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Urinary pesticide mixture patterns and exposure determinants in the adult population from the Netherlands and Switzerland: Application of a suspect screening approach

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ABSTRACT

Introduction: Non-occupational sources of pesticide exposure may include domestic pesticide usage, diet, occupational exposure of household members, and agricultural activities in the residential area. We conducted a study with the ambition to characterize pesticide mixture patterns in a sample of the adult population of the Netherlands and Switzerland, using a suspect screening approach and to identify related exposure determinants.
Methods: A total of 105 and 295 adults participated in the Dutch and Swiss studies, respectively. First morning void urine samples were collected and analyzed in the same laboratory. Harmonized questionnaires about personal characteristics, pesticide-related activities, and diet were administered. Detection rates and co-occurrence patterns were calculated to explore internal pesticide exposure patterns. Censored linear and logistic regression models were constructed to investigate the association between exposure and domestic pesticide usage, consumption of homegrown and organic foods, household members' exposure, and distance to agricultural and forest areas.
Results: From the 37 detected biomarkers, 3 (acetamiprid (-CH2), chlorpropham (4-HSA), and flonicamid (-C2HN)) were detected in ≥40% of samples. The most frequent combination of biomarkers (acetamiprid-flonicamid) was detected in 22 (5.5%) samples. Regression models revealed an inverse association between high organic vegetable and fruit consumption and exposure to acetamiprid, chlorpropham, propamocarb (+O), and pyrimethanil (+O + SO3). Within-individual correlations in repeated samples (summer/winter) from the Netherlands were low (≤0.3), and no seasonal differences in average exposures were observed in Switzerland.
Conclusion: High consumption of organic fruit and vegetables was associated with lower pesticide exposure. In the two countries, detection rates and co-occurrence were typically low, and within-person variability was high. Our study results provide an indication for target biomarkers to include in future studies aimed at quantifying urinary exposure levels in European adult populations.

Abbreviations: CH, Switzerland; EKNZ, Ethikkommission Nordwest-und Zentralschweiz (local ethics committee in Switzerland); HBM4EU, European Human Biomonitoring initiative; MREC, Medical Research Ethics Committee Utrecht; NL, the Netherlands; SPECIMEn, Survey on PEstiCIde Mixtures in Europe; SS, Suspect Screening; WMO, Dutch Medical Research Involving Human Subjects Act.

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1. Introduction

Pesticides are widely used in agriculture to protect crops. In Europe, more than 400 pesticide compounds are registered and marketed (European Commission, 2023). On a daily basis, the general population is exposed to a mixture of various pesticides by consumption of pesticide-containing food or drinks, domestic usage of pesticide-containing products, or living close to agricultural areas. The active ingredients of pesticides are intrinsically toxic and can adversely affect human health (Gilden et al., 2010; Cimino et al., 2017). Adverse health effects of single compounds, particularly reported in occupational settings, include cancer, neurological, mental, respiratory, reproductive, and developmental disorders as well as rheumatoid arthritis (Ohlander et al., 2020). The characterization of pesticide exposure patterns and exposure sources in the general population is an essential step toward understanding the full scope of health impacts of single compounds and mixtures. Exposure characterization by human biomonitoring (HBM) has the advantage, depending on the biomonitoring method chosen, to cover all possible exposure routes (dermal, oral, inhalation), thereby reflecting the internal exposure concentrations of a wide range of chemicals (Ganzleben et al., 2017). Since most pesticides are rapidly metabolized into more polar derivatives and excreted through urine, this matrix is typically used for pesticide exposure assessment (Angerer et al., 2007; Egeghy et al., 2011). Suspect Screening (SS) approaches based on liquid chromatography (LC) combined with high-resolution mass spectrometry (HRMS) make it possible to effectively measure large numbers of pesticides co-occurring in the same urine sample (Bonvallot et al., 2021; Huber et al., 2022; Vitale et al., 2022). This SS approach provides a list with annotations of pesticides and pesticide metabolites in a sample (Pourchet et al., 2020; Huber et al., 2022), and presents the measurements as semi-quantitative signal intensities. Although these signal intensities do not refer to absolute pesticide concentration levels, signal intensities for the same biomarker analyzed under identical laboratory settings can be compared.

Epidemiological studies describing exposure pathways to pesticides are mostly focusing on occupational populations or residents living in agricultural areas, where the exposure levels are typically higher compared to the general population (Deziel et al., 2015; Teysseire et al., 2021). Information on pesticide exposure in the general population is rather limited (Heffernan et al., 2016; Dahiri et al., 2021; Yusà et al., 2022), in particular with regard to exposure to pesticide mixtures at low concentrations (Hernández et al., 2017) and temporal variation of exposure (Attfield et al., 2014; Li et al., 2019). While for the general population, the exposure levels and the total number of exposure pathways might be lower, understanding the contribution of non-occupational exposure sources is crucial to study the link between pesticide exposure and adverse health effects, as well as to propose preventive measures to protect the general population, specifically those most vulnerable (pregnant or nursing women, infants or children, and the elderly) (European Commission, 2022).

The overall aim of this study was to explore pesticide mixture patterns of exposure in a sample of the adult population from the Netherlands and Switzerland using an HBM SS approach and to identify possible determinants.

2. Material and methods

2.1. Study population and sample collection

The two studies presented here, the Dutch arm of the Survey on PEstiCIde Mixtures in Europe (SPECIMEn) and the Swiss pesticide suspect screening study, are part of the European Human Biomonitoring (HBM4EU) initiative and sought to generate new evidence on pesticide exposure in the general population. While the Dutch SPECIMEn study focused on exploring variations of pesticide exposure patterns in parent-child pairs by repeated sampling design in two seasons, the Swiss study provided exposure data of adults by taking single samples during three different seasons.

