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Abstract

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survey. Dietary exposure, especially from cereals and animal products, was the major source of exposure. For the 1% of adults most highly exposed, dermal exposure to permethrin through medicinal and veterinary products was an important source of exposure. Considering alterations of motor, sensory and autonomic division, all individual margins of exposure were higher than 100, suggesting that no neurotoxic risk associated with the cumulative aggregate exposure to these four pyrethroids is expected for the French adult population.

Highlights

- Cumulative aggregate exposure to pyrethroids was estimated from multiple sources
- Sources included diet, dust, inand outdoor air, veterinary and medicinal products
- For more than 99% of the adult population, diet was the major source of exposure
- For the 1% most exposed, veterinary and medicine products were important source
- Risk of specific neurotoxic effects was nul in aggregating six exposure sources

Keywords

Cumulative aggregate exposure, Pesticides, Neurotoxicity, Environmental health, Diet, Physiologically based pharmacokinetic model.

1 Introduction

Through the environment and the diet, human populations are chronically exposed to many substances that can cause adverse health effects. One main challenge of risk assessment is to account for combined exposure to multiple substances in considering the different sources and routes of exposure. Aggregate exposure considers the exposures to a substance from different sources (air, dust, food, water, etc.) and routes (ingestion, inhalation and dermal absorption),

while cumulative exposure combines the exposure to several substances of a mixture under the dose-addition hypothesis (EFSA, 2019; Fox et al., 2017; Meek et al., 2011; Sarigiannis and Hansen, 2012). By aggregating exposure sources of each substance and cumulate them, it is possible to have a complete exposure picture and to estimate the associated cumulative aggregate risk related to a common toxic effect. To define management options to reduce exposure and the associated risk, the identification of sources and the main substances contributing to the overall mixture exposure is essential. In modelling toxicokinetic, the physiologically-based pharmacokinetic (PBPK) models enable to link external exposure calculated from substance concentrations in environment and diet combined with exposure factors such as food consumption and life habits, with internal exposures estimated with human biomonitoring (Bois and Brochot, 2016; Clewell et al., 2008; Fierens et al., 2016; Sarigiannis and Karakitsios, 2018; Sarigiannis et al., 2009). Thus, information carried by biomonitoring data on aggregate exposure can help to support external exposure assessment (Béchaux et al., 2014).

We propose to assess aggregate exposure and cumulative risk to four pyrethroids for the adult population in France. Exposure to pyrethroids in humans, either by ingestion, dermal contact or inhalation, may result in clinical signs of neurotoxicity such as dizziness, headache, nausea, muscle twitching, changes in awareness, convulsions, and loss of consciousness (ATSDR, 2003). These substances share a common mode of action as they bind to the voltage-gated sodium channel of nerve cells, exerting their neurotoxic effects in a dose-additive manner (Cao et al., 2011; Soderlund et al., 2002). In France, high urinary concentrations of pyrethroid metabolites were observed in comparison to United States, Canada and Germany (Dereumeaux et al., 2018; Fréry et al., 2013). Among these metabolites, one or more are shared by cypermethrin, deltamethrin, permethrin and cyfluthrin (Starr et al., 2008; Ueyama et al., 2010). Pyrethroids were observed in France to be largely used in household products

(ANSES, 2019) and present in diet (Darney et al., 2018; Crépet et al., 2019). Cypermethrin and deltamethrin were part of the 15 pesticides which drove the dietary exposure to 144 pesticides with a potential steatosis effect in Europe (Crépet et al., 2019). Moreover, even though its registration was canceled for agricultural use in Europe in 2000, permethrin is still present in food as diet was found as the main source of exposure to this substance in adult population in France (Darney et al., 2018). Consequently, the human health risk associated to pyrethroids needs to consider the aggregate and cumulate exposures to the more common pyrethroids since they share the same mode of action and are largely present in environment and food.

Considering the adult population in France, this study aimed to i) estimate external exposures to cyfluthrin, cypermethrin, deltamethrin and permethrin and identify the main exposures by route, source and substance, ii) simulate the urinary concentrations of the five corresponding pyrethroid metabolites and compare the predictions with human biomonitoring data from a French cohort, and iii) consider these pyrethroid exposures to assess the cumulative risk related to neurotoxic effects

2 Materials and Methods

The overall framework of this study is presented in Figure 1. Firstly, six sources of exposure were identified from a literature review, i.e. food/water, home settled dust, indoor air, outdoor air, veterinary usages for pet treatments, and medicinal usages for humans (step 1a). Corresponding exposure factors such as the food consumption or dust ingestion and time spent outside were searched for in the literature (step 1b). Secondly, external individual aggregate exposures to each pyrethroid were simulated by combining concentrations in the different sources and exposure factors using two dimensional Monte-Carlo simulations (step

2). Thirdly, the urinary concentrations of the pyrethroid metabolites were predicted from the simulated external exposures to each pyrethroid using the PBPK modelling approach developed by Quindroit et al. (2019) (step 3a). The predicted concentrations were then compared to those measured in the national ENNS biomonitoring survey (Fréry et al., 2013) (step 3b). Finally, the aggregate exposures of each four pyrethroids were added to cumulate the exposure that was put in perspective with toxicity indicators (step 4).

