Risks. The association between urinary pesticide metabolites and altered thyroid and reproductive hormones was demonstrated in a study done on 135 adolescents in Spain;[103] the study revealed positive associations between detectable 3-PBA and TT3 (total triiodothyronine) and between detectable 1N and dehydroepiandrosterone sulfate. There were also marginally significant associations of 1N with reduced estradiol and follicle-stimulating hormone. In a recent study done in the US, a linear relationship was observed between elevated pyrethroid exposure, as indicated by the concentrations of 3-PBA in urine, and an increased prevalence of rheumatoid arthritis,[13] a chronic autoimmune disease that primarily affects the joints. A study in the United States examined the prevalence of myopia in relation to urinary pesticide exposure, specifically looking at organophosphate and pyrethroid metabolites. However, the study did not find any significant association between these pesticide metabolites and myopia.[14]

The primary dietary source of exposure to pesticide residues is dominated by fruits and vegetables, which are also linked to the prevention of several chronic diseases. This implies that a substantial intake of foods with health benefits may overshadow any potential negative effects of pesticide residues.[104]

7.5. Transitioning to Organic Diet Association to Health. Transitioning to an organic diet, which leads to lower levels of pesticide residues in urine, is often considered for its potential health benefits. Some studies have found an inverse association between organic food consumption with the risk of type 2 diabetes[105,106] and metabolic syndrome,[107] while other studies have found no clear association between organic food consumption and, e.g., risk of cancer[108] or metabolic syndrome.[109] A recent review published by Guzmann-Torres et al.[3] based on frequency of urinary pesticides in children concluded that the scientific evidence may still be regarded as insufficient with regard to the health effects of pesticides to establish a global recommendation through public policy.

https://doi.org/10.1021/acs.jafc.4c02705
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Table 8. Concentration and Frequency of Detection of Urinary Pesticides/Metabolites in Men and Women[a]

year	country	chemical class	pesticide/metabolite	*N*	concentration unit	concentration men	concentration women	DF (%) men	DF (%) women	ref
2004	Italy	nonspecific metabolite of pyrethroids	3-PBA	25 male; 44 female	mean (nmol/day)	5.3	6.5			27
2017	Canada	nonspecific metabolite of pyrethroids	3-PBA	1785 male; 2165 female	GM (μg/L)	0.30	0.29	47%	53%	14
2021	US	nonspecific metabolite of pyrethroids	3-PBA	92 male; 99 female	median (μg/L)	0.96	0.95			30
2023	Turkey	nonspecific metabolite of pyrethroids	3-PBA	107 boys; 79 girls	GM (ng/g crea)	0.12	0.17			83
2020	Spain	nonspecific metabolite of pyrethroids	3-PBA	27 male; 281 female	median (ng/mL)	1.5	1.7			63
2004	Italy	nonspecific metabolite of organophosphates	alkylphenol	25 male; 44 female	mean (nmol/day)	414	374			27
2017	Canada	nonspecific metabolite of organophosphates	DAP	3076 male; 3440 female	GM (nM)	55	59	47%	53%	14
2018	India	nonspecific metabolite of organophosphates	DAPs	110 male; 105 female*	median (μmol/L)	2	2.1	74%	88%	66
2018	India	nonspecific metabolite of organophosphates	DAPs	78 male; 84 female*	median (μmol/L)	1.9	2.7	74%	88%	66
2019	Spain	nonspecific metabolite of organophosphates	DEDTP	68 boys; 154 girls	GM (μg/g crea)	0.06	0.06			57
2019	Spain	nonspecific metabolite of organophosphates	DEP	68 boys; 154 girls	GM (μg/g crea)	0.11	0.14			57
2018	India	nonspecific metabolite of organophosphates	DEs	110 male; 105 female*	median (μmol/L)	0.95	0.97			66
2018	India	nonspecific metabolite of organophosphates	DEs	78 male; 84 female**	median (μmol/L)	1.2	1.4			66
2019	Spain	nonspecific metabolite of organophosphates	DETP	68 boys; 154 girls	GM (μg/g crea)	0.1	0.11			57
2019	Spain	nonspecific metabolite of organophosphates	DMP	68 boys; 154 girls	GM (μg/g crea)	0.27	0.33			57
2018	India	nonspecific metabolite of organophosphates	DMs	110 male; 105 female*	median (μmol/L)	0.55	0.48			66
2018	India	nonspecific metabolite of organophosphates	DMs	78 male; 84 female**	median (μmol/L)	0.59	0.7			66
2004	Italy	nonspecific metabolite of dithiocarbamates	ETU	25 male; 44 female	mean (nmol/day)	13	6			27
2022	France	phosphonate herbicide	glyphosate	2583 male; 3040 female***	conc (ng/mL)	1.3	1.1			25
2021	Germany	phosphonate herbicide	glyphosate	1110 male; 1034 female	GM (μg/L)	0.11	0.10			31
2020	Spain	specific metabolite of the organophosphate parathion	*p*-nitrophenol	27 male; 281 female	median (ng/mL)	1.4	1.2			63
2004	Italy	specific metabolite of the organophosphate chlorpyrifos	TCPY	25 male; 44 female	mean (nmol/day)	25	26			27
2020	Spain	specific metabolite of the organophosphate chlorpyrifos	TCPY	27 male; 281 female	median (ng/mL)	0.9	1.4			63
2023	Turkey	specific metabolite of the organophosphate chlorpyrifos	TCPY	107 boys; 79 girls	GM (ng/g crea)	0.09	0.12			83

