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Current-use pesticide exposure pathways in Czech adults and children from the CELSPAC-SPECIMEn cohort

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ABSTRACT

Introduction: In this study, we aimed to characterise exposure to pyrethroids, organophosphates, and tebuconazole through multiple pathways in 110 parent–child pairs participating in the CELSPAC–SPECIMEn study.
Methods: First, we estimated the daily intake (EDI) of pesticides based on measured urinary metabolites. Second, we compared EDI with estimated pesticide intake from food. We used multiple linear regression to identify the main predictors of urinary pesticide concentrations. We also assessed the relationship between urinary pesticide concentrations and organic and non-organic food consumption while controlling for a range of factors. Finally, we employed a model to estimate inhalation and dermal exposure due to spray drift and volatilization after assuming pesticide application in crop fields.
Results: EDI was often higher in children in comparison to adults, especially in the winter season. A comparison of food intake estimates and EDI suggested diet as a critical pathway of tebuconazole exposure, less so in the case of organophosphates. Regression models showed that consumption per g of peaches/apricots was associated with an increase of 0.37% CI [0.23% to 0.51%] in urinary tebuconazole metabolite concentrations. Consumption of white bread was associated with an increase of 0.21% CI [0.08% to 0.35%], and consumption of organic strawberries was inversely associated (-61.52% CI [-79.34% to -28.32%]), with urinary pyrethroid metabolite concentrations. Inhalation and dermal exposure seemed to represent a relatively small contribution to pesticide exposure as compared to dietary intake.
Conclusion: In our study population, findings indicate diet plays a significant role in exposure to the analysed pesticides. We found an influence of potential exposure due to spray drift and volatilization among the subpopulation residing near presumably sprayed crop fields to be minimal in comparison. However, the lack of data indicating actual spraying occurred during the critical 24-hour period prior to urine sample collection could be a significant contributing factor.

1. Introduction

Agrochemicals known as pesticides are used as a measure to protect crops from pests such as insects, weeds, infections, and various types of vermin. The worldwide tonnage of applied pesticides amounted to 4.12 million tonnes in the year 2018 (FAO, 2021). In the Czech Republic, the total amount of active substances applied on agricultural land has been decreasing over the last 10 years (CISTA, 2022, SI Fig. 1). Nonetheless, current-use pesticides (hereinafter "pesticides") are poisonous substances by design with a wide or narrow array of target organisms, depending on the specific pesticide. Although, in general, the human population is not exposed to high doses of pesticides, adverse effects of pesticides on human health have been previously reported. For example, pesticide exposure has been associated with behavioural changes in children (Oulhote and Bouchard, 2013), negative effects on the immune system (Costa et al., 2013; El Okda et al., 2017), neurological symptoms (Rastogi et al., 2010), Parkinson's disease (Shrestha et al., 2020), metabolic disorders (He et al., 2020), and respiratory conditions such as asthma, wheezing, or airway irritation (Ye et al., 2013). A few studies have also revealed a possible link between pesticide exposure and cancer

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development (Bonner et al., 2017; Koutros et al., 2016).

Pesticides enter the environment primarily when applied to crop fields. Subsequently, drift, volatilization, and erosion from surfaces can transport pesticides beyond the boundaries of the original application site (Rice et al., 2007). There, pesticides may undergo degradation due to microbial activity (Gangola et al., 2022) or physical–chemical processes like photolysis and hydrolysis (Fenner et al., 2013). However, transported pesticides may also be deposited in dust (Smith et al., 2017), water, and soil (Aznar et al., 2017), or inhaled and absorbed through the skin (Shi and Zhao, 2014). Furthermore, residues of pesticides may be found on crops to which the pesticides were originally applied. The consumption of such crops may then lead to dietary exposure (Rempelos et al., 2022) and such exposure may also occur due to contaminated drinking water (El-Nahhal and El-Nahhal, 2021). Some other possible pathways of pesticide exposure include the ingestion of contaminated household dust (Béranger et al., 2019), contact with fabric or textile contaminated with pesticides (Saillenfait et al., 2015), contact with pets (English et al., 2019), and the household application of pesticides and repellents (Roy et al., 2017). These are the possible pathways of pesticide exposure in the general population. In addition, there is also the possibility of occupational exposure. Workers in the agricultural and agrochemical industries are exposed to higher concentrations of pesticides in comparison to the general population (Figueiredo et al., 2022a). This results from the handling, and application of pesticides (Dereumeaux et al., 2020; Mamane et al., 2015).

Currently in the European Union, only selected active substances can be applied on crops with organic farming certificates. These active substances are often of natural origin and pose a low potential risk (EC, 2021). Thus, consumption of certified organic produce may be one of the ways to limit one's own pesticide exposure. This was observed in past studies, where the consumption of organic produce was associated with lower urinary pesticide concentrations, often organophosphates and pyrethroids (Baudry et al., 2019; Hyland et al., 2019; Oates et al., 2014); although these observations have been not entirely consistent (Aerts et al., 2018; Glorennec et al., 2017).

In this study, we analysed questionnaire data, modelled environmental exposure as well as measured urinary pesticide concentrations: the aims of this study were i) to estimate total intake of pesticides; ii) to estimate dietary intake of pesticides; iii) to identify specific food items associated with urinary pesticide biomarkers, and iv) to estimate inhalation and dermal exposure to pesticides associated with spray drift and volatilization from crop fields.

2. Materials and Methods

2.1. Study design and questionnaire data

The SPECIMEn study (Survey on PEstiCIde Mixtures in Europe) was carried out in the Netherlands, the Czech Republic, Spain, Latvia, and Hungary in 2019/2020 within the HBM4EU project (The European Human Biomonitoring Initiative[1]). The main aim of the SPECIMEn study was to assess exposure to mixtures of pesticides in adults and children across Europe. Details on the SPECIMEn study have been stated elsewhere (Vlaanderen et al., 2019); our study considers only the Czech cohort of the SPECIMEn study: CELSPAC-SPECIMEn (Central European Longitudinal Studies of Parents and Children[2]).

The CELSPAC-SPECIMEn study received ethical approval under ref. no. ELSPAC/EK/3/2019. In brief, the CELSPAC-SPECIMEn study comprises parent–child pairs (110 adults and 110 children, n = 220). These adult-child pairs had direct kinship (mother/father, daughter/son) and shared one household. Farmers were excluded from participant selection to avoid bias due to occupational exposure. All participants collected samples of first-morning urine and filled in questionnaires at the beginning of 2020 (January-March, hereinafter the "winter season") and again in mid-2020 (May-July, hereinafter the "summer season"). Urine samples were analysed for 12 biomarkers of pesticide exposure (SI Table 1) using high-performance liquid chromatography in tandem with mass spectrometer-mass spectrometer. The selection of pesticide biomarkers was based on the recommendation of HBM4EU (Prioritised substance group: Pesticides) (Ougier et al., 2021), the annual reports of Plant Protection Products in the Czech Republic (CISTA, 2022), and also on the European Food Safety Authority (EFSA) report (EFSA, 2021). Only the testing of 3-phenoxybenzoic acid (3-PBA), trans/*cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopro-pane carboxylic acid (t/c-DCCA), 3,5,6-trichloro-2-pyridinol (TCPY), and hydroxy-1-tebuconazole (TEB-OH) yielded a sufficient number of measurements (>40 %) above the limit of quantification (LOQ). Values under the LOQ were imputed using maximum likelihood multiple estimation dependent on observed values with expected lognormal distribution (Lubin et al., 2004). The imputation was done only for compounds detected in at least 40 % of all the samples. More details on the CELSPAC-SPECIMEn cohort and sample collection were provided by Šulc et al., 2022.