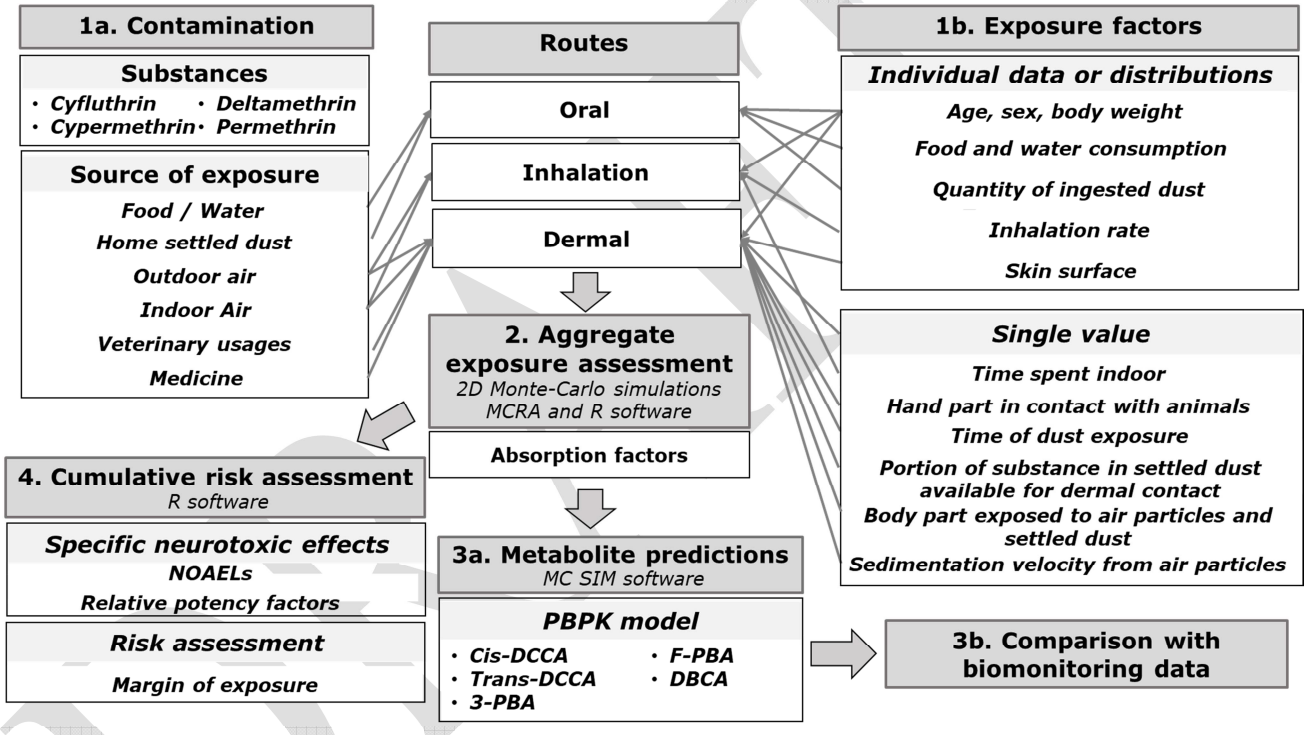

Figure 1. Concept map of the assessment of external aggregate and cumulative exposures and metabolite predictions of pyrethroids for the general adult population.

2.1 Pyrethroid concentrations in the different media

2.1.1 Food

Data on the concentrations of pyrethroids in food, $C_{food,i}$ came from annual control and monitoring programmes carried out by the French ministries in charge of consumer affairs, agriculture and health between 2010 and 2014 (DGAL, 2010-2014, DGCCRF 2010-2014,

DGS, 2010-2014). Depending on the pyrethroid, the limits of detection (LODs) varied between 0.7 and 40 ng/g and the limits of quantification (LOQs) between 1.26 and 50 ng/g (Table 1). In total, 8,196 food samples were analysed for cyfluthrin, 7,735 food samples for cypermethrin, 8 027 food samples for deltamethrin, and 7,077 food samples for permethrin.

2.1.2 Indoor settled dust

Concentrations of pyrethroids in home settled dust $C_{dust;i}$ were measured in a representative sample of dwellings between 2008 and 2009 in France (Mandin et al., 2014). Dust samples were collected with household vacuum cleaner bags and were frozen at -18 °C. Dust from vacuum cleaner bags used for vacuuming the fireplace or the outdoor terrace, as reported by the household, was discarded. Before analysis, samples were sieved at 100 µm. Pyrethroids were analysed by pressurised liquid extraction with dichloromethane and gas chromatography/mass spectrometry (Mercier et al., 2014). Depending on the pyrethroid, the LODs varied between 5.3 ng/g and 26 ng/g and the LOQs between 12.3 and 66 ng/g. In total, 145 measurements of settled dust concentrations in different dwellings were taken into account with their sampling weight (Table 1). Since no data on pyrethroid concentrations in settled dust in other indoor environments are available to date for France, the concentrations observed in dwellings were considered to represent those in all French buildings.

2.1.3 Indoor air

The indoor concentrations of each pyrethroid $C_{ind;i}$ (ng/m^3) were calculated with Eq (1) as the sum of concentrations in the particulate phase ($PM10_{ind;i}$) and concentrations in the gas phase ($Gas_{ind;i}$).

$$C_{ind;i} = PM10_{ind;i} + Gas_{ind;i} \qquad \text{Eq (1)}$$

Concentrations of permethrin in the particulate phase were those collected in Mandin et al., 2016 for 285 dwellings representing the French housing stock, using sampling weights. The particulate phases were collected through active sampling on Teflon filters over 7 days in the living room, and then analysed by gas chromatography/tandem mass spectrometry (GC-MS/MS) (Mercier et al., 2012). Permethrin was detected in 76% of the samples (LOD 20.9 pg/m^3) and quantified in 54% of samples (LOQ 41.8 pg/m^3), Table 1.

The concentrations of permethrin in gas phase, and the concentrations of cypermethrin in the particulate phase and in the gas phase were retrieved from Blanchard et al. (2014) (Table 1). Samples were collected in 30 dwellings between December 2010 and April 2011 in Brittany, Western France. Particulate and gas phases were sampled using a URG personal pesticide sampler (University Research Glassware, Chapel Hill, NC, USA). Airborne particles were collected on 25-mm quartz fiber filters (Whatman QM-A) and the gaseous pollutants were trapped by a polyurethane foam (PUF) plug (22 mm diameter × 76 mm length) encased in a glass holder (Blanchard et al., 2014).

For cyfluthrin and deltamethrin, concentrations were simulated using uniform distributions established from the proportion of detected and quantified observations in 8 dwellings monitored in 2004-2005 in the North of France (ANSES (2010), Table 1). Both gas and particulate phases were sampled in the living room at a flowrate of 3.6 L/min over 7 days.

Since no data on pyrethroid airborne concentrations in other indoor environments are available to date in France, the concentrations retrieved for dwellings were considered to represent the indoor air concentrations in all French buildings.

2.1.4 Outdoor air

Pyrethroid concentrations $C_{out;i}$ (ng/m^3) in outdoor air, including the gas and particulate phases, were collected from the regulatory monitoring network for air quality in nine regions

of France (Table 1). Concentrations were quantified only in three regions (AirPACA, 2015; AIRPARIF, 2016; Lig'Air, 2014). For cyfluthrin, only one concentration value of 1.77 ng/m^3 was recorded in the Centre region in France in 2013 (Lig'Air, 2014). From these values, the concentrations in outdoor air were simulated using uniform distributions (Supplementary material S1).

2.1.5 Veterinary products for pet treatment

Permethrin is a compound used in several veterinary products for dogs in order to control external parasites. In France, 84 veterinary products for dogs contained permethrin on a total of 451 products available on the market (http://www.ircp.anmv.Anses.fr/). The repartition by product category used by French peoples for their dogs was : 39% of collars, 25% of spot-on formulations, 14% of aerosol and cutaneous sprays, and 9% of shampoos (ANSES, 2010). For each category, the percentage of products containing permethrin was used at the recommended dose to be applied on the animal in mg/kg of body weight (Supplementary material S2). All concentration values were uniformly distributed between the minimum and the maximum values. In 2012, 21.3% of French dwellings had at least one dog (ANSES, 2015) and 21.6% in 2014 (ANSES, 2019). Thus, 21% of individuals were considered dermally exposed to veterinary products by integrating the percentage of each category of products.

Cyfluthrin and cypermethrin are not used as veterinary products. Deltamethrin was present in one dog collar, but its transfer to human skin was considered to be insignificant (ANSES, 2010) and was not considered in this study.