A concise summary of the Dutch sampling strategy is provided here, as the study population recruitment and sample collection procedure have already been described in detail elsewhere (Ottenbros et al., 2023). In short, first-morning void urine samples were collected from participants (parent-child pairs) from different locations (closer and further away from orchards) in two seasons (winter 2020: Jan–Mar 2020; and summer 2020: Jun–Jul 2020). For the current study, samples of all 105 adults from the Dutch SPECIMEn study were included, children were excluded. In order to minimize the influence of pesticide applications in nearby agricultural areas on exposure intensity and to better assess baseline exposure of the adult population, only winter samples of adults were included in the main analyses. Farmers and other adults employed in the agricultural sector were not included. Participants mainly lived in the Betuwe area (between Arnhem-Gorinchem-Utrecht). During recruitment of the SPECIMEn study, participants were selected from two areas (close to apple and pear orchards ($<$250 m) and further away ($>$500 m). The study of Ottenbros et al. (2023) did not find any difference based on these locations. For the current study participants from both areas were included and the distance from their address to agricultural areas was calculated. This distance to the nearest agricultural plot and forest from each geo-coded address was calculated using QGIS software (v3.4.4) using publicly available data from the Dutch Central Bureau of Statistics (CBS). At the time of urine collection, a questionnaire was administered covering personal and household characteristics, activities prior to sampling, potential pesticide usage, and food consumption the day prior to sampling.

In the Swiss study, 300 adults from the canton of Basel-Stadt participated in the HBM4EU pesticide suspect screening study (Buekers et al., 2022). A total of five participants indicated that they used pesticides for occupational use, and were thus excluded from further analyses. Data and sample collection were performed between January 08, 2020, and October 10, 2020. Study participants were contacted in five sex-stratified recruitment waves via postal mail containing the study invitation letter, an information leaflet, and a response card. A total of 6000 subjects, selected from the resident register based on age and long-term residency in Basel-Stadt, had been invited. Interested subjects were contacted after their successful electronic registration to the REDCap® (Research Electronic Data Capture) data collection tool (Harris et al., 2009), to identify a date for the urine sample collection. Instructions and a urine sample collection kit were sent by postal mail prior to the day of collection. The participants collected first-morning void urine samples at their homes and were asked to store the morning urine sample at 4 °C using cooling pads and a cooling bag until the study team collected the sample. The urine samples were then transported to and processed in the study center at Swiss TPH, maintaining the cold chain throughout until the biobanking of urine aliquots at −80 °C. An electronic self-administered pre-sample questionnaire (answered before the day of sample collection) and a post-sample questionnaire (answered on the day of sample collection) were distributed. Participant recruitment, data collection, and laboratory workflow were performed and documented using REDCap® (Harris et al., 2009). The "minimal geo data model" (MGDM) for agricultural land use in the Basel-Stadt area was used to calculate the distance of the participants' geo-coded addresses to the nearest agricultural area and forest in QGIS 3.4.4 (*MMQGIS* and *NNJoin* plugin). An exact description of the definitions used for forest and agricultural areas for both countries is provided in the Appendix (Table A1).

The harmonized questionnaires administered in the two countries were developed in the context of the HBM4EU project and mostly contained identical questions in both countries. Where necessary, they were additionally harmonized between the two study countries. Questions and variables of interest for the analysis were manually compared and, where necessary, re-coded by the authors (for details see Appendix, Table A.2). The medical research ethics committee confirmed that the

Table 1
Participant characteristics of the Dutch (NL) and Swiss (CH) studies.

Country	Netherlands (NL)	Switzerland (CH)
Participants, n	105	295
Gender female, n (%)	73 (69.5)	136 (46.1)
Mean age, years [min-max]	42.1 [29–56]	30.8 [20–39]
BMI, n (%)		
Normal/Underweight (<25)	129 (72.3)	217 (73.6)
Overweight (25–30)	60 (22.9)	64 (21.7)
Obese (>30)	18 (4.8)	14 (4.7)
Education level, n (%)		
No or only primary education	1 (1.0)	2 (0.7)
Secondary education	5 (4.8)	1 (0.3)
Tertiary education (post-secondary)	19 (18.1)	67 (22.7)
University (BSc, MSc, PhD)	76 (72.3)	221 (74.9)
Don't Know/NA	4 (3.8)	4 (1.4)
Household income[a], % of country average		
< 25%	1 (1.0)	61 (20.7)
25–50%	6 (5.7)	109 (36.9)
50–75%	49 (46.7)	47 (15.9)
>75%	33 (31.4)	53 (18.0)
Don't Know/NA	16 (15.2)	25 (8.5)
Mean distance to agricultural areas, m [min-max]	976 [21–2618]	979 [24–2221]
Mean distance to forest, m [min-max]	271 [0–1739]	566 [8–1294]

[a] Income categories from the Swiss questionnaire were assigned to the <25th, 25th - 50th, 50th – 75th and >75th percentile categories based on the publication by the Swiss Federal Department of Finance (2014): https://biblio.parlament.ch/e-docs/377581.pdf.

Dutch Medical Research Involving Human Subjects Act (WMO) does not apply to the above-mentioned study and that therefore an official approval of this study by the Medical Research Ethics Committee (MREC) Utrecht was not required under the WMO (reference number WAG/mb/19/027712). The Swiss study acquired ethical approval from the local ethics committee (Ethikkommission Nordwest-und Zentralschweiz (EKNZ), 2019–02136). All participants provided their written informed consent.

2.2. Suspect screening approach

Suspect screening (SS) is a valuable approach to explore the general population's pesticide exposure and the occurrence of mixtures across countries. Currently, analyses conducted in the same laboratory allows for the comparison of the semi-quantitative SS measurements for each biomarker. The urine samples from the Dutch and Swiss studies were both analyzed at the Wageningen Food Safety Research laboratory in the Netherlands under a harmonized and quality-controlled SS analysis framework. As this framework is based on elaborated work including expert reviews and confirmation workflow, we here refer to Huber et al. (2022) and Vitale et al. (2022) for a detailed description of the applied analytical workflow and annotation process, which includes the following steps: 1) pH adjustment and solid phase extraction (SPE) cleanup, 2) LC coupled to full scan HRMS (LC-HRMS) to measure the extracts, 3) data processing and analysis, 4) prioritization of supposed detects, and 5) spectral comparison (retention time and MS2 spectra) of suspected detects with reference standards for final confirmation.

Several metabolites of the same parent compound may be included in the final list of pesticides, but the confidence with which a compound can be determined may vary. Schymanski et al. (2014) developed a confidence score representing the (un)certainty about the identity of a compound, ranging from 1: 'Fully confirmed structure' to 5: 'Exact mass (m/z) of interest'. Only compounds identified by molecular structure, or confidence levels 1 (confirmed structure) and 2b (probable structure by diagnostic evidence), were considered in the current study.