https://doi.org/10.1021/acs.jafc.4c02705
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Table 8. continued

year	country	chemical class	pesticide/metabolite	N	concentration unit	concentration men	concentration women	DF (%) men	DF (%) women	ref
2019	Spain	nonspecific metabolite of organophosphates	ΣDAP	68 boys; 154 girls	GM (μg/g crea)	6.7	8			57
2020	Spain	nonspecific metabolite of organophosphates	ΣDAP	27 male; 281 female	median (ng/mL)	32	30			63
2013	Sudan	metabolite of the organochlorine DDT	DDE	12 male; 12 female				25%	33%	58
2020	China	neonicotinoids	thiamethoxam, clothianidin, *N*-desmethyl acetamiprid	141 boys; 148 girls				49%	51%	85

[a]*N*: number of participants. *Age 6−10 years old. **Age 11−15 years old. ***Farmer.

Another recent review by Baudry et al.[2] based on prospective studies aimed at estimating the associations between dietary exposure to pesticides and noncommunicable diseases among adults found that while there is some indication of a potential health impact from dietary pesticide exposure, the existing research is limited. Further investigation is needed to underscore the significance of transitioning toward organic and sustainable plant-rich diets, emphasizing the potential health benefits associated with reduced exposure to pesticides.

8. PERSPECTIVES

The primary strength of this review is its rigorous literature search, ensuring a thorough exploration of studies concerning pesticide residues in urine while also avoiding the omission of pertinent research findings. Thereby, it enables a deeper understanding of the connections between residency and environmental pesticide exposure and their effects on urinary biomarkers. Additionally, it explores the relation between food consumption, including organic and plant-based rich diets and urinary biomarkers. The limitation of this review lies in the challenge of comparing results across different geographical regions due to variations in data reporting methods. Additionally, the absence of comparable data over different years poses a further obstacle to meaningful comparisons. While the review provides nuanced insights into health effects, its primary focus lies on methodologies used for analysis and risk assessment rather than extensively delving into the health implications.

This review underscores the importance of establishing standardized reporting practices for urinary pesticides and emphasizes the necessity for comprehensive data collection efforts in studies examining pesticide exposure. It highlights the significance of incorporating both temporal and geographical dimensions into data collection to enable robust analyses and meaningful comparisons across regions and over time. Furthermore, the review draws attention to the increasing relevance of collecting data on pesticide exposure when transitioning to sustainable plant-based diets, especially given the growing popularity of such dietary patterns as perceived healthier choice. This becomes particularly important as pesticide applications continue to occur, and viable alternatives to pesticides are still under research and development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jafc.4c02705.

A list of scientific publications on pesticides and metabolites in human urine. It features information such as the date, country, number of participants, participant range, target group, spectrum of urinary investigation, and sampling methods. (XLSX)

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https://doi.org/10.1021/acs.jafc.4c02705
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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The study is part of the OnePlate project funded by the Technical University of Denmark and by the Green Development and Demonstration Programme (GUDP) under the Ministry of Food, Agriculture and Fisheries of Denmark (grant no. 34009-22-2036) as part of the Organic RDD8 programme of the International Centre for Research in Organic Food Systems (ICROFS, Denmark).

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