2.1.6 Medicinal products

Only one product with permethrin is commercialized on the market in France to treat scabies: the cream TOPISCAB 5% (www.vidal.fr). Two applications of 30g during 8 hours without rinsing are recommended, with a period from 7 to 14 days between the two applications. The product contains 5 g of permethrin for 100 g of cream, which correspond of 1.5 g of permethrin in the tube of 30 g. As the standard skin surface of an adult is 1.73 m², the concentration of permethrin considered was 0.867 g/m^2. The occurrence of scabies in France was estimated to be 328 cases for 100,000 individuals in the general population (Bitar et al., 2012) and this value was applied to simulate individuals exposed to permethrin used as medicinal products.

2.1.7 Biomonitoring data

The urinary concentrations were measured during the French Nutrition and Health Survey (ENNS study) conducted from 2006–2007 by the French Institute for Public Health Surveillance (SpF) in adults aged 18 to 74 years old (Fréry et al., 2013; Fréry et al., 2011). For the analysis of pyrethroid metabolites, samples of the first morning urine were collected in a sub-sample of 396 adults. The LOD and LOQ of each metabolite were of 0.03 µg/L and 0.1 µg/L in the urine, respectively. F-PBA was detected of 29.8% of individuals, *cis*-DCCA in 56.1%, *trans*-DCCA in 86.1%, DBCA in 83.1%, and 3-PBA in 98.5% (Fréry et al., 2013).

2.2 Exposure factors

2.2.1 Food consumption data

The second Individual and National Study on Food Consumption (INCA2) was carried out by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES)

between late 2005 and April 2007 to assess consumed food quantities in a nationally representative sample of the French population over 7 days. Participants were surveyed using a three-stage random design stratified by region of residence, size of urban area, and population groups (children and adults). 1,280 different food items were reported by 2,624 adults (1 087 men and 1 537 women) aged between 18 to 79 years (Dubuisson et al., 2010). Sociodemographic data including age, sex, body weight (bw) and body size (bs) were also recorded. The mean consumed quantity Qfood (g/day) of each food item was calculated over the 7 days for each individual. , . .Individual mean consumed quantities and the associated bw and bs were generated from the INCA2 survey using the empirical distribution.

2.2.2 Ingested dust

The daily quantity of ingested dust for each individual $Q_{dust,j}$ (mg/day) was simulated with a lognormal distribution as proposed by (Özkaynak et al., 2011) with percentiles and truncated values recommended in the Exposure Factors Handbook (U.S. EPA, 2011a).

2.2.3 Inhalation rate

As recommended by the US-EPA (2011a), the daily inhalation rate IR_j in m^3/day was calculated for each individual from Eq (2) proposed by Layton (1993). Single values from the Exposure Factors Handbook (U.S. EPA, 2011a) were used for the oxygen uptake U fixed to 0.05 m^3/MJ, the ventilation equivalent VQ equal to 27 (unitless), and the ratio A of the total energy expenditure to the basal metabolic rate (BMR) fixed at 1.59 for males and 1.38 for females. The BMR in MJ/day of each individual was estimated by Eq (3) from INCA2 body weight bw_j and their body size bs_j in cm with three constants, a, b and c, depending on sex and age (EFSA, 2013):

$$IR_j = BMR_j \times U \times VQ \times A \quad \text{Eq (2)}$$

$$BMR_j = abw_j + bbs_j + c \quad \text{Eq (3)}$$

2.2.4 Skin surface

The skin surface of the individual j S_j was estimated directly from INCA2 body weight bw_j and body size bs_j, with Eq (4) of Dubois and Dubois (1916).

$$S_j = 0.007184 \times bw_j^{0.425} \times bs_j^{0.725} \quad \text{Eq (4)}$$

2.2.5 Other exposure factors

The time spent in all indoor environments T_{ind} was simulated using distributions from the recommendations of the US EPA in the Exposure Factors Handbook (2011a). All other exposure factors used for inhalation and dermal exposure, such as the fraction of pyrethroid concentrations in dust available for dermal contact, and time of home dust exposure, are described in Table 1.

2.3 Aggregate exposure from the different sources and routes

The aggregate exposure expressed in ng/kg bw/d of each pyrethroid i and individual j was calculated with Eq (5) by the sum of each exposure route (ingestion, inhalation and dermal contact) multiplied by an absorption factor:

$$E_{Aggregate,x} = EOral_{ij} \times Abs_{Oral} + EInh_{ij} \times Abs_{Inh} + ECut_{ij} \times Abs_{Cut} \quad \text{Eq (5)}$$

An absorption factor of 100% for ingestion and inhalation and of 5% for dermal contact was used as recommended by the U.S. EPA (2011b) for pyrethroids.

2.3.1 Oral route

The exposure by oral route $EOral_{ij}$ expressed in ng/kg bw/d was estimated (6) by the addition of the dietary exposure $EOral_{Dietary;ij}$ and the exposure by dust ingestion $EOral_{Dust;ij}$:

$$EOral_{ij} = EOral_{Dietary;ij} + EOral_{Dust;ij} \quad \text{Eq (6)}$$

Dietary exposure

Dietary exposure $EOral_{Dietary;ij}$ (ng/kg bw/d) was calculated (7) as follows

$$EOral_{Dietary;ij} = \sum_{i \in food} C_{food;i} \times Q_{food;j} / bw_j \quad \text{Eq (7)}$$

where $C_{food,i}$ is the concentration of the pyrethroid in food i (ng/g), $Q_{food,j}$ the consumed quantity of food (g/day), and bw_j the body weight (kg) .

Settled dust ingestion exposure

Exposure by dust ingestion $EOral_{Dust;ij}$ (ng/kg bw/d) was estimated with Eq (8) where $Q_{dust,j}$ is the quantity of ingested dust (mg/day), and $C_{dust;i}$ the concentrations in settled dust (ng/g).

$$EOral_{dust;ij} = \frac{C_{dust;i} \times Q_{dust,j} \times 10^{-3}}{bw_j} \quad \text{Eq (8)}$$

2.3.2 Inhalation route

Exposure by inhalation $EInh_{ij}$ expressed in ng/kg bw/d was calculated with Eq (9) and took into account the concentrations in indoor $C_{ind;i}$ and outdoor $C_{out;i}$ (ng/m^3) air, the time spent indoors T_{ind} (%), and the daily inhalation rate IR_j (m^3/day).

$$EInh_{ij} = \frac{(C_{ind;i} \times T_{ind} + C_{out;i} \times (1-T_{ind}) \times IR_j}{bw_j} \quad \text{Eq (9)}$$

2.3.3 Dermal route

Dermal exposure ($ECut_{ij}$) expressed in ng/kg bw/d was calculated by Eq (10) as the addition of the different sources of skin exposure through dust, air, and veterinary and medicinal products.

$$ECut_{ij} = ECut_{dust;ij} + ECut_{air;ij} + ECut_{veterinary;ij} + ECut_{medicine;ij} \quad \text{Eq (10)}$$

Where each skin exposure is described in Eq 11 to Eq 14, with common parameters as the skin surface S_j (m^2) and the exposed fraction of the body f_{skin} (unitless). More details on the other parameters are given in Table 1.