The results of the SS analysis are presented as semi-quantitative signal intensities of the compound detects, i.e. as indicators of exposure rather than quantitative concentration levels. Higher signal intensity scores generally correspond to higher concentrations for the same compound, but may also depend on levels of ion suppression due to matrix effects. Equal signal intensity scores for different compounds may correspond to different concentration levels depending on their ionization efficiency. Biomarkers are indicated with their parent pesticide name and the respective metabolite in parentheses the first time mentioned in the text. Upon the second mention, the name of the biomarkers will be noted only by the parent pesticide for improved readability. To avoid confusion, metabolites in parentheses will remain stated if two or more biomarkers of the same pesticide were detected.

2.3. Statistical analyses

For the analysis of the suspect screening data, the subset of 37 biomarkers confirmed with high confidence (Schymanski levels 1 and 2b) were considered. The detection frequency for each biomarker was calculated for the pooled dataset, as well as the Dutch and the Swiss population separately (see Appendix A, Figure A1). The biomarkers were plotted with their log-transformed SS signal intensity score and their detection ratio. Co-occurrence of biomarkers (detected together in the same urine sample) was shown graphically using an UpSet plot (UpSetR, v1.4.0).

Temporal differences in both studies were assessed. In the Dutch study, two samples from the same individual were taken, one in each season, for which the intra-class correlation coefficient (ICC) was calculated. A linear mixed effects model with censored data (using the log-transformed intensity scores) was used, i.e. a multilevel Tobit model. This two-level (first: measurements, second: subjects) random intercept model was defined as follows:

$$\log\left(y_{ij}\right) = \beta + u_j^{(2)} + \varepsilon_{ij}^{(1)}$$

where β represents the intercept, u_j the between-subject error, and ε_{ij} the within-subject error.

To assess the temporal differences in the Swiss study, average intensity scores for each season (winter, spring, summer) were displayed in boxplots for the 13 most detected biomarkers (see Appendix A; Figure A.2).

In order to explore determinants of exposure, censored regression models were constructed (Tobit, VGAM v1.1.7) (Henningsen, 2022). Given the explorative nature of the analyses, models were not adjusted for multiple comparisons. For biomarkers of only three pesticides (acetamiprid, chlorpropham and flonicamid), the detection rate was sufficiently high (at least 40% at each study side) to construct a censored linear regression model. For the remaining biomarkers, logistic censored regression models were constructed (based on detected yes/no). All models were *a priori* corrected for age (years), gender (male/female), BMI (normal: <25, overweight: 25–30, obese: >30), level of education (primary, secondary, tertiary, higher), income (<25%, 25–50%, 50–75%, >75% of country average), and country (not for country-specific models). The following exposure variables were mutually included in the models: having a household member who used pesticides occupationally (yes/no), pesticide usage in the garden (up to 3 days (3d) prior to sampling, yes/no), pesticide usage indoors (up to 3d prior sampling, yes/no), pesticide usage on pets (up to 3d prior sampling, yes/no), pesticide usage for hobby use (up to 3d prior sampling, yes/no), homegrown food consumption in summer (not-high (<50%), high (≥50%)), organic food consumption per food category (vegetables and fruit, bread, meat, rice, eggs, dairy; not-high (<50%), high (≥50%)), and distance (m) to the closest agricultural area or forest. Continuous variables were log-transformed (age, distance to agriculture, distance to forest). For sensitivity analyses, following the study of Baudry et al. (2019), a 'low' category was created for less than 10% of homegrown/organic foods consumption (see Appendix A; Table A.3). Missing values in the independent variables were imputed using mice (v3.14.0), with normal distribution for the continuous variables,