The questionnaires were filled in by participants (parents filled in questionnaires for their children) the day before urine sample collection or on the day of urine sample collection, but the information in the dietary part of the questionnaire was always relevant to the last 24 h before urine sample collection. The lifestyle part of the questionnaire inquired about the participant's age, weight, height, educational level, occupation, income, housing conditions, physical activity, pets, domestic pesticide use, smoking habit, and time spent at various places three days before urine sample collection. A summary of the selected variables characterising the study cohort was provided in SI Table 2. The dietary part of the questionnaire inquired about the origin of consumed fruits and vegetables, the frequency of organic food consumption in the past six months, and the percentage of consumed organic food, and diet composition in the 24 h before urine sample collection. The diet composition category of the questionnaire was provided with an option to note the weight of consumed food and mark consumed food as organic or home-grown. Missing information on consumed food weight was filled in on the basis of the EFSA food consumption survey data from the Czech Republic (EFSA, 2018). Food items not marked as organic or home-grown were treated as non-organic. Unanswered closed questions were considered as answered negatively (no, not eaten, no smoker, etc.) in both the lifestyle and dietary parts of the questionnaire. The administered questionnaire was provided by Vlaanderen et al. (2019).

2.2. Data analysis

We estimated pesticide intake by applying three models (Fig. 1, SI Table 3). First, we estimated pesticide intake based on urinary pesticide metabolite concentrations. Second, we estimated pesticide intake based on the consumption of food items with previously determined pesticide residues (EFSA, 2022). We also investigated associations between food consumption and urinary pesticide concentrations and quantified explained variance in urinary pesticide concentrations. And third, we estimated pesticide intake due to inhalation and dermal exposure to ambient air pesticide concentrations. The R programming language v4.2.1 (R Core Team, 2022) was used for statistical analysis and ambient air pesticide concentration modelling.

2.3. Estimated daily intake of pesticides

First, we utilized reverse dosimetry (1) using urinary pesticide metabolites to calculate the Estimated Daily Intake (EDI) of selected pesticides. The EDI was based on model previously used by Šulc et al., 2022:

$$EDI = \frac{c_{metabolite} \times CE \times M_{parent}/M_{metabolite}}{bw \times F_{UE}} \quad (1)$$

[1] HBM4EU.eu

[2] recetox.muni.cz/hear/projects/specimen

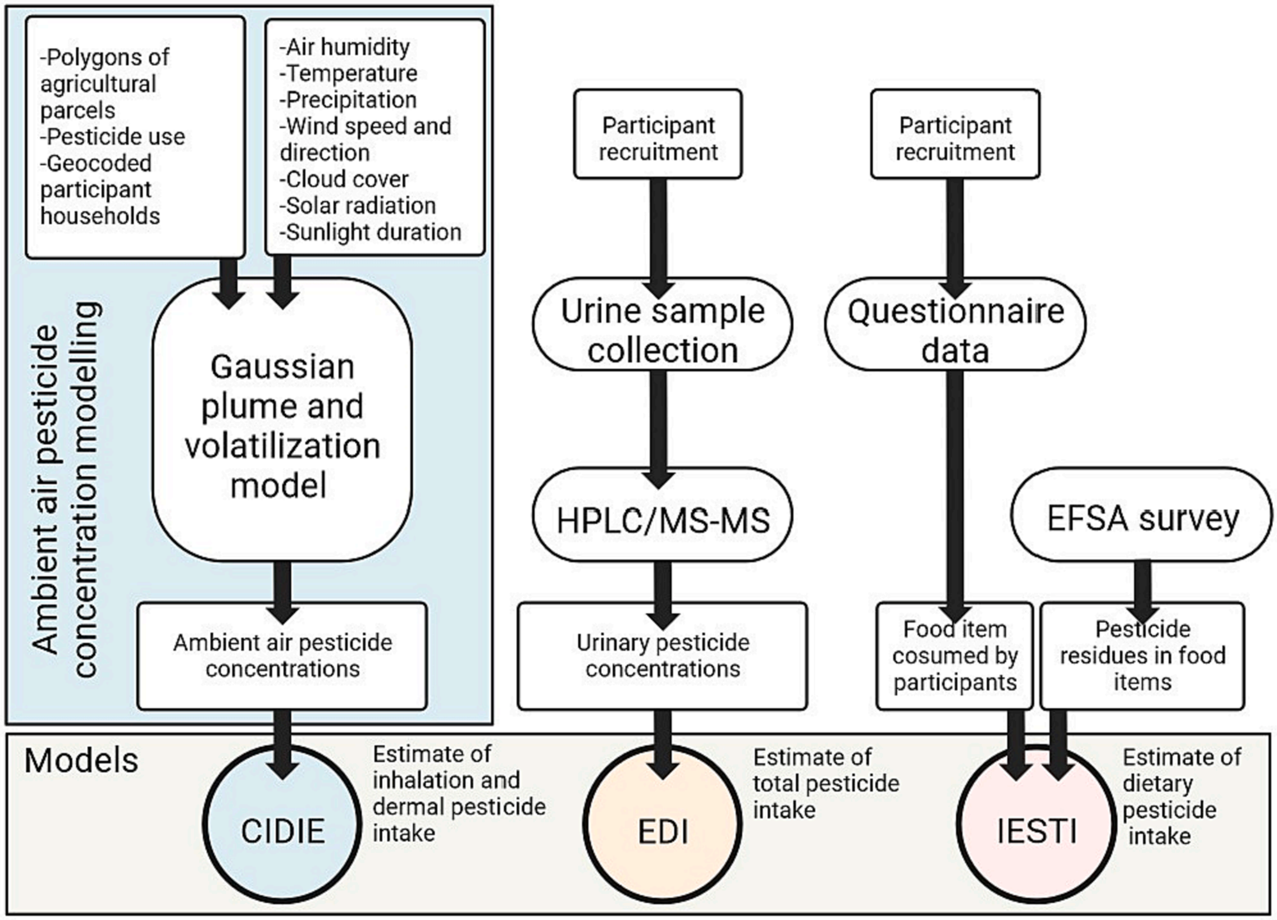

Fig. 1. Diagram of used models and major steps needed to estimate pesticide exposure via each model.