$$ECut_{dust,ij} = \frac{f_{dust} \times M_{ad_{dust}} \times C_{dust;i} \times S_j \times \frac{t_{dust}}{\text{Number of hours in one day}} \times f_{skin}}{bw_j} \quad \text{Eq (11)}$$

$$ECut_{air,ij} = \frac{(vp \times C_{ind;i} \times S_j \times f_{skin} \times t_{ind}) + (vp \times C_{out;i} \times S_j \times f_{skin} \times (1\text{-}t_{ind})}{bw_j} \quad \text{Eq (12)}$$

$$ECut_{animal,ij} = \frac{C_{animal;i} \times 10^6 \times p_{hands}/100 \times S_j \times f_{hands_{animal}} \times \frac{t_{animal}}{\text{Number of minutes in one day}}}{bw_j} \quad \text{Eq (13)}$$

$$ECut_{medicine,ij} = \frac{C_{scabies;i} \times 10^9 \times S_j \times f_{skin} \times \frac{t_{scabies}}{\text{Number of hours in one day}}}{bw_j} \quad \text{Eq (14)}$$

Table 1. Summary of input variables used for the calculation of aggregate exposure to pyrethroids in the adult population in France aged from 18 to 79 years. ED: empirical distribution, SV: single value, LN: lognormal distribution, N: normal distribution, U: uniform distribution. Values estimated from INCA2 using the equation proposed by [1]EFSA (2013) and [2]U.S. EPA (2011a).

Input variable	Symbol	Route	Ref.	Distrib.	Single value	Mean ± SD	Min - Max	P5	P25	P50	P90	P95	LOD (>%)	LOQ (>%)
Contamination data														
Concentration in food (ng/g)			Monitoring											
Cyfluthrin			programmes of	ED			16 - 44						0.7-40 (99%)	4-50 (0.02%)
Cypermethrin	C_{food}	Ingestion	French	ED			11 - 16,400						0.7-8 (99%)	3.4-50 (0.6%)
Deltamethrin			ministries	ED			10 – 1,500						0.6-8 (92%)	1.3-20 (0.54%)
Permethrin			2010–2014	ED			47- 49						0.7-8 (93%)	4-10 (0.08%)
Concentration in settled dust (ng/g)														
Cyfluthrin				ED		52 ± 219	0 – 2,084	<LOD	<LOD	<LOD	59	258	5.3 (49%)	13.2 (23%)
Cypermethrin	C_{dust}	All	Mandin et al.	ED		937 ± 2,593	0 – 24,681	<LOD	<LOD	202	2,373	3,713	10.5 (69%)	26.3 (69%)
Deltamethrin			(2014)	ED		248 ± 2,155	0 – 25,248	<LOD	<LOD	14	66	138	13.2 (54%)	26.3 (22%)
Permethrin				ED		22,130 ± 140,106	0 – 1,643,105	236	542	1,376	24,761	40,320	26 (97%)	66 (97%)
Concentration in indoor particulate phase (ng/m^3)														

Cyfluthrin			ANSES (2010)	U		0 - 1.6				0.25 (29%)	0.65 (14%)
Cypermethrin			Blanchard et al. (2014)	U		0 - 0.28					0.2 (3%)
Deltamethrin	$PM10_{ind}$	Inhalation / Dermal	ANSES (2010)	U		0 - <0.25				0.25 (0%)	
Permethrin			Mandin et al. (2016)	ED	2.33 ± 29.9	0.01 - 502	<LOD	<LOD	<LOD	1.12	1.91	0.22 (76%)	0.42 (54%)
Concentration in indoor gas phase (ng/m^3)											
Cyfluthrin			ANSES (2010)	U		0 - 2.24				0.25 (29%)	0.65 (14%)
Cypermethrin			Blanchard et al. (2014)	U		0 - <0.6					0.6 (0%)
Deltamethrin	GAS_{ind}	Inhalation / Dermal	ANSES (2010)	U		0 - <0.25				0.25 (0%)	
Permethrin			Blanchard et al. (2014)	U		0 - <0.6					0.6 (0%)
Concentration in outdoor air (gas phase + particles) (ng/m^3)											
Cyfluthrin			Regulatory	U		0 - 1.77					0.071 (7%)
Cypermethrin	C_{out}	Inhalation /Dermal	monitoring	U		0 - 0.1				0.005 (7%)	
Deltamethrin			network for air	U		0 - 0.1				0.016 (0.3%)	
Permethrin			quality	U		0 - 1				0.007 (8%)	0.05 (3%)
Concentration on pets skin after treatment (mg/m^2)											
Permethrin	C_{animal}	Dermal	ANMV	U		0 - 11,110					
Concentration on human skin after medical treatment (g/m^2)											

Permethrin	$C_{scabies}$	Dermal	VIDAL	U		0 - 0.867					
Individual exposure factors											
Body weight (kg)											
Male	bw	All	INCA2	ED	78 ± 13	48 - 171	60	70	77	94	102
Female				ED	64 ± 13	35 - 155	47	55	62	81	89
Body size (m)											
Male	bs	Inhalation /	INCA2	ED	1.75 ± 0.07	1.55 - 2.02	1.63	1.7	1.75	1.84	1.87
Female		Dermal		ED	1.62 ± 0.06	1.42 - 1.93	1.52	1.58	1.62	1.70	1.73
Skin surface (m^2)			Estimated from								
Male	S	Dermal	INCA2	Eq (4)	1.93 ± 0.17	1.47 - 2.38	1.68	1.82	1.92	2.14	2.23
Female				Eq (4)	1.68 ± 0.17	1.18 - 2.52	1.45	1.57	1.66	1.89	1.97
Basal metabolic rate[1] (MJ/day)											
Male	BMR	Inhalation	Estimated from	Eq(3)	7.05 ± 0.76	5.11 - 11.70	5.95	6.53	7.00	8.02	8.36
Female			INCA2	Eq(3)	5.51 ± 0.55	3.98 - 9.78	4.75	5.15	5.46	6.21	6.50
Inhalation rate[2] (m^3/day)											
Male	IR	Inhalation	Estimated from	Eq (2)	15.1 ± 1.6	11.0 - 25.1	12.8	14.0	15.0	17.2	17.9
Female			INCA2	Eq(2)	10.3 ± 1.0	7.4 - 16.4	8.9	9.6	10.2	11.6	12.1
Food consumption (g/day)	Q_{food}	Ingestion	INCA2	ED	Depends on the considered food						
Dust ingestion (mg/day)											
Adult <21 years old	Q_{dust}	Ingestion	U.S. EPA	LN		0 – 1,000			60		100
Adult >21 years old			(2011a)	LN		0 – 1,000			30		100