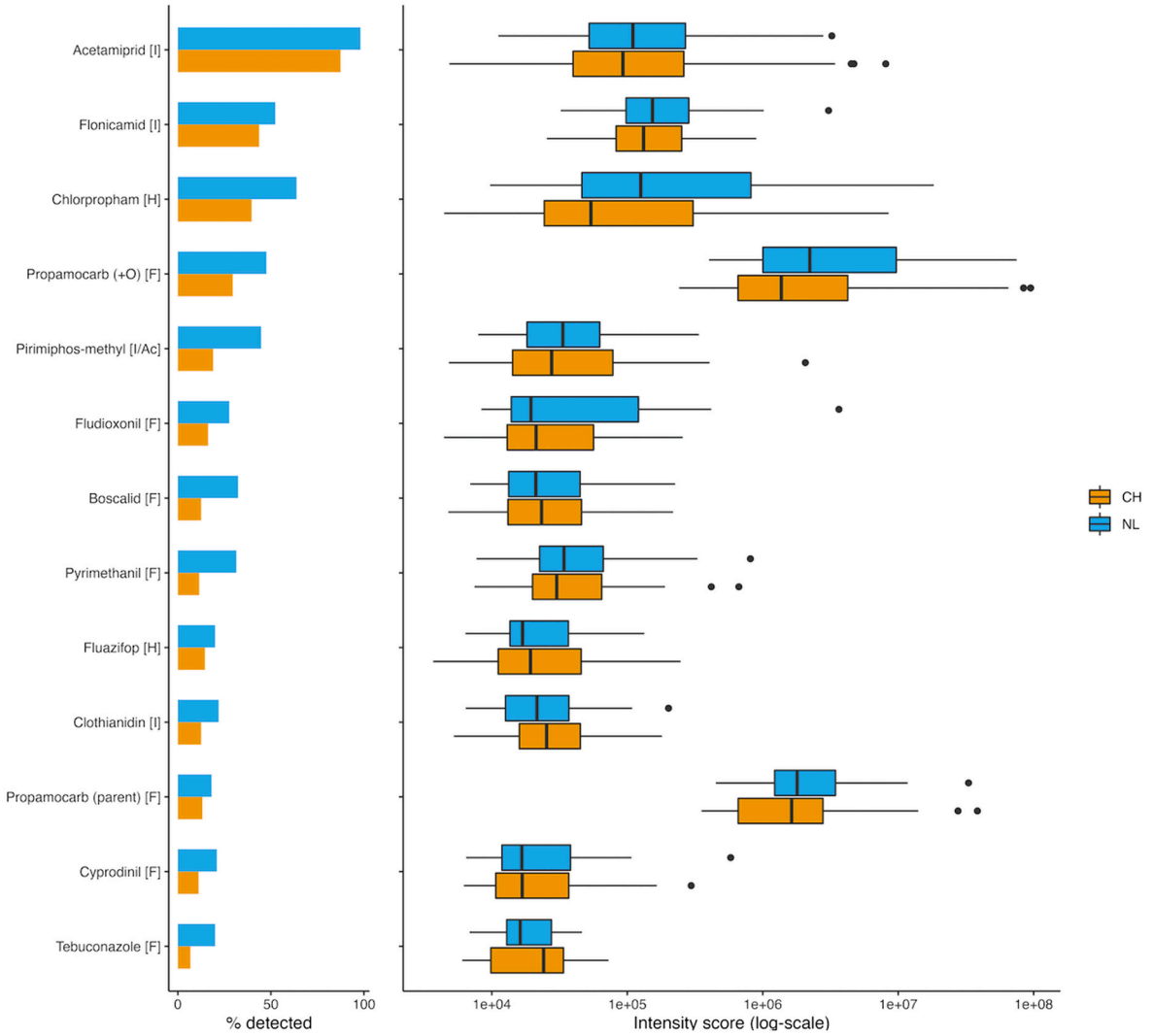

Fig. 1. The distribution of the percentage detected and the intensity scores of the 13 most frequently detected biomarkers for pesticides (noted as parent: F(ungicide), I(nsecticide), H(erbicide), Ac(aricide))**, based on n=105 samples from the Netherlands (NL) and n=295 samples from Switzerland (CH). Note:** Signal intensity scores reported here are semi-quantitative and can therefore not be directly translated into urine concentration levels.

proportional odds model for the categorical (education, income, BMI), and logistic regression for the remaining variables. All regression models were built on the pooled dataset, including an adjustment for country. Additionally, models were constructed for each country separately (see Appendix A, Figures A.3 and A.4). Results of the censored linear and logistic models were shown in forest plots.

To identify whether exposure to the pesticides detected in our study was driven by the consumption of specific food items, we identified food items from the 2020 European Food Consumption Database by the European Food Safety Authority (EFSA) in which the 12 most frequently detected parent pesticides from our study were often detected (European Food Safety Authority et al., 2022). For each compound, the five most frequently contaminated food items from the EFSA database were selected, with contamination frequencies ranging from 2.5% to 75.9%. Food items irrelevant for our study population, i.e. infant formulas and ready-made meals for children, were excluded. A description of these food items and the percentage consumed in the Dutch and Swiss population is provided in Appendix A (Table A.4).

3. Results

3.1. Characteristics of the study samples

An overview of the two study population characteristics is shown in Table 1. A total of 105 (70% female) and 295 (46% female) adults were included from the Dutch (NL) and Swiss (CH) HBM4EU study, respectively. Both the age range as well as the mean age was higher in the Dutch sample (range: 29–56 years, mean: 42 years) as compared to the Swiss participant population (range: 20–39 years, mean: 31 years), reflecting the differences in the target population. With regard to BMI and educational level, the two study populations were similar. Approximately 73% of participants were of normal weight/underweight, and 73% had a university degree. The majority of the Dutch participants had a household income between 50 and 75% of the country average (47%), while the majority of the Swiss participants had an income of 25–50% of the country average (37%). Distance to agricultural areas was similar in both populations, with an average of 976 (NL) and 979 (CH) meters to agricultural areas, but distance to forest areas was higher in Switzerland (NL: average of 271 m; CH: average of 566 m). The distribution of participants based on their distance to both areas is included in Appendix A (Figure A.5).

3.2. Pesticide distribution in the study samples

A total of 37 biomarkers were confirmed with high confidence (Schymanski levels 1 and 2b), relating to 27 different parent pesticides. An additional 44 biomarkers were annotated with lower levels of confidence (Schymanski levels 3, 4, and 5). Due to the higher levels of uncertainty, these biomarkers were not included in the current work. An overview of all 37 confirmed with high confidence biomarkers (including detected metabolites and types of pesticides) is presented in Appendix A (Table A.5). A graphical presentation of the detection rates and the distribution of the signal intensity scores (log-transformed) of the 13 most frequently detected biomarkers (related to 12 parent pesticides) are shown in Fig. 1. Supplementary Figure A.1 (Appendix A) shows the distribution of the intensity scores and the detection rates of all 37 biomarkers. The magnitude of detection rates was comparable in both countries, but detection rates were generally higher in the Dutch population than in the Swiss population, regardless of the between-country differences in the biomarkers' intensity scores. Metabolites of the three pesticides acetamiprid (-CH2, insecticide), flonicamid (-C2HN, insecticide), and chlorpropham (4-HSA, herbicide) had detection rates above 40% in both the Dutch and Swiss study samples. In the Netherlands, also propamocarb (+O, fungicide) and pirimiphos-methyl (-CH2, insecticide/acaricide) were detected in at least 40% of the samples. Biomarkers of an additional eight pesticides, namely fludioxonil (+O + C6H8O6), boscalid (+O + SO3), pyrimethanil (+O + SO3), fluazifop (parent), clothianidin (parent), propamocarb (parent), cyprodinil (+O + SO3), and tebuconazole (-2H +2O), were detected in at least 20 urine samples in each country (total detection ratio of >10%). The intensity scores of each biomarker were comparable for both countries. The highest intensity scores were found for metabolites of propamocarb (+O and parent), yet intensity score differences between biomarkers cannot be directly translated into concentration differences.

Based on the 13 most frequently detected biomarkers, the combinations that co-occurred the most in each country are shown in Fig. 2. Only combinations occurring at least four times (arbitrary cut-off point) are shown, resulting in a co-occurrence pattern based on eight biomarkers and 17 different combinations. In 211 out of 400 samples (52.8%), at least two biomarkers were detected. The most frequent co-occurring pesticide biomarker patterns included different combinations of acetamiprid-flonicamid-chlorpropham, of which the acetamiprid-flonicamid combination occurred in 22 urine samples, or 5.5%. In general, the frequency of co-occurrence for a specific combination of biomarkers was low. In the Netherlands, fewer co-occurrences were detected (relatively), while in Switzerland more co-occurrences were identified, with the most common pair acetamiprid-flonicamid found in 7.1% of the samples (see Appendix A; Figure A.6).