where $c_{metabolite}$ (μg/g creatinine) is the concentration of the specific pesticide metabolite in urine, *CE* (g creatinine/day) is the anthropometry and gender-based reference value for creatinine excretion in urine-derived for children (Remer et al., 2002) and adults (Forni Ogna et al., 2015), M_{parent} and $M_{metabolite}$ are the molar mass of the parent pesticide and metabolite, respectively, *bw* (kg) is the body weight, and F_{UE} is the ratio between the intake of parent pesticide and the amount of metabolite excreted in the urine. In the case of pyrethroid metabolites, cypermethrin and lambda-cyhalothrin were selected as parent compounds. By weight, cypermethrin was the most applied pyrethroid pesticide in the Czech Republic in 2020 (CISTA, 2022), while residues of mostly lambda-cyhalothrin were found in samples of food in the Czech Republic in 2020 (EFSA, 2022). Cypermethrin can be metabolized into 3-PBA and t/c-DCCA; for this reason, mean F_{UE} values of 0.2 and 0.47, respectively, were used (Ratelle et al., 2015; Woollen et al., 1992). Lambda-cyhalothrin is metabolized only into 3-PBA; thus, a F_{UE} value of 0.3 was used (Khemiri et al., 2017). Values of F_{UE} used for TCPY and TEB-OH were 0.7 and 0.38, respectively (Nolan et al., 1984; Oerlemans et al., 2019). To illustrate the worst-case scenario (i.e., the maximum intake of pesticide), when only 5 % of the parent pesticide is excreted in urine as a metabolite, a F_{UE} value of 0.05 was used in EDI for each parental pesticide (Bravo et al., 2020, 2019). We created an intake estimate interval for each participant with an estimate of the central tendency and an estimate of the worst-case scenario (maximum intake).

2.4. Estimated dietary intake

Second, the International Estimate of Short-Term Intake (IESTI) for each pesticide was calculated (2) on the basis of the consumption of food items with previously found residues of pyrethroids, organophosphates, and tebuconazole in the Czech Republic in 2020:

$$IESTI = \sum \frac{P \times (R_{mean}\ or\ R_{max})}{bw} \tag{2}$$

Where *P* (g) is the portion of consumed food in the last 24 h before urine sample collection, and *R* (ng/g) is the mean or maximum residue of pesticide measured in the respective consumed food item (EFSA, 2015), and *bw* (kg) is a body weight. Pesticide residues were extracted from Czech data concerning the monitoring of pesticide residues in commodities (EFSA, 2022). Both mean and maximum values of pesticide residues in food items were used to calculate the interval of IESTI for each pesticide. Mean pesticide residues in food items were estimated by first imputing values below the LOQ according to the maximum-likelihood estimation giving values above the LOQ. Subsequently, the mean pesticide residues in food items were calculated for each food item. Minimum values of pesticide residues in food items were not used in the IESTI calculation. This was because minimum values tend to approach 0 and, as such, are always below the LOQ. IESTI mean to maximum interval was subsequently compared to the EDI central tendency to maximum interval.

2.5. Linear mixed-effect models

Linear mixed-effect (LME) models (Peng and Lu, 2012) were utilized to identify associations between the concentrations of log-transformed urinary pesticide metabolites (3-PBA, t/c-DCCA, TCPY, TEB-OH) and the consumption of food items included in the models as fixed effects. LMEs were also used to assess the impact of the consumption of organic and non-organic foods on the concentration of the same urinary pesticide metabolites. Organic food consumption was included in the LME as an interaction between the weight of consumed food and the type of food item variant (non-organic, organic) was added as a dichotomous variable. Models were adjusted for age, sex, BMI, season, having own garden, crop field area in a 500 m buffer, and self-reported pesticide use. House ID and participant ID served as random effects. To limit the number of false positive results, we used the p-value correction method according to Benjamini and Hochberg, 1995.

LME were also employed to quantify explained variance of urinary pesticide metabolite concentrations by the consumption of food items and ambient air exposure. The explained variance was expressed in terms of marginal and conditional coefficients of determination (R^2). The selection of consumed food items (variables) was based on the presence of pesticide residues found in food items sampled in the Czech Republic in 2020 (EFSA, 2022) and also on the application of parental pesticides in the Czech Republic in 2020 (CISTA, 2022). Ambient air pesticide exposure was included in the LME as modelled pesticide concentrations. This was replaced by a crop field area in a 500 m buffer (a proxy to pesticide drift and volatilization and strongly correlating to modelled pesticide concentrations, SI Table 4) in a separate model. Models were adjusted for common confounders (age, sex, BMI) and for other characteristics likely related to pesticide exposure, such as season, having own garden, and self-reported pesticide use. House ID and participant ID were used as nested random effects in the LME. In the models with modelled pesticide concentrations, only data relevant to the summer season were considered (i.e., the season was omitted as an adjusting variable), since ambient air pesticide modelling was done only for the summer season, adding house ID as random effects to the model.

2.6. Inhalation and dermal intake of pesticides

Pesticide concentrations in ambient air associated with the boom spraying of crop fields were modelled as a first step to estimate inhalation and dermal intake. We used a simplified deterministic modelling approach derived from the OBO modelling framework project (Figueiredo et al., 2022b) to model the drift, volatilization, and dispersion of sprayed pesticides.

The participants' household addresses were geocoded. Polygons of crop fields around participants' households were gathered from the Land Parcel Identification System[3] of the Czech Republic. Each crop field contains information on crop field shape, area, location, and general crop field use (e.g., field, orchard, meadow, forest). The used crop fields were relevant to March 2020 and only crop fields with potential pesticide use were considered (fields, orchards, and vineyards). Each crop field was attributed with estimate of pesticide use. These estimates were derived from total pesticide use in an individual districts of the Czech Republic in 2020 supplied by The Czech Hydrometeorological Institute.[4] Total pesticide use (kg) in each district was equally disaggregated and attributed to each crop field in each respective district based on crop field area and general use type (fields, orchards, and vineyards). The uses of alfa-cypermethrin, beta-cyfluthrin, cypermethrin, zeta-cypermethrin, chlorpyrifos, chlorpyrifos-methyl, and tebuconazole were attributed to crop fields where can be expected use of such pesticides based on above mentioned criteria. These pesticides were parental compounds 3-PBA and t/c-DCCA (alfa-cypermethrin, beta-cyfluthrin, cypermethrin, zeta-cypermethrin), TCPY (chlorpyrifos, chlorpyrifos-methyl), and TEB-OH (tebuconazole) and were actively used in the Czech Republic in 2020 (CISTA, 2022). We assumed that spraying in the crop fields occurred around participants' households during the daytime on the day before urine sample collection if favourable meteorological conditions for pesticide application were present. If not present, we assumed no pesticide application the day before urine sample collection. These conditions included wind speed $<$ 5 m/s, temperature $\leq$ 25 °C, no precipitation, and humidity $>$ 60 % (CISTA, 2007). Buffer with radii of 250 m, 500 m, and 750 m was created around participants' households to associate crop fields attributed with pesticide use information with each household (SI Fig. 6).

