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Estimated Uncertainty of Dietary Exposure to Residues of 14 Pesticides

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Abstract

The dietary exposure to pesticides and its uncertainty depend on the types and amounts of foods consumed, their pesticide residue content, therefore should be calculated on a case-by-case basis. The contribution of quantifiable uncertainties of input parameters of deterministic model to the combined uncertainty of the estimated exposure is shown using the residues of 14 different pesticides (acibenzolar-S-methyl, benzovindiflupyr, bifenthrin, chlorantraniliprole, cyantraniliprole, ethephon, flonicamid, flupyradifurone, flutriafol, fluxapyroxad, metrafenone, pendimethalin, spiromesifen, teflubenzuron) in food consumed in two days. The daily intakes of pesticide residues calculated for the daily consumption of the reporting person were between 0.000065 mg/kg of bw/day (pendimethalin) and 0.0063 mg/kg of bw/day (flupyradifurone) for day 1 and between 0.00028 mg/kg of bw/day (flonicamid) and 0.012 mg/kg of bw/day (flupyradifurone) for day 2, with a range of combined uncertainty between 25% (bifenthrin) and 60% (metrafenone) for day 1, and between 40% (cyantraniliprole) and 80% (fluxapyroxad) for day 2. The contribution of the individual steps to the combined uncertainty depends on the particular food item, the residue levels and procedures involved in the preparation of the food. The major contributors to the total known relative uncertainty of the calculated dietary intake of pesticide residues in our study were fruits (apple, pear, berries, blackberry fruits, apple and orange juice), apple pie and pancake filled with strawberry jam.

The contributions of the individual input parameters to the combined uncertainty of the calculated intake were recipes of meals (RSD_{cu} = 22.3 - 144%), STMR or STMR-P (RSD_{STMR} = 4.5 - 153%), processing (RSD_{Pf}= 3.9 - 138%), estimated mass of consumed food (RSD_{di} = 29 - 98%), sampling (RSD_{S}; sampling of fresh fruits 20 - 30% processed solid products: about 10%) and analysis of pesticide residues in supervised trials (≤ 15%).

The results presented may not reflect the true dietary intakes and their uncertainties, as several uncertainty factors could only partly or could not be quantified, because of the lack of relevant information. Therefore, the possibility of the refinement of available information should be considered and additional information be collected, especially in those cases where the calculated intake is close to the ADI.

Keywords: *Pesticide Residues; Food Consumption; Dietary Exposure Assessment; Relative Standard Uncertainty; Combined Uncertainty of Daily Intake*

Abbreviations

ADI: Acceptable Daily Intake; BfR: German Federal Institute for Risk Assessment; bw: Bodyweight; EDI: Estimated Daily Intake; EFSA: European Food Safety Authority; EU: European Union; FAO: Food and Agriculture Organization of the United Nations; IPCS: International Programme on Chemical Safety; ISO: International Organization for Standardization; IUPAC: International Union of Pure and Applied Chemistry; JMPR: FAO/WHO Joint Meeting on Pesticide Residues; MRL: Maximum Residue Limit [mg/kg]; OECD: Organisation for Economic Cooperation and Development; P_f: Processing Factor; SCCS: Scientific Committee of the European Commission on Consumer Safety; SCENIHR: Scientific Committee of the European Commission on Emerging and Newly Identified Health Risks; SCHER: Scientific Committee of the European Commission on Health and Environmental Risks; RSD: Relative Standard Deviation; SD: Standard Deviation; STMR: Supervised Trial Median Residue; STMR-P: Supervised Trial Median Residue in Processed Commodity; WHO: World Health Organization

Introduction

Reporting the uncertainty of measurement results is a standard practice in metrology [1-3] for a long time and it is a basic requirement for laboratories performing pesticide residue analysis [4]. The scientifically correct interpretation of the results of dietary exposure assessment of consumers to pesticide residues should also be done by considering the uncertainty of the exposure estimates and comparing them to the corresponding toxicological reference value. The importance of uncertainty analysis in risk assessment has also been recognized and a number of guidance documents [5-10] and scientific opinions [5,11,12] have been published. The latest relevant EFSA document 'The principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessment' [10] provides detailed general guidance including among others combining uncertainties from different parts of the uncertainty analysis and combining uncertainties by calculation with a quantitative model involving only non-variable quantities.

The methods for the estimation of the quantitative uncertainty of the daily dietary intake values were demonstrated [13-15] with an example. The daily intake (EDI) was calculated with the basic equation used by the JMPR [16]:

$$IEDI = \sum(STMR_i \times F_i) or \sum(STMR - P_i \times F_i) \quad (1)$$

Based on the food consumption (F_i) reported during a 2 × 24 hours dietary survey carried out according to the ongoing EU Menu methodology [17] and the supervised trial median residues ($STMR_i$ and/or STMR-P_i) of bifenthrin [IUPAC name: 2-methylbiphenyl-3-yl-methyl (Z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethyl-cyclopropanecarboxylate] reported by the JMPR [18,19].

The combined uncertainty of the EDI was calculated applying the basic rules of error propagation [1,3]. These basic equations can be used for continuous data populations following various distributions, such as normal, rectangular or triangular.

The authors concluded that the uncertainty of the calculated dietary exposure to pesticide residues depends on the variability of input parameters, therefore general conclusions cannot be drawn, and it should be calculated for each case.

The objective of our paper is to examine how the combined uncertainties of the estimated daily intakes are affected by the relevant experimental data available for 14 pesticides, used for example, applying the same methods described in our previous publications [13-15].

Materials and Methods

Food consumption data

The same consumption data (Table 1), reported previously [13], are used for determining EDIs of 14 different pesticides and their uncertainties.