3.3. Temporal variation in pesticide distribution

Since the study design in the Netherlands included two samples per individual from two different seasons, we utilized this opportunity to calculate the ICC based on the intensity scores. The ICC values (considering within-individual and between-season variation) for all 13 biomarkers were low (<0.3), indicating high within-person variability.

The Swiss samples were collected across multiple seasons (ranging from January until October 2020). Seasonal averages of intensity scores (winter, spring and summer) for the Swiss samples showed no temporal differences. Results of the ICC calculations (Table A.6) and Swiss seasonal averages in boxplots (Figure A.2) are displayed in Appendix A.

3.4. Determinants of exposure to acetamiprid, chlorpropham and flonicamid

For acetamiprid, chlorpropham, and flonicamid, censored linear regression (Tobit) models were constructed to explore the potential role of exposure determinants. The covariate mutually adjusted associations of product usage (orange box around the variable names), occupational exposure of household members (blue), homegrown food consumption (yellow), organic diet (yellow), and distance to agricultural areas and forest (green) with the intensity score of the respective metabolite in the pooled study sample are shown in Fig. 3 by forest plots. For the country-stratified analyses, see Appendix A (Figure A.3).

The only discernible association for the pooled data models was a lower urinary intensity score for acetamiprid and chlorpropham when organic vegetables and fruit were frequently (>50%) consumed. For flonicamid, no effect was detected in the pooled data model.

3.5. Determinants of exposure to biomarkers detected in <40% of samples

For the 10 biomarkers detected in between 10% and 40% of the samples, logistic regression models revealed no discernible association (log odds) with any potential determinant across biomarkers and countries. For the pooled dataset, forest plots for each biomarker are

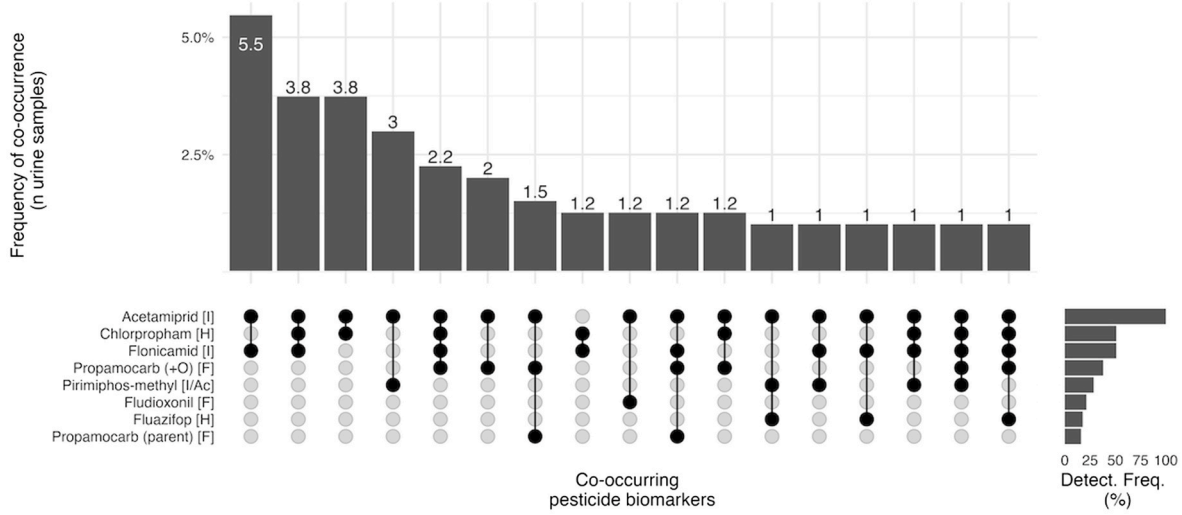

Fig. 2. Frequency of co-occurrences of the 13 most detected pesticide biomarkers in the pooled dataset, (noted as parent: F(ungicide), I(nsecticide), H(erbicide), Ac(aricide)). Only the most frequent combinations (in at least four urine samples) are presented, based on n = 105 samples from NL and n = 295 samples from CH.

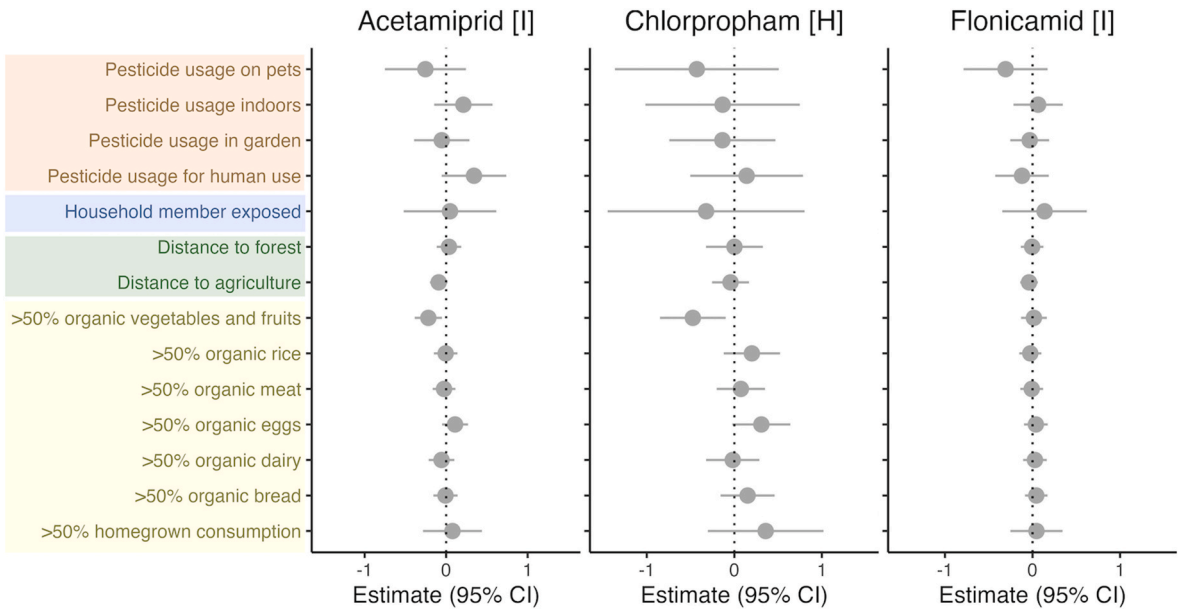

Fig. 3. Association between potential exposure determinants with the intensity scores of acetamiprid, chlorpropham, and flonicamid in urine; results of the Tobit regression models for the pooled dataset. All models were corrected for age, gender, BMI, level of education, income, and country. Factors related to pesticide usage (orange box), household member exposure (blue), distance to agriculture/forest (green), and diet (yellow) are shown. All variables are mutually adjusted.