Spray drift from boom sprayers (D. K. Giles et al., 2008) was modelled according to a Gaussian plume model using an average droplet size of 150 μm (Lebeau et al., 2011). Volatilization was modelled according to the PEARL model, without taking competing processes in the volatilization model (i.e. the conservative scenario) into account (van den Berg et al., 2016). Finally, dispersion was calculated based on the mathematical formulations from the OPS-St model (short range transport model) (Sauter et al., 2020). Crop field position, distance, area, pesticide use as well as meteorological conditions at the time of assumed spraying (the day before urine sample collection) served as inputs into these models. Meteorological conditions included wind speed and direction, air humidity, temperature, precipitation, cloud cover, duration of sunlight, and level of solar radiation. Used meteorological data were specific to the location of participants' households one day before urine sample collection and were supplied by meteoble AG.[5] Ambient air pesticide concentrations were modelled in variants considering crop fields in radii of 250 m, 500 m, and 750 m around participants households as a form of sensitivity analysis. The modelling of environmental pesticide concentrations was carried out solely for the summer season of 2020 since lesser spraying activity can be expected in the winter season. The final output, environmental pesticide concentrations, further served as input for the calculation of estimates of inhalation and dermal exposure.

Finally, we calculated the Cumulative Inhalation and Dermal Intake Estimate (CIDIE) which was based on equation (3) derived from Shi and Zhao, 2014:

$$CIDIE = \frac{(C_i \times IR \times ED_i + C_o \times IR \times ED_o) + (C_i \times SA \times f_{SA} \times ED_i + C_o \times SA \times f_{SA} \times ED_o)}{24 \times bw} \quad (3)$$

where C_i (ng/m^3) is the pesticide concentration indoors, C_o (ng/m^3) is the pesticide concentration outdoors, IR (m^3/day) is the long-term inhalation rate, ED_i (h/day) is the indoor exposure duration, ED_o (h/day) is the outdoor exposure duration, SA (m^2) is skin surface area, f_{SA} is the fraction of exposed skin, and bw (kg) is body weight. Output concentrations from drift, volatilization, and dispersion model were used as C_o. To account for the difference between outdoor and indoor concentrations, the ratio of outdoor to indoor pesticide concentrations was taken to be 1:1.16, as this was observed in a previous study on pesticides (Figueiredo et al., 2021). Long-term IR for children was 11.05 and for adults, 15.9 (US EPA, 2011). Information on ED_i and ED_o was acquired from questionnaires. To calculate SA, we used the formula proposed by Wang and Hihara, 2004, and f_{SA} was set to 1 (Shi and Zhao, 2014).

[3] eagri.cz
[4] chmi.cz
[5] meteoblue.com

3. Results

3.1. Estimated daily intake

Comparison of EDI between children and adults showed statistically significant differences between the two age groups. EDI was generally higher in children in comparison to adults in both seasons. Only tebuconazole EDI was not statistically different between age groups in the winter and summer seasons. Also, there was no difference between the EDI of chlorpyrifos but only in the winter season. Cypermethrin (based on urinary t/c-DCCA) and chlorpyrifos were significantly higher in the winter season in comparison to the summer season in adults. In children, all pyrethroids and chlorpyrifos were higher in the winter season in comparison to the summer season. The median intake of cypermethrin based on urinary t/c-DCCA in children was the highest (242.79 ng/kg-bw/day) among all analysed pesticides. On the other hand, the lowest median intake was that of chlorpyrifos (8.31 ng/kg-bw/day) in the summer season and in adults. Complete results are included in SI Table 5 and 6.