Meal-time	1st day's recorded consumption	
	Recorded weights	**Foods and drinks**
Breakfast	100g	Cornflakes with mixed berries
	100mL	Milk
	100mL	Coffee with 10% milk
Brunch	Medium-size	Apple
	Medium-size	Pear
Lunch	100g	Stew (made of pork)
	200g	Galuska (noodles)
	300 mL	Apple juice
Afternoon snack	Medium-size	Banana
	Medium size	Orange
Dinner	12g	Butter
	2 slices	Semi-brown bread
	300 mL	Cocoa
Meal-time	**2nd day's recorded consumption**	
	Recorded weights	**Foods and drinks**
Breakfast	80g	Whole meal bread
	10g	Delma margarine
	50g	Sliced ham
	50g	Green peppers
	300 mL	Orange juice
Brunch	150g	Apple pie
Lunch	100g	Meatloaf (made of pork)
	370g	Pea vegetable
	120g	Blackberry fruits
Afternoon snack	Medium-size	Kiwi
	Medium-size	Mandarin
Dinner	4 pieces	Pancake with strawberry marmalade
	300 mL	Cocoa
Daily liquid consumption	1000 mL/day	Water

Table 1: *Food and drink consumed during two non-consecutive days.*

Pesticide residues

Fourteen pesticides selected for our calculations, as example, are listed below together with the definitions of their residues in plant and animal commodities to be considered for testing compliance with MRLs and dietary risk assessment.

Acibenzolar-S-methyl [20] [S-methyl benzo[1,2,3]thiadiazole-7-carbothioate]

Definition of the residue for compliance with MRLs for animal and plant commodities and for dietary risk assessment for animal commodities: sum of acibenzolar-S-methyl and 1,2,3-benzothiadiazole-7-carboxylic acid (acibenzolar acid) (free and conjugates), expressed in terms of acibenzolar-S-methyl.

Definition of residue for dietary risk assessment for plants: sum of acibenzolar-S-methyl and 1,2,3-benzothiadiazole-7-carboxylic acid (acibenzolar acid), (free and conjugated) and 1,2,3-benzothiadiazole-4-hydroxy-7-carboxylic acid (4-OH acibenzolar acid) (free and conjugated), expressed as acibenzolar-S-methyl.

Benzovindiflupyr [20,21] [N-[(1RS,4SR)-9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl] 3-(difluoromethyl)-1-methylpyrazole-4-carboxamide]

Definition of the residue for compliance with the MRL and for estimation of dietary risk assessment for plant and animal commodities: benzovindiflupyr.

Bifenthrin [18,19]

Definition of the residue for compliance with the MRL and for estimation of dietary intake for plant and animal commodities: bifenthrin (sum of isomers).

Chlorantraniliprole [20,22] [3-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-1-(3-chloropyridin-2- yl)-1H-pyrazole-5-carboxamide]

The definition of residue for compliance with MRL and for dietary intake for plant and animal commodities: chlorantraniliprole.

Cyantraniliprole [21,23] [3-bromo-1-(3-chloro-2-pyridyl)-4′-cyano-2′-methyl-6′-(methylcarbamoyl)pyrazole-5-carboxanilide]

Definition of residue for compliance with MRL for both animal and plant commodities: cyantraniliprole. Definition of residue for estimation of dietary intake for unprocessed plant commodities: cyantraniliprole. Definition of residue for estimation of dietary intake for processed plant commodities: sum of cyantraniliprole and IN –J9Z38, expressed as cyantraniliprole.

Definition of residue for estimation of dietary intake for animal commodities: sum of cyantraniliprole, 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazol-5-yl]-3,4-dihydro3,8-dimethyl-4-oxo-6-quinazolinecarbonitrile [IN-J9Z38], 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1Hpyrazol-5-yl]-1,4-dihydro-8-methyl-4-oxo-6-quinazolinecarbonitrile [IN-MLA84], 3-Bromo-1-(3-chloro-2-pyridinyl)-N-[4-cyano-2-(hydroxymethyl)-6-[(methylamino)carbonyl]phenyl]-1H-pyrazole5-carboxamide [IN- N7B69] and 3-Bromo-1-(3-chloro-2-pyridinyl)-N-[4-cyano2[[(hydroxymethyl)amino]carbonyl]-6-methylphenyl]-1H-pyrazole-5-carboxamide [IN-MYX98], expressed a cyantraniliprole.

Ethephon [19] [2-Chloroethylphosphonic acid]

Definition of the residue for compliance with the MRL and for estimation of dietary intake: ethephon.

Flonicamid [19,20] [N-cyanomethyl-4-(trifluoromethyl)nicotinamide]

Definition of the residue for compliance with MRL and estimation of dietary intake for plant commodities: flonicamid.

Definition of the residue for compliance with MRL and estimation of dietary intake for animal commodities: flonicamid and the metabolite TFNA-AM, expressed as parent.

Flupyradifurone [20] [4-[(6-chloro-3-pyridylmethyl)(2,2-difluoroethyl)amino]furan-2(5H)- one]

Definition of the residue for compliance with MRLs for plant commodities: flupyradifurone.
Definition of the residue for dietary risk assessment for plant commodities: sum of flupyradifurone, difluoroacetic acid and 6-chloronicotinic acid, expressed as parent equivalents.

Flutriafol [24] [(RS)-2,4′-difluoro-α-(1H-1,2,4-triazol-1-ylmethyl)benzhydryl alcohol]

Definition of the residue (for compliance with the MRL for plant and animal commodities and for estimation of dietary intake for plant and animal commodities): flutriafol 2011, 2015.

Fluxapyroxad [19,25] [3-(difluoromethyl)-1-methyl-N- (3′,4′,5′-trifluoro [1,1′-biphenyl]- 2-yl)-1H-pyrazole-4-carboxamide]

Definition of the residue for compliance with the MRL for plant and animal commodities: fluxapyroxad.

Definition of the residue (for estimation of dietary intake for plant commodities): Sum of fluxapyroxad and 3-(difluoromethyl)-N-(3′,4′,5′-trifluoro[1,1′- biphenyl]-2-yl)-1H-pyrazole-4-carboxamide (M700F008) and 3-(difluoromethyl)- 1-(ß-D-glucopyranosyl)-N-(3′,4′,5′-triflurobipheny-2-yl)-1H-pyrzaole-4- carboxamide (M700F048) and expressed as parent equivalents.