Other factors									
Time spent indoors (%)									
Adult <21 years old	T_{ins}	Inhalation / Dermal	U.S. EPA (2011a)	SV	86.7				
Adult > 21 and < 65 years old				SV	80.5				
Adult > 65 years old				SV	79.3				
Fraction of pyrethroid concentration in home dust available for dermal contact (unitless)	f_{dust}	Dermal	Beko et al. (2013)	SV	0.15				
Quantity of dust adherent to the skin (g/m²)	Mad_{dust}	Dermal	Beko et al. (2013)	SV	0.96				
Time of home dust exposure (h)	t_{dust}	Dermal	Hermant et al. (2017)	SV	24				
Sedimentation velocity from air particles to the skin (m/h)	vp	Dermal	Hermant et al. (2017)	SV	2.15				
Fraction of body that is exposed									
Male	f_{skin}	Dermal	U.S. EPA (2011a)	SV	0.63				
Female				SV	0.67				
Time spent for animal care (minutes/day)									
18 to 64 years old	t_{animal}	Dermal	U.S. EPA (2011a)	N		45.9 ± 66.6	1 - 760	30	109	150
> 64 years old				N		54.8 ± 64.5	1 - 383	30	135	180
Mean body surface corresponding to hand size (%)									

< 21 years old				SV	4.5					
Male > 21 years old	P_{hands}	Dermal	U.S. EPA (2011a)	SV	5.2					
Female > 21 years old				SV	4.8					
Hand surface fraction in contact with animals (unitless)	f_{hands}	Dermal	U.S. EPA (2011a)	N		0.18	0.02 - 0.27	0.2	0.26	0.26
Period of cream application (h)	$t_{scabies}$	Dermal	VIDAL	SV	8					

2.4 Prediction of the urinary metabolite concentrations using a PBPK modelling approach

The approach based on PBPK models for the pyrethroids and one-compartment models for the metabolites developed by Quindroit et al. (2019) was used to predict the concentrations of pyrethroid metabolites in urine. The modelling approach links external exposure through inhalation, oral and dermal contact to the four pyrethroids and their isomers (*cis* and *trans*-permethrin, *cis* and *trans*-cypermethrin, *cis* and *trans*-cyfluthrin and deltamethrin) to the urinary concentrations of some of their common metabolites: *cis* and *trans*-DCCA, F-PBA, DBCA and 3-PBA. DBCA is specific to deltamethrin and F-PBA can be formed from the two cyfluthrin isomers (*cis* and *trans*-cyfluthrin). *Cis* and *trans*-DCCA can be formed from the *cis* and *trans* isomers of permethrin, cypermethrin and cyfluthrin, respectively. The metabolite 3-PBA is common to cypermethrin, deltamethrin, and permethrin and can also be generated from other pyrethroids.

For each simulated individual, the external exposure estimates were used as input for the models. Because the toxicokinetics of the *cis* and *trans* isomers are known to be different in mammals (Tornero-Velez et al., 2012; Willemin et al., 2016; Willemin et al., 2015), a PBPK model was defined for the *cis* and *trans* isomers of permethrin, cypermethrin, and cyfluthrin. Since the exposures estimated in the first step of the workflow did not distinguish the two isomers, a factor was applied to the exposure estimates to separate them. *Cis*/*trans* ratios observed in the commercial formulas were used: 40% *cis* and 60% *trans* for permethrin and cyfluthrin, and 42% *cis* and 58% *trans* for cypermethrin.

To account for the variability and uncertainty in the toxicokinetic processes, truncated normal distributions with a coefficient of variation of 30% (the lower and upper bounds defined as 0.01% and 100% of the mean value of the parameter) were set to each compound-specific parameter (absorption rates, metabolic clearances, partition coefficients, permeability

coefficients, and urinary excretion). The model was run until the steady-state in blood was achieved (i.e. 1 month) and the urinary concentrations of the five metabolites were calculated.

2.5 Cumulative aggregate exposure and risk assessment

These four pyrethroid substances share the same insecticidal mode of action (i.e.: disrupting neuronal function by binding to voltage-gated sodium channels), which is also responsible for the neurotoxic effects observed in mammals exposed to pyrethroids. EFSA has recently published cumulative assessment groups (CAGs) of pesticides for their effects on the nervous system (EFSA, 2019a). Cyfluthrin, cypermethrin, deltamethrin and permethrin are all included in the three CAGs on functional alterations of the motor division, the sensory division and the autonomic division. The corresponding NOAELs for specific effects for chronic exposure duration have reported in Table 2.

Under the additivity hypothesis, the cumulative exposure to the four pyrethroids was calculated using the relative potency factor (RPF) approach (EFSA, 2019b; U.S. EPA, 2011b). Regarding a common toxicity effect, the RPF of each substance in a CAG was calculated by dividing the toxicity reference point of the substance (NOAEL) by those of the index compound chosen among the studied substances, Eq (16), Table 2. The four substances had similar quality data, thus deltamethrin was chosen as index compound in the present work to be consistent with previous surveys (Jardim et al., 2018; Quijano et al., 2016; U.S. EPA, 2011b; Xue et al., 2014). As proposed by U.S. EPA (2011b), it was assumed that the NOAELs and the associated RPFs estimated from oral exposure can be applied to inhalation and dermal routes considering absorption factors of 100% and 5%, respectively.

Table 2: NOAELs and RPFs of the four pyrethroids for the EFSA CAGs on functional alterations of the motor division, the sensory division and the autonomic division (EFSA, 2019a)

Substances	Motor division		Sensory division		Autonomic division	
	NOAEL mg/kg bw/d	RPF	NOAEL mg/kg bw/d	RPF	NOAEL mg/kg bw/d	RPF
Cyfluthrin	2.4	0.417	0.3	13.3	0.3	3.333
Cypermethrin	5	0.2	5	0.8	6	0.167
Deltamethrin	1	1	4	1	1	1
Permethrin	40	0.025	100	0.04	100	0.01

Thus, for each of the three specific neurotoxic effects, the cumulative exposure $E_{cumulative}$ was calculated in Eq (15) as the sum of each pyrethroid aggregate exposure multiplied by its RPF:

$$E_{cumulative} = \sum_x (E_{aggregate,x} \times RPF_x) \quad \text{Eq (15)}$$

$$\text{with } RPF_x = NOAEL_{deltamethrin} / NOAEL_x \quad \text{Eq (16)}$$

and the risk was estimated in Eq (17) by calculating the margin of exposure (MOE) by dividing the NOAEL of deltamethrin by the cumulative aggregate exposure of the four pyrethroids $E_{cumulative}$:

$$MOE = NOAEL_{deltamethrin} / E_{cumulative} \quad \text{Eq (17)}$$

Considering a default uncertainty factor of 100 multiplying 10 to account for interspecies differences by 10 for intraspecies variability, if the MOE is lower than 100, the risk related to the specific neurotoxic effect resulting from the cumulative aggregate exposure to these four pyrethroids cannot be excluded.