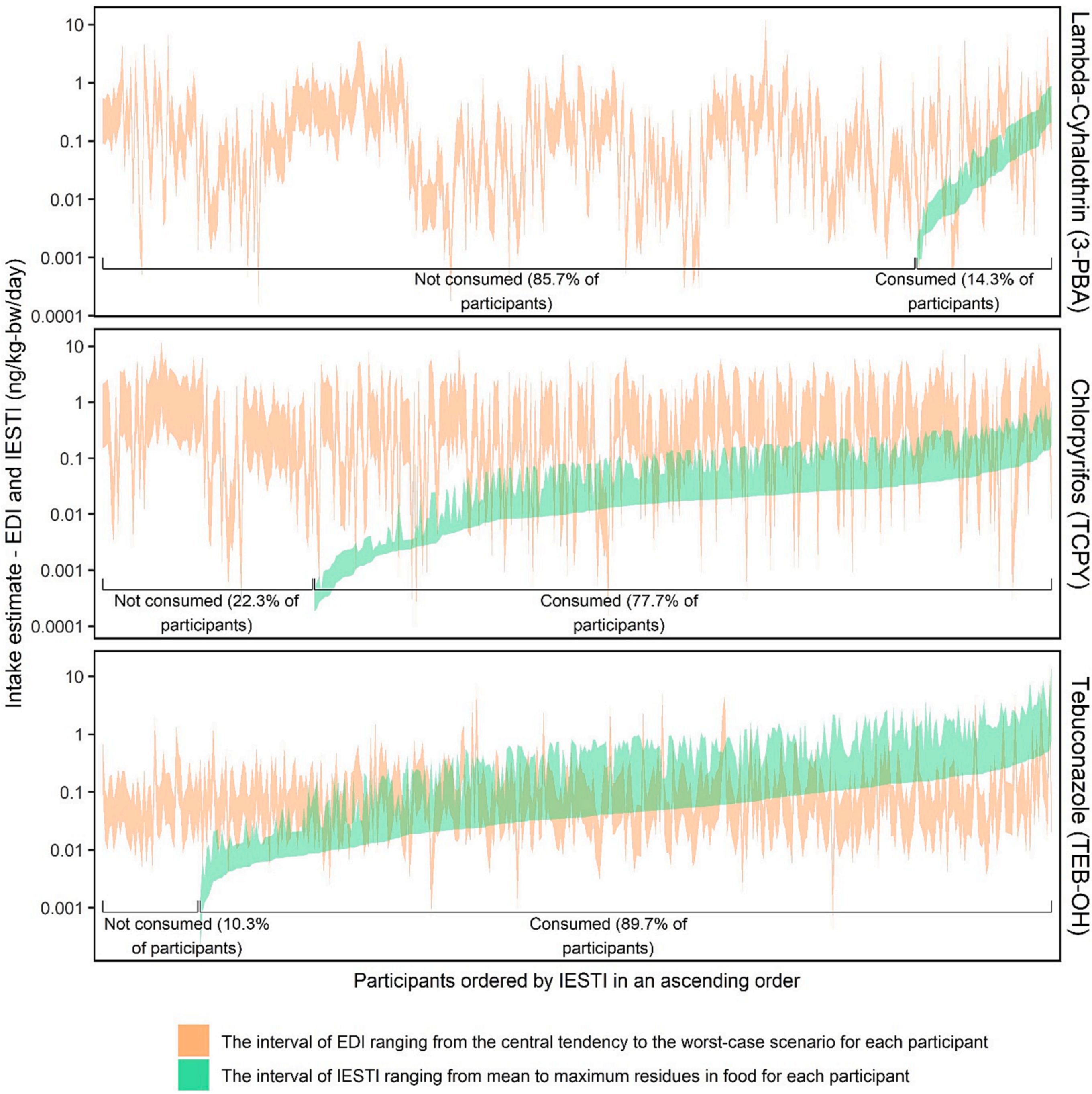

Fig. 2. Graphical comparison of overlap between overall intake of pesticides (EDI, orange area) and pesticide intake from food (IESTI interval, green area) for each participant and parental pesticide (Not consumed = participants who did not consume any food item with the respective pesticide residue, Consumed = participants who consumed at least one food item with the respective pesticide food residue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Percentage of EDI explained by IESTI for pyrethroids, organophosphates, and tebuconazole.

Pesticide (metabolite)	Share of participants with calculated IESTI	% of EDI interval explained by IESTI interval				
		5th percentile	25th percentile	50th percentile	75th percentile	95th percentile
Lambda-Cyhalothrin (3-PBA)	14.3 %	0 %	0 %	40.6 %	115.3 %	596 %
Chlorpyrifos (TCPY)	77.7 %	0 %	0 %	0.1 %	19.4 %	559.6 %
Tebuconazole (TEB-OH)	89.7 %	0 %	47.2 %	277.9 %	750.2 %	2738.7 %

3.2. Pesticide food intake estimates

The IESTI was then compared to the EDI of parent pesticides shown in Fig. 2 and as a percentage of the total intake (EDI) covered by food intake (IESTI) in Table 1. Only parental pesticides matching measured urinary pesticide metabolites were considered (SI Table 7). For pyrethroids (lambda-cyhalothrin), only 14.3 % of participants consumed food items that, in the 2020 EFSA survey, were found to contain residues of these pesticides. Substantially more participants reported the consumption of food items which were found by the same survey to contain residues of organophosphates and tebuconazole (77.7 % and 89.7 % respectively). It is important to note that residues of organophosphates and tebuconazole were found in more food items compared to pyrethroid residues, and these food items also belonged to more commonly consumed ones (SI Table 7).

In the case of tebuconazole, the median IESTI levels among all considered participants was 277.9 % of EDI and the 75th percentile corresponded to 750.2 % of EDI. Overall, we observed an overestimation reaching up to 2738.7 % at the 95th percentile. At the same time, there was limited underestimation of EDI when considering the mean to maximum interval of tebuconazole residues in food. Food items with measured organophosphate residues were less frequently consumed in comparison to those with tebuconazole residues. The median IESTI of all considered participants was equal to only 0.1 % of EDI in the case of organophosphates. The 75th percentile of IESTI corresponded to 19.4 % of the EDI. These results show that available information on food consumption and organophosphate residues in consumed food items was not sufficient to explain total organophosphate intake. Lastly, IESTI for pyrethroids could reflect 40.6 % of EDI in the median value and 115.3 % in the 75th percentile. Calculated IESTI for both organophosphates and pyrethroids were less prone to the overestimation of EDI when compared to IESTI for tebuconazole. It appeared that IESTI can reflect EDI more accurately for pyrethroids than for organophosphates or tebuconazole. However, the number of observations was substantially lower in comparison to other pesticides.

3.3. Association between a specific food and urinary pesticide metabolites

Questions inquiring about lifestyle were answered on average in 88 % of cases, with a slightly lower proportion in the number of complete answers in the summer season. Questions inquiring about diet 24 h before urine sample collection were answered on average in 87 % of cases (SI Table 8 and 9). The most consumed food items with expected pesticide residues were apples, white bread, potatoes, onions, and carrots in the winter season. In the summer season, the most consumed food items were white bread, fresh tomatoes, strawberries, apples, and potatoes. More home-grown food items, but also more organic food items were consumed in the summer season compared to the winter season. The most frequently consumed organic food items were oat products, bell pepper, pasta, and rice. The most frequently consumed home-grown products were apples, strawberries, onions, fresh leafy vegetables, carrots, and potatoes. However, the overall consumption of organic foods in the winter season was relatively low (the average share of consumed organic food items was approx. 5 %) and only slightly higher in the summer season (the average share of consumed organic food items was approx. 8 %), given that unanswered organic food-related questions were considered as negatively answered. For this reason, consumed food items marked as home-grown were also treated as organic. The full food basket is presented in SI Table 10 and 11.

We assessed possible links between the consumption of various food items and concentrations of urinary pesticide metabolites. Beta coefficients were expressed as the % change in urinary pesticide metabolite concentration per g of consumed food item. Of all included food items with potential pesticide residues, fifteen combinations of food item and urinary pesticide metabolites were statistically significantly associated with urinary pesticide metabolite concentrations, although sometimes in opposite direction. These included white and wholegrain bread, nuts, wheat flour products, pasta, oranges, apples, rice, beans, peaches/apricots, grapes, strawberries, and fruit juice (SI Table 12). However, after p-value correction (Benjamini and Hochberg, 1995), only white bread, apples, and peaches/apricots remained statistically significant (Table 2).

The association between TEB-OH and peaches/apricots was the most notable for its strength of effect of 0.37 % [0.23 % to 0.51 %] increase per gram of consumption. The consumption of white bread was associated with an increase in urinary metabolite of pyrethroids (3-PBA). Lastly, the consumption of apples was associated with a decrease in urinary metabolites of organophosphates (TCPY).

The possible effect of the consumption of organic food items on urinary pesticide metabolite concentrations was also studied. The results expand previously calculated associations that did not consider if consumed food items were of organic or conventional produce. When we considered organic consumption, results were not materially different (SI Table 13), although consumption of organic strawberries was associated with lower concentrations (-61.52 % [-79.34 % to -28.32 %]) of urinary pyrethroid metabolite (t/c-DCCA) in comparison to the participants not consuming organic strawberries. In line with the main analysis, consumption of non-organic peaches/apricots was associated with a slight increase in urinary concentrations of TEB-OH (0.50 % [0.34 % to 0.66]). The negative association between the consumption of apples and urinary organophosphate metabolite (TCPY) remained statistically

Table 2
Significant associations between urinary pesticide concentrations and the weight of consumed food items; presented beta coefficients are expressed as % change in urinary pesticide metabolite concentration per g of consumed food item (adjusted for season, sex, age, BMI, having own garden, crop field area in a 500 m buffer, and self-reported pesticide use).