Definition of the residue (for dietary risk assessment) for plant commodities: the sum of fluxapyroxad and 3-(difluoromethyl)-N-(3′,4′,5′-trifluoro[1,1′- biphenyl]-2-yl)-1H-pyrazole-4-carboxamide (M700F008) and 3-(difluoromethyl)- 1-(ß-D-glucopyranosyl)-N-(3′,4′,5′-triflurobipheny-2-yl)-1H-pyrzaole-4- carboxamide (M700F048) and expressed as parent equivalents.

Metrafenone [20,22] [3-bromo-6-methoxy-2-methylphenyl) (2,3,4-trimethoxy-6-methylphenyl)-methanone]

Definition of the residue for compliance with the MRL and estimation of dietary intake for plant and animal commodities: metrafenone.

Pendimethalin [20] [N-(1-ethylpropyl)-2,6-dinitro-3,4-xylidine] 2016

Definition of the residue for compliance with MRL and for dietary intake for plant and animal commodities: pendimethalin.

Spiromesifen [20] [3-mesityl-2-oxo-1-oxaspiro[4.4]non-3-en-4-yl 3,3-dimethylbutyrate]

Definition of the residue for plant and animal commodities for compliance with the MRL: sum of spiromesifen and 4-hydroxy-3-(2,4,6-trimethylphenyl)-1-oxaspiro[4.4]non-3-en-2-one, expressed as spiromesifen.

Definition of the residue for plant commodities for dietary risk assessment: sum of spiromesifen, 4-hydroxy-3-(2,4,6-trimethylphenyl)-1-oxaspiro[4.4]non-3-en-2-one, and 4-hydroxy-3-[4-(hydroxymethyl)-2,6-dimethylphenyl]-1-oxaspiro[4.4]non-3-en-2-one (free and conjugated), all expressed as spiromesifen.

Definition of the residue for animal commodities for dietary risk assessment: sum of spiromesifen and 4-hydroxy-3-(2,4,6-trimethylphenyl)-1-oxaspiro[4.4]non-3-en-2-one, expressed as spiromesifen.

Teflubenzuron [20] [1-(3,5-dichloro-2,4-difluorophenyl)-3-(2,6- difluorobenzoyl)urea]

Definition of the residue for compliance with the MRL and for estimation of dietary intake for plant and animal commodities: teflubenzuron.

The dietary intake of pesticide residues, being in the edible portion of food items, should be calculated with residues determined according to the residue definition defined for risk assessment purposes. The definitions of residues for the two purposes are either the same or it is more complex for risk assessment purposes (sometimes the total measurable residue) as it includes all specified (toxicologically significant) metabolites as well. The JMPR reports the residues for the two purposes, where available, separately and calculates the dietary intake from the corresponding residue data. In our calculation of daily intake, the residue data corresponding to the definition of residues for risk assessment purposes were taken into account.

Components of combined uncertainty

The combined uncertainty of residue concentration (RSD_{comb}) comprises of:

- The uncertainty of STMR and/or STMR-P values (RSD_{STMR});
- The uncertainty of pesticide residues reported:

  The relative standard deviations of residues (RSD_R), including the uncertainty of sampling (RSD_{S1}) of raw food item, and the laboratory phase of determination of pesticide residues (RSD_L) which consists of the homogenization of laboratory sample, extraction of test portions and qualitative, quantitative determination of extracted residues. The sampling uncertainty of fruits (RSD_{S1} = 0.19-0.35), green pepper (RSD_{S1} = 0.38), pea (RSD_{S1} = 0.27), cereal grains (RSD_{S1} = 0.25) and a typical RSD_L of 0.15 for the analysis of samples in supervised trials reported by Farkas and co-workers [26] were taken into account in our calculations.
- The variability deriving from the industrial processing or kitchen operations (RSD_{Pf});
- The variability deriving from the recipes (RSD_{cu}):

  It is different for various components of composite food, though it is the component of the uncertainty of the reported food, it has to be taken into account in the calculation of combined uncertainty of residues being in individual constituents of composite foods.
- The reported quantity of consumed food (RSD_{di}).

Relative uncertainties of the supervised trial median residue value (RSD_{STMR})

The number of supervised trials submitted for evaluation by the JMPR is most frequently 6 - 8, ranging from three to over 20. The uncertainty of the median residue depends on the spread and number residue values making up the dataset. The approximate relative uncertainty of the STMR value can be calculated, assuming normal distribution, from the residues ($R_{P0.975}$ -$R_{P0.025}$) corresponding to the rank numbers of the ordered dataset covering the 95% probability range of the median (R_{med}).

$$RSD_{STMR} = \frac{(R_{P0.975} - R_{P0.025})}{2 \times 1.96 \times SD_{STMR} \times R_{med}} \quad (2)$$

It is pointed out that residue data from minimum 9 valid trials are required for calculation of the uncertainty reflecting the 95% probability interval of STMR [27]. For trial numbers between 5 and 8, the 90% confidence limit can be calculated by inserting 1.645 instead of 1.96 in equation 2.

The estimated relative uncertainties of the STMR of the pesticides in case of relevant food items are summarized in table 2.