2.6 Exposure and risk simulations

To combine data from heterogeneous surveys and literature, the method proposed by Vanacker et al. (2020), which is based on two dimensional Monte-Carlo simulations (2DMC), was applied. This method defined a reference population, here that of the INCA2 survey, to be representative of the target population and stratification variables, here age and region, to combine surveys. To reconstruct the aggregate exposure considering inter-individual variability, a population of 100,000 individuals was simulated by randomly sampling individuals in the reference population and simultaneously assigning exposure factors and concentration values from other surveys by using sampling weights and age and regions as stratification variables. To account for uncertainty due to data combination, 100 populations of 100 000 individuals were simulated. Pyrethroid concentrations in the different sources contained values reported under the limit of detection (<LOD) or quantification (<LOQ). The optimistic, pessimistic and refined scenarios proposed by EFSA (EFSA (2012), (van Klaveren et al., 2019)) were applied to treat these censored data in the computation of the dietary and non-dietary exposure estimates. The optimistic scenario consists in replacing the values by the lower limit, i.e., zero when < LOD, or <LOQ when only the LOQ was reported, and by LOD when <LOQ. In the pessimistic scenario, values were replaced by the upper limit, i.e., the LOD or the LOQ. With the refined scenario, the same proportion of quantified values and agricultural usages was applied to replace non-detect data by (LOD + LOQ)/2, while the other non-detected values were left at zero. Dietary exposures were estimated using MCRA software 8.2.12 (van der Voet et al., 2015). Non-dietary exposure assessment, exposure aggregation, risk estimates and statistical analyses were performed using the R-Shiny application RSExpo developed by ANSES from R software (R Core Team, 2017), in which the method of Vanacker et al. (2020) was implemented. The PBPK model was run in GNU MCSim v5.6.6 simulation software (Bois, 2009).

3 Results

3.1 Aggregate exposure and routes of external exposure

Significant differences in aggregate exposure estimates were observed between the three censored scenarios as uncertainty intervals did not overlap (Fig. 2, Supplementary material S3). The pessimistic exposure can reach values approximately 2 orders of magnitude higher than optimistic values, especially for cyfluthrin. The refined scenario presented intermediate values which were, except for cyfluthrin, closer to the optimistic scenario than the pessimistic one. Looking at the substances, cypermethrin and deltamethrin had the highest exposure values for almost all percentiles except for higher percentiles for which the . permethrin presented the highest exposures. .

The oral route via dietary ingestion was the main exposure route for at least all individuals under the P95th for three censored scenarios (Fig. 2). In particular, the four pyrethroids were mainly found in cow's milk (Supplementary material S4). Depending on the substance, some were also observed in meats (e.g. poultry meat for cypermethrin and deltamethrin and swine meat for deltamethrin and permethrin), in cereals (e.g. in wheat for cyfluthrin and in rice for deltamethrin), fruits (e.g. in bananas for cyfluthrin and in tomatoes for cypermethrin), and one vegetable (e.g. in cauliflower for cyfluthrin).

The dermal route is the second most important route for the three censored scenarios. From the P99th, exposure to permethrin for the dermal route was significantly higher than the other sources and routes due to dermal contact with veterinary products (Fig. 2.). In comparison to the other routes, the inhalation route was marginal.

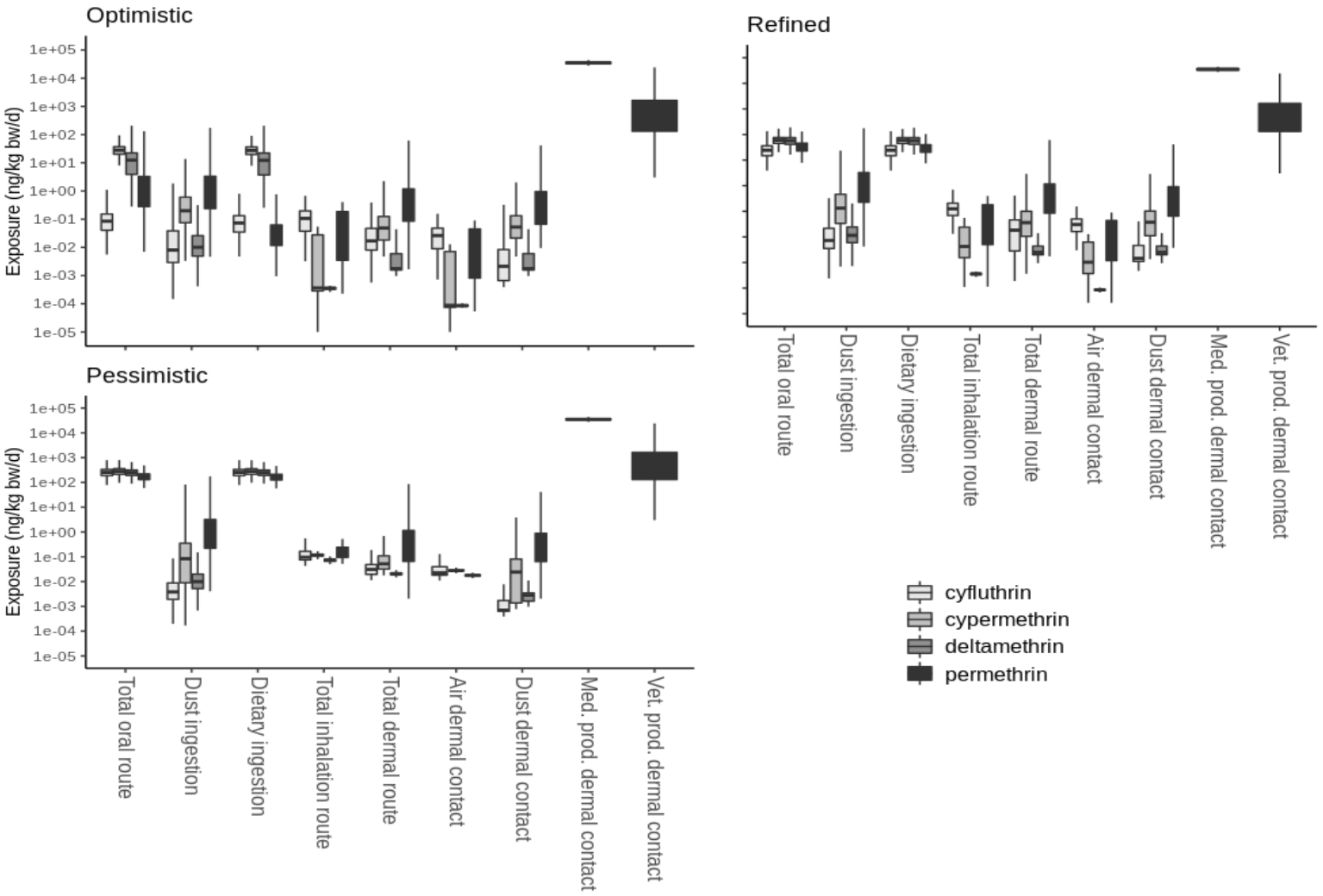

Figure 2. Boxplots of exposure (ng/kg bw/d) of the French adult population to pyrethroids according to routes and sources of exposure and to the three censored scenarios

3.2 Urinary metabolite predictions and sources of internal exposure

The refined scenario produced the closest metabolite concentrations to those of the ENNS survey (Fréry et al., 2013) for all urinary metabolite concentrations (Fig. 3). For example, the simulated urinary concentrations with the refined scenario of 3-PBA were 0.34 µg/L for the $P5^{th}$, 0.74 µg/L for the median and 1.5 µg/L for the $P95^{th}$. In comparison, the measured values were 0.14 µg/L for the 5^{th} percentile, 0.58 µg/L for the median, and 4.4 µg/L for the $P95^{th}$. The optimistic scenario underestimated the urinary metabolite concentrations, and the pessimistic scenario overestimated them. For all metabolites, the refined scenario slightly overestimated low percentiles and underestimated high percentiles compared to the ENNS survey. This was particularly the case for F-PBA and *cis*-DCCA. For example, the predicted median of F-PBA was of 0.19 µg/L compared to the measured one of 0 µg/Land the predicted P95th was 0.18 µg/L, compared to the measured one of 1.09 µg/L.