Metabolite	Food Item	β % change [95 % confidence interval]	p	Corrected p	Parental pesticide residues were reported in food item in 2020 (EFSA)
3-PBA	White bread	0.21 [0.08 to 0.35]	**	*	No
TCPY	Apples	-0.14 [-0.23 to -0.04]	**	*	Yes
TEB-OH	Peaches & Apricots	0.37 [0.23 to 0.51]	****	****	Yes

*significant at $p \leq 0.05$; **significant at $p \leq 0.01$; ****significant at $p \leq 0.0001$.

Table 3
Percentage of explained variance (marginal and conditional R^2) from LME models in urinary pesticide metabolites (n = 220), including dietary variables (consumed food), ambient air pesticide exposure (modelled pesticide concentrations), adjusting variables (sex, age, BMI, having own garden, and self-reported pesticide use), and random effect (participant house ID).

Metabolite	Marginal R^2 (%)				Conditional R^2 (%)			
	Overall	Fixed effect - diet variables	Fixed effect – modelled ambient air pesticide concentrations	Fixed effect - adjusting variables	Overall	Fixed effect - diet variables	Fixed effect - modelled ambient air pesticide concentrations	Fixed effect - adjusting variables
3-PBA	32.47	21.91	<0.01	5.04	65.16	54.61	32.61	37.74
t/c-DCCA	27.84	17.40	0.08	9.11	61.37	50.92	33.60	42.63
TCPY	37.65	21.39	0.42	12.57	47.69	31.43	10.46	22.61
TEB-OH	32.67	26.66	0.10	3.67	42.81	36.80	10.24	13.81

Marginal R^2 – exclude random effect.
Conditional R^2 – Includes random effect.

significant. With a few exceptions (strawberries, fresh leafy vegetables), the overall number of consumed organic produce (only statistically significant associations) was low in comparison to the conventional produce.

3.4. Explained variance of pesticide metabolites

Table 3 summarizes the explained variance in urinary pesticide metabolites expressed as R^2 and explained by i) the consumption of food items with potential pesticide residues and ii) modelled ambient air pesticide exposure due to drift and volatilization. Pyrethroids exhibited the highest explained variance (65.16 % and 61.37 %) but random effects and adjusting variables contributed to more than half of this. In the case of organophosphates and tebuconazole, the overall explained variance was lower (under 50 %). In any case, based on our model the contribution of ambient air pesticide exposure to the variance of pesticide metabolites was under 0.5 %, while dietary exposure contributed more than 20 % in the case of 3 out of 4 metabolites. Similar results were found when using crop field area in a 500 m buffer instead of modelled ambient air pesticide concentrations. Overall, these models explained less variance compared to previous models (SI Table 14). However, the results are largely of a similar nature. The contribution of dietary exposure was still considerably higher than the contribution of the proxy to environmental exposure. Increase in the proportion of explained variance by dietary pathway can be seen (SI Table 15) when restricted only to the subpopulation of participants with modelled ambient air pesticide concentrations (pyrethroids n = 133, organophosphates n = 126, tebuconazole n = 132).

3.5. Pesticide exposure due to spray drift and volatilization

Ambient air pesticide exposure was modelled accounting for crop field areas in 250 m, 500 m, and 750 m buffer radii around participants' households. Variant with 500 m buffer resulted in the highest modelled exposure to pesticides. Results of all model variants (250 m, 500 m, and 750 m buffer radius) were provided in SI Table 16. Ambient air pesticide exposure was modelled for 133 (60.5 %), 126 (57.3 %), and 132 (60.0 %) participants (sum of pyrethroids, sum of organophosphates, and tebuconazole respectively) residing near crop fields where these pesticides might have been applied during the growing season. According to the model, more than half of all participants (n = 220) were potentially exposed to the studied pesticides due to volatilization and drift although we were unable to validate that spraying occurred within a 24-hour period prior to urine sample collection. Approximately the same number of participants were potentially exposed to each of the studied pesticide groups if pesticide drift occurred. Likewise, exposure to specific parental pesticides might have been limited (e.g., beta-cyfluthrin, chlorpyrifos-methyl), due to the uncertainties in the pesticide application timing and the fact that previously mentioned favourable meteorological conditions are intended to limit pesticide drift. Organophosphate pesticides had the highest modelled median concentration, this equal to 0.56 pg/m^3 (mean = 26.19 pg/m^3). The median concentrations for pyrethroids and tebuconazole were similar and corresponded to 0.005 pg/m^3 (mean = 3.01 pg/m^3) and 0.004 pg/m^3 (mean = 47.83 pg/m^3), respectively. Pesticide intake was further estimated for each participant on the basis of inhalation and dermal exposure (CIDIE, SI Table 17). Medians of calculated CIDIEs ranged from 1×10^{-4} to 0.2886 ng/kg-bw/day. These were substantially lower in comparison to calculated EDI medians, which ranged from 21.67 to 62.97 ng/kg-bw/day. This means there was a difference of two orders of magnitude for organophosphates, and even larger differences for the remaining pesticides (SI Fig. 7). This shows substantial differences between EDI based on measured urinary pesticide metabolite concentrations and CIDIE based on modelled ambient air pesticide concentrations. Spearman rho coefficients between CIDIE and EDI indicated none to slight correlations (SI Table 18–20). Correlation between EDI and CIDIE only in participants exposed to each respective parental pesticide yielded similar results (SI Table 21–47).

4. Discussion

4.1. Estimated daily intake of pesticides

The studied cohort of adults and children manifested a higher intake of pesticides in children compared to adults in most of analysed pesticides. Previously published studies on similar topics reported analogous results (Barr et al., 2010; Iglesias-González et al., 2022; Wielgomas and Piskunowicz, 2013). This phenomenon is likely associated with physiological differences between developing children and adults. Children have higher food intake in relation to their body weight, higher breathing rate, faster metabolism, and different diet composition and needs (Garry, 2004; Landrigan and Goldman, 2011; Molnár and Schutz, 1997). An important role may be also played by children's hand-to-mouth behaviour, although this is arguably more relevant in smaller children (Makri et al., 2004). The differences in pesticide intake in the winter and summer seasons are also interesting. Lower pesticide intake can be assumed in the winter season due to the expected decrease in agricultural activity (Doğanlar et al., 2018; Figueiredo et al., 2021). This may not always be the case as shown by our study and others (Galea et al., 2015; Stajnko et al., 2020). An increase in pesticide intake in the winter season suggests the importance of other exposure pathways such as the diet.

4.2. Dietary exposure

We put EDI and IESTI into perspective. For tebuconazole, the total intake (EDI) was often overestimated by IESTI; at the same time, there was a relatively low number of cases in which IESTI underestimates tebuconazole exposure. Such underestimation can be attributed to the misreporting in the questionnaires, sampling error, but also by consumption of other contaminated food items not covered by EFSA. These can be, for example, peanuts (Hou et al., 2017), watermelon (Dong and

Hu, 2014), and cucumber (Golge et al., 2018). However, tebuconazole residues can also be found in contaminated drinking water (Chau et al., 2015). Although our results point to the overestimation of tebuconazole exposure, it appears that the main sources of exposure, contaminated food items, were identified by EFSA reasonably well.