presented in Fig. 4. Country-specific results of the logistic regression models can be found in Appendix A (Figure A.4). A high organic vegetable and fruit consumption was associated with a lower detection rate in the pooled data models for propamocarb (+O) and pyrimethanil (+O + SO3). For fluazifop, a greater distance to forest areas was associated with an increase in detection rate in the pooled data models. In the pooled data model for pyrimethanil, distance to agricultural areas was positively associated with the detection rate. In general, the log odds of the non-dietary determinants had large confidence intervals, mainly due to low numbers of occurrence in the study population (see Appendix A; Table A.3). In addition, some exposure variables dropped out of the regression models for certain biomarkers due to the same reason of low occurrence (see Appendix, Table A3).

4. Discussion

The present study examines and compares human biomonitoring data on pesticides collected in a sample of the adult population in the Netherlands and in Switzerland as part of the HBM4EU project. Overall, 37 biomarkers (relating to 27 parent pesticides) were detected in 400 urine samples by a suspect screening methodology conducted at the same laboratory. The pesticides present in the urine samples obtained in the two countries were comparable, despite some differences in population characteristics. Detection rates were typically low, co-occurrence of biomarkers not common, and temporal variation at the level of individuals high. Detection rates were highest for acetamiprid, chlorpropham and flonicamid. We observed that consumption of organic fruit and vegetables was an important determinant for exposure to several of the measured pesticide metabolites. In contrast, no clear association of other determinants, such as non-occupational pesticide usage, household member's exposure, distance to agricultural or forest areas, and other dietary habits, with signal intensity and exposure probability was found.

4.1. Detection rates and exposure pathways

Despite the considerable number of detected biomarkers (confirmed by molecular structure, n = 37), only three biomarkers of the parent pesticides acetamiprid, chlorpropham and flonicamid were detected in at least 40% of all samples. In the Dutch data, two additional compounds (pirimiphos-methyl and propamocarb) had a detection rate of ≥40%. These 3 most frequently detected parent pesticides were also part of 8 selected pesticides for targeted analysis by the OBO (Research on exposure of residents to pesticides in the Netherlands) study, based on their usage frequency, monitoring data, analytical possibilities, and possible exposure of the residential population Figueiredo et al. (2021). Two of our frequently detected biomarkers (chlorpropham and flonicamid) have hardly been studied thus far, but our data suggests including these markers in future pesticide exposure studies.

The high detection frequency in the Dutch (98%) and the only slightly lower detection frequency in the Swiss data (87%) indicate ubiquitous exposure to acetamiprid, despite its relatively quick excretion time. The negative association between high organic vegetable and fruit consumption and acetamiprid exposure in our study points to conventionally grown vegetables and fruits as potential determinants of exposure. Acetamiprid is a neonicotinoid (insecticide) and is approved in the EU as well as in Switzerland for professional use on mainly fruit trees and vegetables, as well as for non-occupational use (only certain acetamiprid-containing products). Due to neonicotinoids' systemic mechanism of action, i.e. their ability to enter and persist in plant tissue, residues of neonicotinoids in food cannot be removed by peeling or washing (Magalhaes et al., 2009; Simon-Delso et al., 2015). Hence, for the general population, fruit and vegetable intake is likely to be the main exposure pathway and target to reduce exposure to acetamiprid (Zhang et al., 2018; Zhang and Lu, 2022). Based on the EFSA database, residues of acetamiprid are mainly found in cherries (48%), chili peppers (38%), pomelos (30%), roman rocket (29%), and pears (26%) (see Appendix A; Table A.4). While data on cherries, chili peppers, pomelos, and roman rocket consumption is not available for the Dutch and Swiss study population, leafy greens were consumed by 32% of the Dutch, and 54% of the Swiss participants. Pears were consumed slightly less in Switzerland (NL: 11%, CH: 7%).

Detection rates for chlorpropham, an herbicide and plant growth regulator, were high in both the Dutch (63%) and Swiss (40%) samples, indicating frequent exposure in both populations. Our Tobit regression results for chlorpropham point to dietary exposure as an important