Considering the correlations between predicted urinary metabolite concentrations and sources of exposure of the refined scenario (Table 4), the metabolite concentrations were significantly influenced by exposure through food consumption, especially for 3-PBA. The urinary concentrations of DBCA and F-PBA were highly correlated to their unique specific parent, deltamethrin and cyfluthrin, respectively, via exposure from food. However, they were also moderately correlated to permethrin exposure, which is not bio-transformed into these two metabolites. This was also observed for *cis* and *trans*-DCCA, whose urinary concentrations were significantly correlated to deltamethrin via food, while deltamethrin was not metabolised into DCCA.

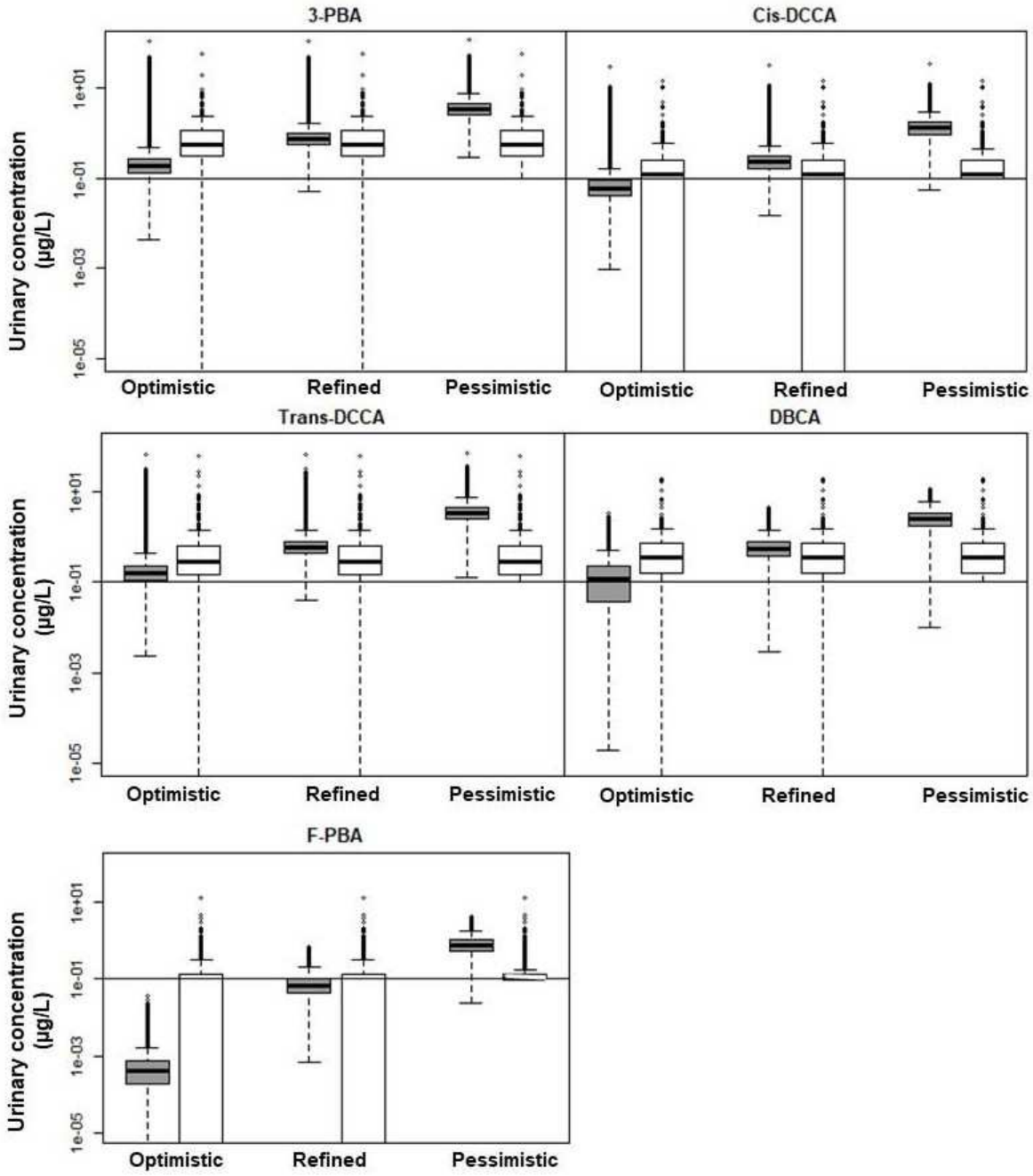

Figure 3. Comparison between simulated (grey bars) and measured (white bars) metabolite urinary concentrations (µg/L), according to the censored scenarios. The horizontal black line represents the LOQ of 0.1 µg/L of the measured concentrations.

Table 4. Spearman's rank correlations between simulated metabolite urinary and exposure concentrations (aggregate, by main sources and by route) estimated with the refined scenario.

Spearman's rank correlations in bold were considered significant as proposed by the rank: * moderate (0.400 to 0.690), ** strong (0.700 – 0.890), *** very strong (0.900 – 1.0).