Like tebuconazole, organophosphate residues were found in relatively often consumed food items (e.g., pome fruits, stone fruits, cucumber, tomatoes); however, in many cases, the IESTI substantially underestimated organophosphate EDI while overestimation was limited. Also, 22.3 % of participants did not report consumption of any food items for which standard monitoring had observed organophosphate residues (EFSA, 2022). This implies that organophosphate residues can be found in less frequently consumed food items in comparison to tebuconazole and that there are important exposure pathways missing from the picture. Apart from contaminated drinking water (El-Nahhal and El-Nahhal, 2021), organophosphate residues have been found in spinach (Calderon et al., 2022) and cauliflower (Sinha et al., 2012), both of which can be considered quite common foodstuffs in Czech cuisine. Both can be locally produced but also shipped from abroad. In 2020, only one organophosphate pesticide (pirimiphos-methyl) was legally allowed to be used, with a low amount applied across the whole Czech Republic (less than 250 kg) (CISTA, 2022). In fact, organophosphate insecticides comprise only 3 % of total insecticide sales in the EU (EUROSTAT, 2022). Thus, it seems unlikely that contaminated food items would originate from the Czech Republic. Arguably, more significant sources may be less-consumed foreign food items like chilli (Fatunsin et al., 2020) or mango fruit (Srivastava et al., 2014), where residues of organophosphates are possibly more likely in comparison to other food items. There might also be an issue with the biomarker of exposure to chlorpyrifos (TCPY). TCPY was previously found in non-negligible amounts in various matrices together with its parental compound chlorpyrifos (Morgan et al., 2011). Animal testing showed that ingested TCPY passes through the organism largely unchanged (Timchalk et al., 2007). Therefore, the EDI may overestimate actual exposure to chlorpyrifos.

In the case of pyrethroids, residues were found in a limited number of food items (SI Table 7) and the overall consumption of these food items was low, as 85.7 % of participants did not consume them. However, the IESTI can explain the EDI reasonably well in those participants who reported the consumption of these presumably contaminated food items. Ultimately, the measurement of pyrethroid residues in various types of food items by EFSA is not sufficient as it does not reflect exposure in the Czech cohort very accurately but misreporting in the questionnaire is another possible source of uncertainty. As suggested by our results, bread and other wheat products could be plausible source of pyrethroid exposure. Previous studies have also reported pyrethroid residues in broccoli (Łozowicka et al., 2012), oregano (Drabova et al., 2019), and hops (Dušek et al., 2022). Wearing clothing (Appel et al., 2008; Bradman et al., 2007) or contact with carpet (Berger-Preiß et al., 2002) impregnated with pyrethroids as protection from insects can also be a source of exposure. Pyrethroid residues have been found in household dust samples in multiple studies (Tang et al., 2018). The accumulation of contaminated dust in household fabrics (e.g., carpets, curtains) is another exposure pathway, although this is probably more important for children due to their hand-to-mouth behaviour (Saillenfait et al., 2015). Nonetheless, the involuntary ingestion of dust particles can contribute to pyrethroid exposure as well. Darney et al., 2018 assessed pyrethroid exposure in the French population and found that the ingestion of dust was the second most important source of exposure after diet. We suspect that this exposure pathway may be an important source of pyrethroids in the Czech cohort as well, although further studies are needed to confirm this notion.

4.3. Pesticide exposure associated with specific food items and organic diet

Next, we found several associations between the consumption of food items and pesticide exposure – for example, in wheat products, rice, grapes, and nuts. These findings are in agreement with previously conducted studies suggesting these food items as possible source of pesticide exposure (Duman and Tiryaki, 2022; Liu et al., 2016; Luo et al., 2020; Nardelli et al., 2021). However, after p-value correction (Benjamini and Hochberg, 1995), the majority of associations between urinary pesticide metabolites and food item consumption were no longer significant. The only remaining statistically significant associations were between peaches/apricots and TEB-OH, white bread and 3-PBA, and apples and TCPY.

Tebuconazole is an important pesticide applied in order to protect crops from various types of fungal infections. It is used on stone fruits as protection from rot such as *Monilinia fructicola* (Thomidis et al., 2009). After application, tebuconazole can be retained in crops even after harvest. This was demonstrated on samples of peaches and nectarines from Turkey, in which residues of tebuconazole ranged from 23.1 to 56.9 μg/kg (Dülger and Tiryaki, 2021), and in peach samples from China, in which tebuconazole residues ranged from 2.1 to 550 μg/kg (Li et al., 2018). Pyrethroids serve to protect cereals from insects like *Eurygaster integriceps* and *Aelia rostrata* (Pansa et al., 2015). Pyrethroid residues were found in wheat flour after milling (Mebdoua and Ounane, 2019), but also in bread prepared from the same wheat flour (Sharma et al., 2005; Yu et al., 2021). This demonstrates that pyrethroids can not only be retained in cereals but also endure through the pastry preparation process. Based on our literature search and our results, it seems that peaches/apricots and white bread can be considered as sources of tebuconazole and pyrethroid exposure respectively. Other considered food items such as beans, grapes, pasta, and nuts (SI Table 12) might also be associated with pesticides. However, these associations were weaker in comparison to those between peaches/apricots and TEB-OH and white bread and 3-PBA. The last-studied category of pesticides, organophosphates, are also widely used to protect fruits from many species of insects such as *Cydia pomonella* (Szpyrka et al., 2017). Residues of chlorpyrifos in a variety of apples were found in previous studies (Mebdoua and Ounane, 2019; Pirsaheb et al., 2017). These reports indicate apples as possible sources of organophosphate exposure and this was also supported by EFSA (EFSA, 2022). Nonetheless, we found the opposite association, where the consumption of apples seemingly decreased urinary organophosphate concentrations (TCPY). The reason for this may be the fact that apples are a widely available fruit with high consumption in the studied cohort. That is, the high consumption of apples may lead to the decreased consumption of other fruits with higher residues of organophosphates, an idea proposed by Wang et al., 2020. Another reason may be the consumption of home-grown apples with potentially lower pesticide residues in comparison to non-organic store-bought apples.