Pesticides	Foods	Apple	Banana, pulp	Blueberry	Chili, dry	Citrus fruits	Meat	Milk	Onions	Pea in pods	Pears	Pepper	Strawberry	Tomato	Wheat
Acibenzolar-S-methyl	n	16	15			21			12				10	13	
	STMR	0.01	0.02			0.01	0	0	0.05				0.045	0.09	
	RSD_{STMR}	0.13	0			0			0.12				0.18	0.13	
Benzovindiflupyr	n	22										9		20	30
	STMR	0.058										0.093		0.089	0.023
	RSD_{STMR}	0.06										0.59		0.47	0.06
Bifenthrin	n		9	6						6		11	19	7	13
	STMR		0.00	0.67			0.07	0.05		0.05		0.14	0.46	0.06	0.25
	RSD_{STMR}			0.52						0		0.20	0.13	0.57	0.045
Chlorantraniliprole	n	16		9	9	15			10		10	11		20	5
	STMR	0.155		0.75	0.1	0.06	0	0	0.015		0.195	0.08		0.071	0.23
	RSD_{STMR}	0.13		0.24	0.40	0.07			0.11		0.40	0.40		0.07	0.48
Cyantraniliprole	n	26		9		26			10			11		20	
	STMR	0.16		0.75	0.7	0.0405	0.041	0.21	0.015			0.1		0.08	
	RSD_{STMR}	0.09		0.24	0.32	0.10			0.11			0.32		0.07	
Ethephon	n	13												21	8
	STMR	0.15					0.002	0.0004						0.52	0.095
	RSD_{STMR}	0.20												0.06	0.70
Flonicamid	n	7									4		8	20	15
	STMR	0.13					0.047	0.04			0.01		0.37	0.09	0.01
	RSD_{STMR}	0.42									0.30		0.24	0.10	0
Flupyradifurone	n	10		8						6	9	14	10	19	28
	STMR	0.505		0.725	2.4		0.3	0.11	0.12	1.8	0.45	0.24	0.525	0.27	0.72
	RSD_{STMR}	0.36		0.36	0.18					0.54	0.15	0.18	0.09	0.11	0.07
Flutriafol	n		12									8	10	18	8
	STMR		0.05		2.3							0.275	0.43	0.11	0.015
	RSD_{STMR}		0.18		0.10							0.10	0.18	0.13	1.43
Fluxapyroxad	n			5					5	7		23		23	20
	STMR			2.4	0.7		0.02	0.02	0.23	0.03		0.07		0.07	0.085
	RSD_{STMR}			0	0.11				0	0.31		0.11		0.11	0.09
Metrafenone	n	11									6	9	8	18	18
	STMR	0.23			3.5						0.29	0.35	0.13	0.11	0.01
	RSD_{STMR}	0.45			0.17						0.41	0.17	0.38	0.14	0.12
Pendimethalin	n					19			9	15					
	STMR					0.005	0.026	0.006	0.01	0.01					
	RSD_{STMR}					0.117			0.85	0.13					
Spiromesifen	n											10	8	16	
	STMR				0.55		0.01	0.0021				0.055	0.52	0.165	
	RSD_{STMR}				0.88							0.88	0.51	0.12	
Teflubenzuron	n	12												10	
	STMR	0.155						0.01						0.295	
	RSD_{STMR}	0.12												0.19	

Table 2: *Estimated relative uncertainty of the STMR of the pesticides of food items.*

Note: STMR are expressed in mg/kg.

Zero STMR indicates that no residue is expected in the edible portion of the food item.

Empty cells indicate that no residue data were available.

**The RSD_{STMR} could only be estimated at 90% probability level because of the number of studies (6-8).*

Relative uncertainties of the processing factors (RSD_{Pf})

The effect of processing is described by the so-called processing factor (P_f) defined as the quotient of the concentration of residues in processed commodity [mg/kg] and the concentration of residues in raw agricultural commodity [mg/kg]. Processing studies, simulating industrial processes, aim to define the processing factors. The results usually show large variation, if sufficient number of studies was conducted. The JMPR evaluations of pesticide residues summarize the results of available processing studies. The JMPR recommends using generally the median of several processing factors, because it is a robust estimate of the mean value and the extreme values do not affect it. When the difference is very large in a few studies, as a worst-case assumption, the use of the highest P_f is recommended for further calculations. In addition to the studies reported by the JMPR, the compilation of processing factors updated regularly by the BfR [28] provided the raw data for the calculation.

The standard uncertainties (SD_{Pf}) of professing factors were calculated from the experimental data assuming equal probability of their occurrence (rectangular distribution), in cases where the number of processing studies was > 2 [3]:

$$SD_{Pf} = \frac{a}{\sqrt{3}} \quad (3)$$

where $Pf_{max} - Pf_{min} = 2a$.

In case of 2 studies, based on the evaluation of the variability of processing factors in other studies reported by the JMPR, the standard deviation was calculated from the range of $1.4Pf_{max} - 0.6Pf_{min}$ with equation 3 [13]. Following the same principle, the RSD_{Pf} was assumed to be 0.46 for cases where only one processing study was available.

The relative uncertainty was obtained by dividing the SDPf with the median Pf. The relevant processing factors and their uncertainty for calculation of dietary exposure based on the model diet are given in table 3.