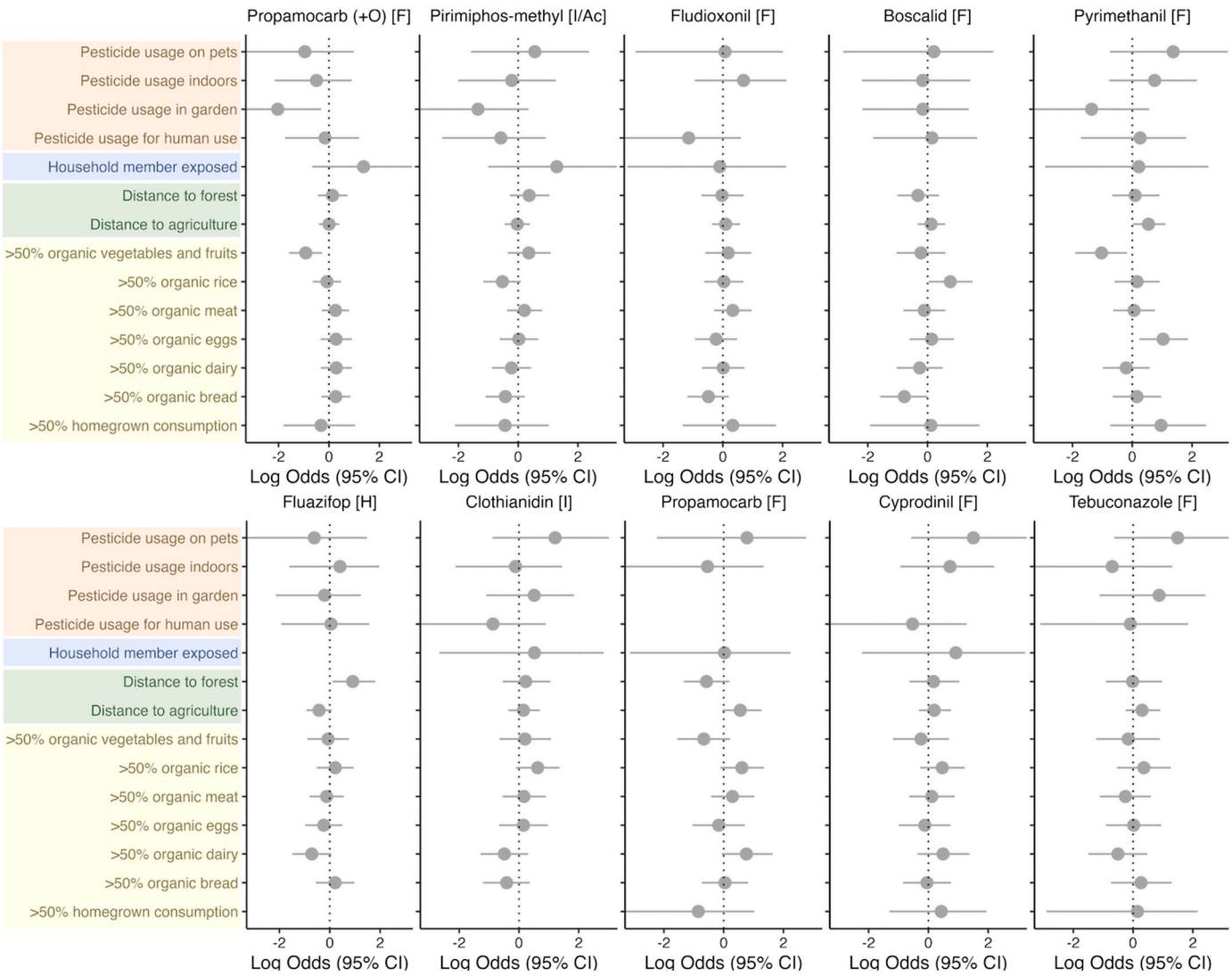

Fig. 4. Association between potential exposure determinants with the urinary presence of biomarkers detected 10–40%; results of the logistic regression models for the pooled dataset. All models were corrected for age, gender, BMI, level of education, income, and country. Factors related to pesticide usage (orange box), household member exposure (blue), distance to agriculture/forest (green), and diet (yellow) are shown. All variables are mutually adjusted. **Note**: Odds for certain exposure variables are missing due to low frequency of participants using pesticides, e.g. in the garden. Hence, variation in the detected biomarkers was too low for the variable to be included in the regression model.

exposure pathway, showing a negative association between organic vegetable and fruit consumption and chlorpropham exposure. The pesticide is mainly used to prevent sprouting of potatoes during storage, and the application is usually done using fogging or spraying equipment (Arena et al., 2017). EU and Swiss approval for chlorpropham was withdrawn in 2019, but periods of grace lasted until autumn 2020 (European Commission, 2019). Hence, exposure through diet in the two study populations was still possible and likely in the year 2020. EFSA data shows that residues of chlorpropham can be found in 15–29% of potatoes (see Appendix A; Table A.4). The relatively high consumption of potatoes in the Netherlands (72 kg/year), as compared to Swiss consumption (47 kg/year), might explain the difference in detection rates (Helgi Library, 2020). Results from the food frequency questionnaires (FFQ) additionally show frequent consumption of potatoes in both the Dutch and Swiss study population (see Appendix A; Table A.4), with 38.1% of Dutch and 28.7% of Swiss participants stating they consumed potatoes within 24 h before urine collection.

The insecticide flonicamid is authorized for occupational use in both countries and is mainly applied on fruit, vegetables, wheat, and potatoes. Detection rates in the Netherlands were slightly higher (52%) than in Switzerland (43%), and point towards a frequent exposure to flonicamid in both populations. The regression model for flonicamid exposure in the Netherlands indicates that having a household member who is occupationally exposed to pesticides (self-assessment by the participant) is associated with higher exposure. The occupational exposure to flonicamid specifically in orchards was confirmed in another study as well (Zhao et al., 2015). Preferential consumption of organic bread was also associated with lower exposure to flonicamid in the Dutch model. In the Dutch study population, bread was consumed by 83.8% participants within 24 h before urine collection, as compared to 49% in the Swiss population. The top-5 flonicamid-contaminated food items in the EFSA database, however, do not include bread or other wheat products (see Appendix A; Table A.4). Instead, residues of flonicamid were mainly found in cucumbers, sweet peppers, peas, peaches, and brussel sprouts. In the Dutch study, data on the consumption of sweet peppers (30%) and peas (12%) is available, but the Swiss FFQ did not inquire about these food items.

The logistic models for propamocarb (+O), pirimiphos-methyl, fludioxonil, fluazifop, clothianidin, propamocarb (parent), boscalid, cyprodinil, pyrimethanil, and tebuconazole revealed no consistent

direction of association between the determinants and exposure probability across biomarkers and countries. However, a high consumption of organic vegetables and fruit was associated with lower exposure probability for propamocarb (+O) and pyrimethanil. Based on the EFSA database, residues of propamocarb are found in about 24% of lettuces, and pyrimethanil is found in about 35–45% of citrus fruit (see Appendix A; Table A.4). Data on the consumption of lettuces and various citrus fruits within 24 h before urine collection is not available for the Dutch and Swiss study population.

Our findings add evidence to previous studies indicating that food choices have an influence on pesticide exposure in the general population (Fortes et al., 2013; Ye et al., 2015; Rempelos et al., 2022). Especially for vegetable and fruit consumption, prior research consistently shows negative correlations between organic food consumption and urinary pesticide concentrations (Baudry et al., 2019, 2021; Hyland et al., 2019). In our study, a high consumption of organic fruits and vegetables was related to a lower exposure to four biomarkers. However, for the other food groups, the direction of association varied, with high levels of uncertainty. Although not assessed in this study, consumption of imported foods might explain rather small differences in detection frequencies for compounds which are applied in much larger quantities in the Netherlands (see Appendix A; Table A.4) as compared to Switzerland, such as chlorpropham (NL: 39t, CH: 0.06t).