Although in limited number of participants, we also considered the consumption of organic produce and its impact on urinary pesticide metabolites. When accounting for organic diet, we again found that peaches/apricots and white bread drove tebuconazole and pyrethroid exposure, respectively, in the Czech cohort when consumed in non-organic form. And the consumption of apples seemingly decreased organophosphate exposure even when in non-organic form. However, we also found that the consumption of organic strawberries had a relatively strong negative effect on pyrethroid urinary metabolite concentrations (t/c-DCCA). Similar effects were observed for 3-PBA, but this was not statistically significant after p-value correction. An organic diet can have a substantial positive impact on pesticide exposure (Hyland et al., 2019; Lu et al., 2006; Rempelos et al., 2022). However, some studies also reported mixed results, where the consumption of some organic food items was associated with an increase in pesticide exposure (Glorennec et al., 2017), while the consumption of some non-organic food items was associated with a decrease in pesticide exposure (Li et al., 2022). In our study, the number of consumed food items of organic produce was substantially lower compared to the number of consumed non-organic food items (e.g., apples, oranges, bell pepper). This meant that we were limited in the ability to quantify differences of urinary pesticide concentrations due to the consumption of organic instead of conventional produce. Home-grown produce is often perceived by the general population as a better alternative to purchased produce, as home-grown produce presumably contains less pesticide residues and other chemicals. However, there is a possibility of the contamination of home-grown produce by the mishandling of products containing pesticides for domestic use (Davis et al., 1992; Grey et al., 2005).

4.4. Inhalation and dermal exposure to pesticides

Out of all tested variants, the 500 m buffer radius of crop fields around participants' households in most cases appears to return the highest ambient air concentrations of pesticides. The lower exposure at 250 m buffer was probably attributed to the overall lower crop field area in comparison to 500 m and 750 m buffer. While the dispersion of applied pesticides most likely played important role in the variant with 750 m buffer, resulting in lower modelled exposure in comparison to 500 m buffer. In any case, based on our modelling results, and recognizing the limitation that we had no means for validating pesticide applications within the critical 24 h prior to urine sample collection, ambient air pesticide concentrations accounted for a relatively low contribution when evaluating associations with median CIDIE and median EDI in the summer season. There was also virtually no correlation between CIDIE and EDI. Based on measured levels in the urine samples, our findings suggest ambient air intake of pesticides during the 24 h prior to sample collection constitutes only a minor proportion of the total pesticide exposure among our study population, even those residing within 500 m of crop fields where our target study pesticides might have been applied during the growing season. In some part, this finding could be attributable to some degree by the criteria we used to restrict meteorological data input to optimal spraying conditions, which are designed to minimize pesticide drift. Furthermore, our estimation of ambient air pesticides CIDIE is arguably limited due to lack of precise data on pesticide use. Nonetheless, measured levels of metabolites of our target pesticides demonstrate the importance of the dietary pathway. In line with our findings, Lu et al., 2006 found evidence of organophosphate pesticide exposure in school-age children primarily due to the consumption of contaminated food. Luo and Zhang, 2009 estimated the intake of pesticides via various media (e.g., air, ground soil, animal products) and found the average inhalation dose of chlorpyrifos to be 0.881 ng/kg-bw/day which is about two orders of magnitude lower compared to our results (23.434 ng/kg-bw/day when considering 500 m buffer). The lower exposure may be attributed to the fact that mentioned study did not consider dermal exposure and used a different modelling approach. Luo and Zhang, 2009 concluded that dietary exposure plays a major role in pesticide exposure as compared to other exposure pathways (e.g., air, ground soil). Panuwet et al., 2009 came to the same conclusion when evaluating occupational exposure. Although inhalation and dermal exposure appears to be secondary to dietary exposure during the 24-hour period prior to urine sample collection, the fact that it does take place has been demonstrated by this study and many others (Coronado et al., 2011; Kawahara et al., 2005; Zivan et al., 2016).

The quantification of explained variance in urinary pesticide metabolites supports our finding that dietary pathways were more important compared to ambient air pathway for the 24-hour period prior to collection of urine samples used in our study. Ambient air contribution was negligible, accounting for less than 1 % of explained variance. Another important variable that may significantly affect the short-term contribution of ambient air pesticide exposure is the timing of pesticide application. Urinary pesticide biomarkers used as outcome variables in our analyses were relevant only for a short period of time, typically 24 h. We were unable to validate that our assumed pesticide application occurred within this period.

4.5. Limitations and uncertainties

This study is subject to some limitations and uncertainties. Although urine samples were collected in repeated design in the winter and summer seasons, this may not be entirely representative of usual exposure patterns. This is because measured pesticides from spot urine samples have biological half-life in an order of hours (SI Table 1). Transportation of urine samples from participants to the laboratory may have had negative impact on stability of urinary pesticide metabolites and culminate into skewed results. Mean and maximum residues for each pesticide were used to calculate pesticide food intake (IESTI) ranges for each participant instead of actual residues in consumed food. Self-reported weight of consumed food items was only estimated by participants, thus possibly introducing uncertainties in the analyses. In general, the self-reported consumption of organic food was relatively low which means that we were limited in our ability to evaluate its impact on measured pesticide metabolite concentrations. Consumed food items reported as home-grown were also not reported frequently and such food items were considered organic, although we were not able to assess if this assumption was true. We assumed that pesticide application was conducted only under the favourable meteorological conditions limiting the drift of applied pesticides which may also be considered a limiting factor. Nonetheless, this study also has advantages. The study included measured urinary concentrations of four pesticide metabolites in adults and children. Questionnaire data included lifestyle and food consumption including organic food in the 24 h before urine sample collection for each participant. Urine samples and questionnaires were collected repeatedly in the winter and summer seasons. Estimates of inhalation and dermal exposure were based on detailed meteorological and field crop data location and time-specific for each participant.

6. Conclusion

In this work, we focused on the investigation of exposure pathways to pyrethroids, organophosphates, and tebuconazole in the Czech cohort. We estimated inhalation and dermal exposure to pesticides, the results indicate that although exposure could have occurred via this pathway during the critical 24-hour period prior to urine sample collection, there were other more relevant sources of exposure. Intake patterns of mentioned pesticides suggest the importance of dietary pathways especially in the case of tebuconazole. In this respect, we found that the consumption of various food items (peaches/apricots, white bread) was associated with higher concentrations of urinary pesticide metabolites. We also attempted to evaluate the impact of an organic diet on exposure levels but were limited in our ability to quantify exposure differences due to the low proportion of self-reported consumption of organic produce. Available data also suggest other substantial exposure sources in addition to food. These could include contaminated drinking water and household dust; therefore, future studies should focus on these under-investigated matrices.

CRediT authorship contribution statement

Libor Šulc: Formal analysis, Investigation, Writing – original draft, Visualization. **Daniel Figueiredo:** Conceptualization, Methodology, Writing – review & editing. **Anke Huss:** Conceptualization, Writing – review & editing. **Jiří Kalina:** Methodology, Writing – review & editing. **Petr Gregor:** Methodology, Writing – review & editing. **Tomáš Janoš:** Formal analysis, Investigation, Writing – original draft. **Petr Šenk:** Validation, Investigation, Writing – review & editing. **Andrea Dalecká:** Investigation, Writing – review & editing. **Lenka Andrýsková:** Investigation, Validation. **Vít Kodeš:** Data curation, Writing – review & editing. **Pavel Čupr:** Conceptualization, Resources, Writing – review &

editing, Supervision.

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

Data will be made available on request.

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Appendix A. Supplementary material

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