Pesticide	Product	No. of studies	Min P_f values	Max P_f values	P_f	STMR-P mg/kg	SD_{Pf}	RSD_{Pf}
Acibenzolar-S-methyl	Orange juice	1				0.006	0.23	0.46
	Tomato juice	4	0.67	1.00	0.78	0.07	0.095	0.12
	Tomato puree	4	1.17	3.33	1.88	0.02	0.62	0.33
Benzovindiflupyr	Apple juice	4	0.05	0.07	0.06	0.003	0.0058	0.096
	Tomato puree	2	0.15	0.18	0.17	0.02	0.047	0.28
	Wheat white flour	4	0.33	0.50	0.33	0.01	0.049	0.15
	Whole meal flour	4	0.33	1.50	0.67	0.02	0.34	0.50
	Whole meal bread	4	0.33	1.00	0.50	0.01	0.19	0.39
	Coffee roasted	2	0.33	0.50	0.42	0.01	0.15	0.35
Bifenthrin	Whole meal flour	30	0.29	1.10	0.77	0.19	0.23	0.31
	Whole meal bread	22	0.11	0.97	0.75	0.19	0.25	0.33
	White flour	22	0.04	0.52	0.31	0.078	0.14	0.45
	White bread	22	0.04	0.31	0.25	0.06	0.08	0.32
	Rape seed refined oil	1			1.60	0.08	0.23	0.46
	Tomato paste	2	0.63	0.71	0.67	0.04	0.18	0.27
	Tomato puree	2	0.63	0.71	0.67	0.04	0.18	0.27
	Chili pepper dry				10.00	1.43	0.32	0.23
Chlorantraniliprole	Tomato juice	4	0.57	1.1	0.835	0.0589	0.15	0.18
	Tomato paste	4	0.61	2.4	1.55	0.109	0.52	0.33
	Apple juice	4	< 0.06	< 0.19	< 0.14	0.0098	0.04	0.27
	Orange juice	1			0.03	0.006	0.23	0.46
	Wheat flour	1			0.38	0.04	0.23	0.46
	Wheat bran	1			1.04	0.11	0.23	0.46
Cyantraniliprole	Apple juice	3	0.19	0.38	0.31	0.05	0.055	0.18
	Orange juice	1			0.03	0.006	0.23	0.46
	Tomato juice	3	< 0.15	0.19	<0.17	0.014	0.012	0.068
	Tomato puree	3	0.23	0.43	0.25	0.02	0.058	0.23
Ethephon	Apple juice	5	0.40	1.50	0.50	0.08	0.32	0.64
	Tomato juice	4	0.10	0.34	0.22	0.18	0.069	0.32
	Tomato puree	4	0.10	0.60	0.15	0.31	0.14	0.96
	Tomato paste	3	0.50	0.75	0.60	0.31	0.072	0.12
	Wheat flour	3	0.10	0.30	0.15	0.01	0.058	0.39
	Wheat bran	3	0.40	3.50	3.10	0.29	0.89	0.29
Flonicamid	Tomato paste	1			16.10	1.45	0.23	0.46
	Rapeseed oil	1			0.10	0.004	0.23	0.46
Flupyradifurone	Wheat white flour	4	0.25	0.67	0.45	0.59	0.12	0.27
	White bread	4	0.25	0.51	0.32	0.42	0.075	0.24
	Whole meal	4	1.10	1.60	1.25	1.64	0.14	0.12
	Whole meal bread	4	0.67	0.96	0.80	1.05	0.083	0.11
	Orange juice	2	0.11	0.14	0.14	0.07	0.038	0.28
	Orange marmalade	2	0.17	0.21	0.16	0.08	0.055	0.36
	Apple whole fruit washed	4	0.50	1.40	1.10	0.25	0.26	0.24
	Tomato juice	4	0.50	0.73	0.60	0.14	0.066	0.11
	Tomato puree	3	1.50	1.70	1.50	1.10	0.058	0.039
	Tomato paste	1			1.90	1.30	0.23	0.46
Flutriafol	Apple juice	2	0.45	0.50	0.48	0.04	0.12	0.26
	Strawberry jam	4	0.75	0.96	0.88	0.39	0.061	0.069
	Tomato puree	1			1.20	0.13	0.23	0.46
	Tomato paste	1			2.60	0.29	0.23	0.46
	Wheat bran	1			2.10	0.03	0.23	0.46
	Wheat flour	1			0.33	0.01	0.23	0.46
Fluxapyroxad	Apple juice	2	0.19	0.23	0.21	0.06	0.060	0.21
	Tomato puree	4	0.25	0.67	0.37	0.03	0.12	0.33
	Tomato paste	4	0.17	1.21	0.73	0.05	0.30	0.41
	Tomato juice	4	0.08	0.32	0.18	0.01	0.069	0.39
	Rapeseed oil refined	1			0.23	0.03	0.23	0.46
	Sunflower oil refined	1			0.08	0.004	0.23	0.46
	Wheat flour	8	0.09	0.63	0.16	0.014	0.16	0.97
	Wheat bran	8	2.43	4.54	2.90	0.25	0.61	0.21
	Whole meal bread	8	0.50	1.21	0.64	0.05	0.21	0.32
Metrafenone	Apple juice	2			2.10	0.05	0.23	0.11
	Tomato juice	4	0.26	0.40	0.34	0.04	0.040	0.12
	Whole meal flour	4	0.94	1.90	1.40	0.01	0.28	0.20
	Flour type 550	4	0.14	0.29	0.19	0.002	0.043	0.23
	Fine bran	4	2.60	5.30	4.20	0.01	0.78	0.19
Spiromesifen	Strawberry jam	4	0.44	0.58	0.46	0.24	0.040	0.088
	Strawberry preserve	4	0.27	0.32	0.28	0.15	0.014	0.052
	Tomato puree	5	0.72	2.30	1.20	0.20	0.46	0.38
	Tomato paste	1			2.60	0.43	0.23	0.46

Table 3: *Relative uncertainties of the processing factors.*

Variability of recipes of composite foods and the reported portion of food consumed

The uncertainties of the recipes of composite foods and food portions (RSDcu: 0.24 - 1.44) of the model diet were obtained from different recipes [13].

Calculation of EDIs and their combined uncertainties

The methods for the estimation of the quantitative uncertainty of the dietary intake values were described by Szenczi-Cseh and Ambrus [13,14]. In the present work the same method was applied for the 14 different pesticide residues.

The stepwise method of calculation of residue concentration and its uncertainty is briefly described below. The principle of calculation is the same for all food items - pesticides combinations.

In the first step the mg residue of a pesticide in the mass (M_i) of ith ingredient of a given food was calculated from the STMR or STMR-P values as $R_i = M_i \times STMR(-P)$. In the second step the total residue [mg] of the pesticide derived from the 'k' ingredients of the given food were calculated as $R_T\,[mg] = \sum_{i=1}^{k} R_i$. The concentration of the residue (R_c) in the food item was calculated from the total residue [mg] (R_T) and the total mass (M_T) as $R_c = \frac{R_T}{M_T}$.

The combined uncertainty of the residue concentration (RSD_{comb}) in the i[th] ingredient of the processed product was calculated as:

$$RSD_{comb(i)} = \sqrt{RSD_{STMR}^2 + RSD_{Pf}^2 + RSD_{S_1}^2 + RSD_{S_2}^2 + RSD_L^2 + RSD_{cu}^2} \qquad (4)$$

where RSD_{STMR}, RSD_{Pf}, RSD_{S1}, RSD_{S2}, RSD_L and RSD_{cu} are the relative uncertainties of the residues in the raw ingredient, the processing factor, sampling of the raw ingredient, sampling of the processed solid ingredient (excluding liquids or puree), determination of the residues in the laboratory (including sample processing, homogenization and analysis) and recipes of composite food, respectively.