4.2. Within-individual variability and mixture exposure patterns

For all biomarkers, correlation between winter and summer season samples of the same individual in the Dutch population was low ($\leq$0.3). This indicates a high within-individual variability of exposure and pesticide levels in urine. Potentially important sources of within-individual variability are changes in lifestyle, including dietary habits, and environmental influences. Longer-term exposure profiles are not well captured in the light of quick metabolization of most pesticides and short biological half-lives (Egeghy et al., 2011). This is in line with previous research on pesticide exposure levels over time, showing high within-individual variability of pesticide levels in urine (Morgan et al., 2016; Li et al., 2019). High within-individual variability was also detected in occupationally highly exposed groups, which can lead to challenges in capturing exposure windows (Fuhrimann et al., 2020). Similarly, a previous study analyzing the Dutch SPECIMEn and HBM4EU data of four other countries found no consistent effect of season on detection frequencies (Ottenbros et al., 2023). Considering also the absence of seasonal differences in average exposure in Switzerland, day-to-day variations of lifestyle and environmental exposures may be more important drivers of exposure than seasonal variations.

Based on the exploration of co-occurrence of biomarkers within the same sample, the most frequent combination (acetamiprid with flonicamid) was only detected in 5.5% (n = 22) of the samples. The 17 most frequent combinations (found in at least four urine samples) were based on different variations of eight biomarkers, which also reflect the most frequently detected biomarkers in the studies. This points towards individualized and variable pesticide mixture exposure profiles among the general population, as found in previous HBM studies (Aerts et al., 2018; Ottenbros et al., 2023). This is also in agreement with the observed high within-person variability of exposure in our study. The fewer co-occurrence patterns in the Netherlands likely can be explained by the overall smaller number of biomarkers detected in comparison to Switzerland.

4.3. Strengths and limitations

The harmonized data collection with questionnaires filled in at the time of urine sampling and standardized urine sample analysis at the same laboratory within the HBM4EU project allowed for the joint analysis of the two datasets. The comparison of pesticide mixtures and exposure pathways in adult populations across the Netherlands and Switzerland was additionally justified by similar pesticide regulations in both countries. The employment of an innovative SS methodology offered the opportunity to semi-quantitatively measure exposure to a large number of compounds and pesticide mixtures previously rarely examined within a single study. The results of this SS approach can also assist in setting priorities for future targeted analyses.

Despite the informative insights gained from our study, a few limitations have to be addressed. Regarding sample collection, it should be noted that many pesticides are metabolized and excreted quickly. Hence, the distribution of individual long-term exposures will not adequately be captured by the collection of one first morning void urine sample. Longitudinal and repeated study designs (or longer sampling times, such as 24h voids) will be necessary to adequately monitor temporal variations and estimate temporally integrated pesticide exposure in the general population. We should also point out that part of the urine samples from Switzerland and all samples from the summer season in the Netherlands were collected during the COVID-19 pandemic. This might have affected diet, daily activities, and habits (Bertrand et al., 2021).

Second, a myriad of labels for organic and biological foods exist within the EU and in Switzerland. Thus, it might not have been straightforward for participants to declare how much of their usual food intake is produced organically and participants' might have based their answers on different labels. Additionally, the employed FFQs did not query the consumption of specific food items frequently contaminated with pesticide residues, as reported by the EFSA database. Hence, we did not include single food items in the regression models, which could have diminished the ability to detect any effect. Future studies may profit from a more detailed FFQ that is better aligned with pesticide exposure databases. Additionally, there might be country-specific differences in the proportion of consumption of imported foods, which was not assessed in this study.

Third, we did not observe any effect of distance to agricultural or forest areas on the exposure estimates. Although it must be noted that definitions for agricultural and forest areas were different in the two geospatial datasets for the two study countries (see Table A1), with the Dutch definitions being more precise. In addition, in contrast to the Swiss sample, the Dutch study design focused specifically on distance to orchards.

Lastly, although the SS approach is a useful analytical methodology to explore exposure to large numbers of pesticides, targeted methods have a higher specificity and sensitivity (Pourchet et al., 2020). Moreover, due to time and budget reasons, experts reviewed and prioritized the tentative annotations before starting the compound confirmation workflow, resulting in a suspect screening analysis biased toward halogenated and PO3-containing pesticides (Huber et al., 2022). The list of 37 identified biomarkers is additionally limited by technical possibilities and conventions. Therefore, technological advances might increase the number of identified biomarkers in the future. This might be one of the reasons why the three most commonly detected pesticides might not reflect the most commonly used pesticides in the Netherlands and Switzerland.

For the most commonly detected pesticides, targeted methods will need to be applied for a more precise estimation of determinants. In addition, future studies should carry out improvements regarding the compilation of the list of tentative annotations.

Nonetheless, taking these limitations into account, the results of this multi-country study contribute to the growing field of HBM of pesticides and offer first insights into pesticide mixture patterns and exposure sources and pathways in two countries in the European context. Future studies with a more detailed dietary and behavioral assessment, as well as targeted quantitative, ideally multi-biomarker, screenings of several HBM samples will be able to draw on these results for a more complete assessment of the general population's exposure to pesticides and determinants thereof.

5. Conclusion

Using a semi-quantitative suspect screening approach, 37 well-annotated pesticide metabolites (relating to 27 parent pesticides) were present in urine collected from participants of the adult population in the Netherlands and Switzerland. Detection rates were typically low, yet three pesticides (acetamiprid, chlorpropham, flonicamid) were detected in at least 40% of the samples at both study sites. High consumption of organic fruits and vegetables was associated with decreased urinary levels for acetamiprid, chlorpropham, propamocarb and pyrimethanil. The suspect screening applied in this study provides an example of how a first-tier screening exercise for pesticide exposure can be conducted. Our study provides an indication for target biomarkers to include in follow-up studies dedicated to the quantification of urinary exposure levels. Also, it highlights the importance of repeated sampling in light of substantial within-individual variability, as well as food contamination reduction as a preventive target to lower pesticide exposures.

Credit author contribution statement

JV, NPH, SF, RV - Conceptualization; **HM, RN, AL** - Data curation; **IO, PA** - Formal analysis; **NPH, RV, EL, JV** - Funding acquisition; **IO, MI, JPZ** - Investigation; **IO, PA, JV, NPH, SF** - Methodology; **JV, NPH** - Project administration; **IO, PA** - Visualization; **IO, PA** - Writing - original draft; **All Authors** - Writing - review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

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