For obtaining the uncertainty of the residue concentration in a food item, first we have to calculate the standard deviation of the total residues from the pooled variances of individual residues (R_i). Dividing the pooled SD with the R_T we obtain RSD_{res}, the relative uncertainty of total residues in the food item (e.g. filled pancake). In case of flupyradifurone the calculations are summarized in table 4.

Ingredients	Mass [kg]	STMR or STMR-P [mg/kg]♥	Contributors to combined uncertainty of residue					RSD_{comb}	Flupyradifurone			
			RSD_{STMR}	RSD_{Pf}	RSD_{S1}	RSD_L	RSD_{cu}		mg[a]	SD_R[mg][b]	RSD_{RTE} [mg/kg][c]	RSD_{res}[d]
Eggs**	0.14	0.15	-		-	0.15	n.a	0.15	0.021			
Rapeseed oil	0.18								0.00	0.00		
Milk**	0.37	0.11	-		-	0.15	0.34	0.37	0.041	0.015		
White flour	0.41	0.59	0.07	0.27	0.25	0.15	0.24	0.49	0.24	0.12		
Total mass of ingredients	1.49			0.27	0.25				0.30	0.12		
Fried pancake (16 pcs)	1.34										0.23	0.39
F_{cu}	0.899											
Mass of 4 pieces of fried pancake	0.34								0.076	0.030		
Filling: strawberry marmalade for 4 pancakes	0.022	0.525	0.09		0.27	0.15		0.33	0.01	0.003		
Mass of 4 pieces of filled pancakes	0.36								0.086	0.030	0.24	0.35

Table 4: *Calculation of flupyradifurone residue concentration and its uncertainty in pancake filled with strawberry marmalade*.*

Notes:

♥: Empty cells under STMR or STMR-P indicate that flupyradifurone residues were not present in the given food item.

** The table shows rounded values, but calculations shown above were made before rounding.*

*** In case of food of animal origin, the relative uncertainty of values cannot be determined due to the method applied for determining STMR, HR and MRL, therefore it has to be considered as non-quantifiable uncertainty, due to lack of information.*

F_{cu}: cooking factor, which may vary substantially depending on the actual methods of preparation of food.

[a]: The residues [mg] is calculated from median residues obtained in supervised trials and the mass of ingredients.

[b]: SD_R is the standard deviation of the residues expressed in mg.

[c]: The flupyradifurone concentration [mg/kg] is calculated from the sum of residues [mg] and the mass of ready-to-eat (RTE) food.

[d]: RSD_{res} is the relative uncertainty of residue concentration in RTE.

In a further step the relative uncertainty of the estimated portion sizes due to memory effect (between 24h and 3 - 4 days of recall) (RSD_{di}) were calculated from the SD_{di} obtained assuming equal probability of occurrence (rectangular distribution) and the mean ($\overline{X}_{di}$) of estimated portion sizes (P_i-s) as

$$RSD_{di} = \frac{SD_{di}}{\bar{x}_{di}}$$

The daily exposure to each pesticide was calculated as the sum of the residue content of food consumed. The combined relative uncertainty ($RSD_{total(i)}$) of i^{th} food item consumed is calculated from the uncertainty of residues (RSD_{res}) and the estimation of the portion of food consumed (RSD_{di}) as:

$$RSD_{total(i)} = \sqrt{RSD_{res}^2 + RSD_{di}^2} \quad (5)$$

Data related to RSD_{di} (0.28 - 0.94) was obtained from relevant publications [29-32].

The combined relative uncertainty ($RSD_{total(n)}$) for all (n) foods consumed on one day can be calculated as:

$$RSD_{total(n)} = \frac{SD}{m_{res}} \quad (6)$$

where SD is the relative standard deviation of the total amount of the residue on one day calculated from the pooled variances of residues of the individual food items. Dividing SD with the m_{res}, expressing the total amount of residues of one day, we obtain $RSD_{total(n)}$, the relative uncertainty of total residues in the food items consumed on one day. The results in case of flupyradifurone for day 1 are shown in table 5.

Food consumed of 1st day	Quantity[1] [kg]	Mass[2]	STMR or STMR-P [mg/kg]	Residue[3] [mg/kg]	Residue [mg]	RSD_{res}	RSD_{di}	$RSD_{total(i)}$	SD_R	SD_R^2	Contribution %
Cornflake	0.09								0.00		
Berries	0.01	0.08							0.00	0.00	0.00
Milk	0.10	0.10	0.11		0.012	0.15	0.37	0.40	0.0046	0.00	0.104
Coffee	0.09								0.00	0.00	0.00
Apple	0.17	0.17	0.23		0.039	0.30	0.89	0.94	0.037	0.0013	6.64
Pear	0.20	0.20	0.45		0.090	0.21	0.89	0.92	0.082	0.0068	33.54
Stew (made of pork)	0.10			0.27	0.027	0.31	0.52	0.60	0.017	0.00028	1.36
Noodles	0.20			0.26	0.052	0.52	0.42	0.67	0.035	0.0012	5.92
Apple juice	0.33	0.45	0.14	0.046		0.21	0.37	0.43	0.00	0.00	0.00
Banana	0.11	0.09							0.00	0.00	0.00
Orange	0.20	0.14	0.505		0.10	0.46	0.89	0.99	0.101	0.0102	50.38
Butter	0.01								0.00	0.00	0.00
Semi-brown bread	0.07			0.32	0.022	0.42	0.56	0.70	0.015	0.0002	1.14
Cocao	0.31		0.11[4]		0.034	0.15	0.37	0.40	0.014	0.0002	0.92
Water	1.00										
Amount of food consumed [kg]	1.99										
Sum of residues [mg]					0.38						
Daily intake	0.0063										
$RSD_{total (n)}$								0.38			

Table 5: *Flupyradifurone residue in consumed food on day one and the uncertainty of daily exposure*.*

*Notes: *The table shows rounded values, but calculations were made before rounding. [1]: kg equivalent of food consumed.*

[2]: Edible part equivalent of raw material. [3]: Mass of residue in consumed food. RSD_{res}: Relative uncertainty of residues in consumed food item.[4]: derived from milk

RSD_{di}: Relative uncertainty of portion size estimation. RSD_{total}: Relative uncertainty of daily residue intake.

Standard uncertainty of residues in consumed food (mass of residue×RSD_{comb}). SD_R^2: Variance of standard uncertainty.

Contribution %: Percentage contribution of individual consumed food items to the total variance of residues consumed on day one.

Assuming that an ordinary bathroom balance was used (±0.5 kg accuracy), the corresponding standard deviation of bodyweight measurement (RSD_w) is calculated as:
SD = 0.5/1.96 = 0.255 kg with relative uncertainty of RSD_w = 0.255/60 = 0.0042.

The combined relative uncertainty of estimated daily residue intake (RSD_{EDI}) of one day is calculated as:

$$RSD_{EDI} = \sqrt{RSD^2_{total(n)} + RSD^2_w} \quad (7)$$

Results and Discussion

The calculated daily intakes and their uncertainties are summarized in table 6. The upper 95% confidence limits ($CL^{0.975}$) are calculated from the EDI+1.96×SD_{EDI}. The daily intakes of the examined pesticide residues are between 0.000063 (pendimethalin) and 0.0049 (flupyradifurone) for day 1 and between 0.00028 (flonicamid) and 0.012 mg/kg of bw/day (flupyradifurone) for day 2, respectively. The daily exposures did not exceed the ADI, the highest residue level was less than 30% of ADI.

Consumption day 1						ADI	ADI%	Consumption day 2					ADI%
	Pesticide [mg]	Standard uncertainty	Daily intake [mg/kg of bw]	Upper 95% daily intake [mg/kg of bw]	RSD_{EDI}			Pesticide [mg]	Standard uncertainty	Daily intake [mg/kg of bw]	Upper 95% daily intake [mg/kg of bw]	RSD_{EDI}	
Acibenzolar-S-methyl	0.012	0.0037	0.0002	0.0003	0.32	0.08	0.24	0.028	0.013	0.0005	0.0009	0.45	0.58
Benzovindiflupyr	0.044	0.016	0.0007	0.0013	0.36	0.01	7.27	0.046	0.033	0.0008	0.0019	0.72	7.64
Bifenthrin	0.043	0.011	0.0007	0.0011	0.25	0.05	1.43	0.12	0.049	0.0019	0.0036	0.42	3.90
Chlorantraniliprole	0.17	0.067	0.0029	0.0051	0.38	2	0.14	0.30	0.14	0.0050	0.010	0.48	0.25
Cyantraniliprole	0.18	0.052	0.0031	0.0048	0.28	0.03	10.18	0.24	0.095	0.0040	0.0071	0.40	13.24
Ethephon	0.083	0.041	0.0014	0.0027	0.50	0.05	2.75	0.025	0.013	0.0004	0.0009	0.55	0.82
Flonicamid	0.088	0.029	0.0015	0.0024	0.32	0.07	2.11	0.017	0.0080	0.0003	0.0005	0.49	0.39
Flupyradifurone	0.38	0.14	0.0063	0.011	0.38	0.08	7.84	0.73	0.37	0.012	0.025	0.51	15.30
Flutriafol	0.050	0.021	0.0008	0.0015	0.41	0.01	8.37	0.040	0.021	0.0007	0.0014	0.52	6.64
Fluxapyroxad	0.17	0.076	0.0029	0.0054	0.44	0.02	14.46	0.35	0.28	0.0058	0.015	0.80	29.22
Metrafenone	0.12	0.070	0.0019	0.0043	0.60	0.3	0.65	0.056	0.025	0.0009	0.0018	0.45	0.31
Pendimethalin	0.004	0.0016	0.00007	0.0001	0.41	0.1	0.07	0.017	0.011	0.0003	0.0006	0.62	0.29
Spiromesifen	0.0087	0.0029	0.00015	0.0002	0.33	0.03	0.48	0.017	0.011	0.0003	0.0007	0.66	0.93
Teflubenzuron	0.064	0.037	0.0011	0.0023	0.57	0.005	21.22	0.017	0.0078	0.0003	0.0005	0.46	5.58

Table 6: *Estimated daily intakes of pesticide residues and their combined uncertainty[1].*

[1]: The table contains the calculated values which do not reflect their uncertainty.

The combined uncertainty ranged between 25% (bifenthrin) and 60% (metrafenone) for day 1, and between 40% (cyantraniliprole) and 80% (fluxapyroxad) for day 2.

The proportions of food items or ingredients containing relatively high pesticide residue concentrations were generally low, consequently they did not contribute substantially to the calculated dietary intake and its combined uncertainty. The other major factor affecting the percentage contribution of residues to the ADI and the combined uncertainty of the daily intake was the number of food ingredients treated with a given pesticide.

For instance, the flonicamid residues in apple contributed to 59.34% of the variance of the 1st day's intake (Table 7) amounting to 2.10% of ADI (Table 6), while on the second day only the apple pie contained flonicamid residues making up almost 100% of the variance of calculated daily intake and 0.39% of ADI. Comparing the results presented in tables 6, 7 and 8, even lager differences can be seen in the contribution of pesticide residues to the total variances of the daily intakes and the percentage of ADI. Therefore, the contribution of residues to the ADI and the uncertainty of daily intake should always be evaluated together.

1st day	Acibenzolar-S-rmethyl	Benzovindiflupyr	Bifenthrin	Chlorantraniliprole	Cyantraniliprole	Ethephon	Flonicamid	Flupyradifurone	Flutriafol	Fluxapyroxad	Metrafenone	Pendimethalin	Spiromesifen	Teflubenzuron
Apple	17.38	31.42	0	13.00	22.59	33.26	59.34	6.64	36.00	36.85	31.70	0	0	41.88
Apple juice	13.85	24.42	0	10.41	1.93	20.65	35.84	0	5.95	1.19	0.87	0	0	0.03
Banana	32.04	0	0	0	0	0	0	0	6.79	0	0	0	0	0
Berries, dry	0	0	9.36	1.41	2.33	0	0	0	0	10.52	0	0	0	0
Cocoa	0	0	37.44	0	36.55	0	3.00	0.92	0	0.11	0	0	0.81	0.11
Coffee	0	0.02	0	0	0	0	0	0	0	0	0	0	0	0
Milk	0	0	4.22	0	2.84	0	0.34	0.10	0	0.01	0	2.37	0.09	0.01
Noodles	0	0.07	21.94	0.21	0	0.04	0	5.92	0.01	0.03	0	0.25	88.57	0
Orange	9.71	0	0	41.68	2.26	0	0	50.38	0	0	0	33.14	0	0
Pear	24.06	43.49	0	33.28	31.27	46.03	0.44	33.54	49.82	51.00	67.16	0	0	57.96
Semi-brown bread	0	0.17	13.31	0	0	0.01	0	1.14	0	0.01	0	0	0	0
Stew	2.96	0.41	13.72	0	0.22	0.01	1.04	1.36	1.43	0.29	0.26	64.24	10.53	0

Table 7: *Contributors to the total known variance of the calculated dietary intake of pesticide residues in percentage (%) for consumption day 1.*

The contribution of food items to the total relative uncertainty of the calculated dietary intake varies depending on the pesticide. In our study the main contributors were fruits (apple, pear, berries, blackberry fruits, apple and orange juice), apple pie and pancake filled with strawberry jam (Tables 7 and 8).

2nd day	Acibenzolar-S-methyl	Benzovindiflupyr	Bifenthrin	Chlorantraniliprole	Cyantraniliprole	Ethephon	Flonicamid	Flupyradifurone	Flutriafol	Fluxapyroxad	Metrafenone	Pendimethalin	Spiromesifen	Teflubenzuron
Apple pie	0	0.80	0.28	0.35	0.74	34.04	92.08	0.49	3.64	0.28	29.85	0	0	97.15
Blackberry fruits, frozen	0	0	59.65	39.65	73.57	0	0	0	0	99.39	0	0	0	0
Cocoa	0	0	1.82	0	10.90	0	0	0.13	0	0.01	0	0	0.06	2.18
Green peppers	0	1.89	1.36	0.06	0.20	0	0	0.07	63.48	0.01	30.61	0	5.00	0
Kiwi	0.28	0	0	0	0	0	0	0	0	0	0	0	0	0
Mandarin	0	0	0	2.71	0.23	0	0	2.29	0	0	0	0.28	0	0
Orange juice	33.19	0	0	0.14	0.02	0	0	0.09	0	0	0	0.01	0	0.67
Pancake	66.26	96.22	29.45	1.39	12.35	65.92	0	5.36	19.39	0.25	18.52	95.86	91.25	0
Pea vegetable dish	0	0	0	0	1.75	0	0	89.03	0.15	0.04	0	2.47	0	0
Pork meatloaf	0.26	1.06	2.17	0	0.15	0.03	7.73	0.36	13.34	0.01	20.93	1.35	3.63	0
Sliced ham	0	0	0.13	0	0.09	0	0.19	0	0	0	0	0.03	0.07	0
Whole meal bread	0	0.03	5.15	55.70	0	0	0	2.17	0	0.01	0.09	0	0	0

Table 8: *Contributors to the total variance of the calculated dietary intake of selected pesticide residues in percentage (%) for consumption day 2*

The contributions of individual input parameters to the combined uncertainty of the calculated daily intake were the recipes of meals (RSD_{cu} = 22.3-144%), STMR or STMR-P (RSD_{STMR} = 4.5-153%) values, processing of raw food (RSD_{Pf} = 3.9-138%), the estimated mass of consumed food (RSD_{di} = 29-98%), sampling (RSD_S; sampling of fresh fruits 20 - 30% processed solid products: about 10%) and analysis of pesticide residues in supervised trials (≤ 15%).

Their percentage contribution to the total variance of the known combined uncertainties depends on numerous factors including, for instance, the composition of food consumed on various days, the authorized use of pesticides and their residue concentration in the individual food ingredients, the number of supporting residue studies, etc.

It is noted that if no data is available, the uncertainty cannot be quantified, and their percentage contribution to the total variance cannot be estimated, therefore they are counted with zero. These cases belong to the "missing information" category. However, in those cases where a pesticide is not authorized in a given commodity no residue is expected. Such cases are not counted as missing information. Some of the quantifiable uncertainties can be reduced at a certain extent by increasing the number of available data or, for instance, by improving the quantification methods of dietary surveys.

Conclusions

The dietary intake calculations performed with the residues of 14 different pesticides present in the food consumed on 2 different days illustrate the widely varying contribution of the same food items to the combined uncertainty of daily residue intake depending on the pesticide.

The range of combined relative uncertainty of estimated daily intake was between 25% (bifenthrin) and 60% (metrafenone) for day 1, and between 40% (cyantraniliprole) and 80% (fluxapyroxad) for day 2. Since the RSD_{total} (25% - 80%) is much larger than the RSD_{w} (0.42%), the uncertainty of the body mass determination does not affect at all the calculated uncertainty (RSD_{EDI}) of daily intake. Consequently, expensive precision balances need not be used during dietary surveys.

The uncertainties of parameters influencing the calculated dietary exposure vary at a great extent depending on the components of food consumed, residue levels, procedures involved in the preparation of the food, therefore typical values cannot be given, and the dietary exposure should be calculated on a case-by-case basis.

The results presented may not reflect the true dietary intakes and their uncertainties, as several factors could only partly or could not be quantified, because of the lack of relevant information. Therefore, the possibility of the refinement of available information should be considered and additional information be collected, especially in those cases where the calculated intake is close to the ADI.

In view of the relatively large uncertainties of the calculated intakes, their upper 95% confidence intervals should also be considered by risk managers when the safety of the use of pesticide is evaluated.

Conflict of Interest

The authors report no conflicts of interest.

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