		3-PBA	DBCA	*cis*-DCCA	*trans*-DCCA	F-PBA
Aggregate exposure	**Cyfluthrin**	**0.624***	0.381	**0.676***	**0.677***	**0.847****
	Cypermethrin	**0.602***	0.378	**0.632***	**0.642***	**0.575***
	Deltamethrin	**0.634***	**0.721****	**0.498***	**0.507***	**0.411***
	Permethrin	**0.756****	**0.464***	**0.670***	**0.681***	**0.533***
Home settled dust	**Cyfluthrin**	-0.001	0.004	-0.002	0.000	0.002
	Cypermethrin	0.043	0.004	0.030	0.035	-0.002
	Deltamethrin	-0.017	0.009	-0.016	-0.016	-0.001
	Permethrin	0.200	-0.002	0.157	0.164	0.004
Dietary intake	**Cyfluthrin**	**0.655***	**0.412***	**0.703****	**0.704****	**0.863****
	Cypermethrin	**0.622***	**0.412***	**0.643***	**0.654***	**0.555***
	Deltamethrin	**0.641***	**0.746****	**0.492***	**0.502***	0.376
	Permethrin	**0.749***	**0.610***	**0.668***	**0.677***	**0.639***
Total oral route	**Cyfluthrin**	**0.624***	0.381	**0.676***	**0.677***	**0.848****
	Cypermethrin	**0.602***	0.379	**0.633***	**0.642***	**0.576***
	Deltamethrin	**0.634***	**0.721****	**0.498***	**0.507***	**0.412***
	Permethrin	**0.801****	**0.499***	**0.711****	**0.723***	**0.573***
Total inhalation route	**Cyfluthrin**	-0.009	-0.004	-0.009	-0.007	-0.009
	Cypermethrin	-0.002	-0.001	-0.003	-0.001	-0.005
	Deltamethrin	-0.001	-0.001	0.000	0.001	0.001
	Permethrin	-0.013	-0.009	-0.011	-0.013	-0.022
Total dermal route	**Cyfluthrin**	0.007	-0.002	0.007	0.009	0.003
	Cypermethrin	0.042	0.002	0.030	0.035	-0.002
	Deltamethrin	-0.019	0.005	-0.017	-0.018	0.000
	Permethrin	0.187	-0.005	0.148	0.155	0.004

3.3 Cumulative aggregate exposure and risk assessment

Considering the refined scenario, the cumulative aggregate exposures ranged from less than 5 to up than 1000 ng/kg bw/d ng/kg bw/dng/kg bw/dng/kg bw/dconsidering the three specific

effects (Fig. 4). The individual MOEs estimated from the cumulative aggregate exposure were all higher than 100 for the three censored scenarios and the three specific effects (Fig. 5). The MOEs estimated for the P99.9th of the cumulative aggregate exposure with the refined scenario were 995, 1,891 and 1,603 for the alteration of motor division, sensory division and autonomic division, respectively.

Contribution to the cumulative exposures obtained with the refined scenario are described hereafter from Table 5. For 50% of the most exposed adults, the oral route contributed between 98% and 99% to the cumulative exposure for the three effects and was essentially due to diet exposure. Considering the 5% most exposed individuals, the mean contribution of the dermal route increased to 4.5%, 5% and 10.5% for alteration on autonomic, sensory and motor division respectively. For the 1% most exposed adults, the mean contribution of the dermal route reached 19%, 24% and 42% for alteration on autonomic, sensory and motor division respectively but the oral route was still the main exposure route contributing to 81%, 75% and 58% for alteration on autonomic, sensory and motor division respectively. Exposure through inhalation was very low compared to the other exposure routes (Table 5). The oral exposure was mainly due to deltamethrin in food for the alteration of the motor division, to cyfluthrin for the alteration of sensory division and to both substances for the alteration of the autonomic division, whatever the percentage of the most exposed adults. The dermal route exposure of the 1% most exposed adults was essentially due to the presence of permethrin in medicinal and veterinary products for the alteration of the motor division with a respective contribution of 30% and 12%, and to the presence of permethrin in medicinal products for the alteration of sensory and motor division with a respective contribution of 24% and 19%. Similar results were obtained with the optimistic and pessimistic censored scenarios, except that with the optimistic scenario the oral exposure was shared between deltamethrin and

cypermethrin for the three specific effects, with a low contribution of the cyfluthrin (Supplementary materials S5a and S5b).

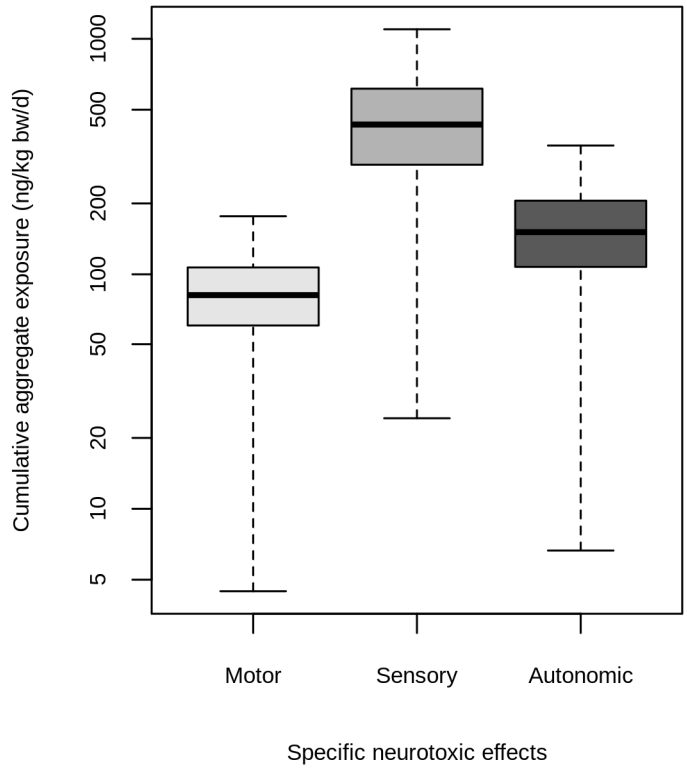

Figure 4. Cumulative aggregate exposure (ng/kg bw/d) for the three specific effects using the refined scenario

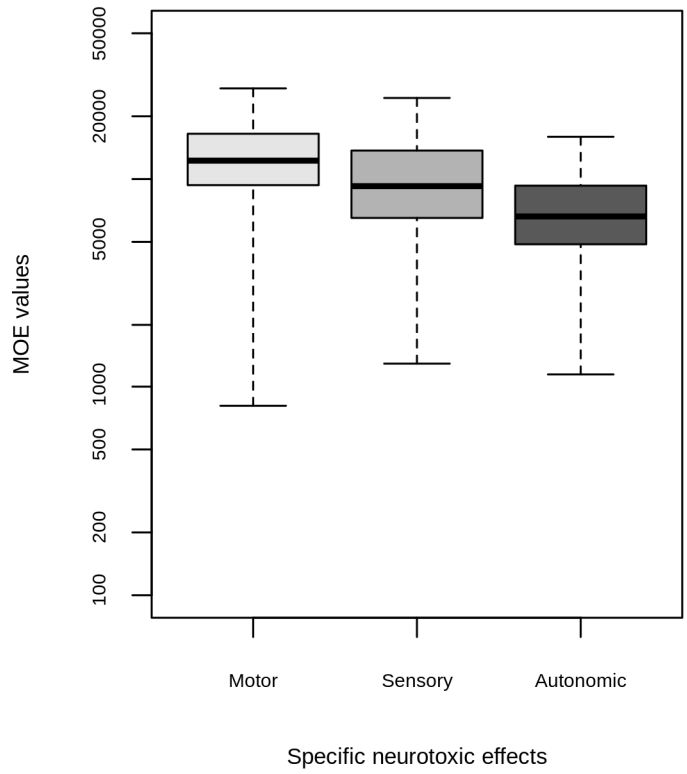

Figure 5. Margin of exposure (MOE) for the three specific effects using the refined scenario.

Table 5. Mean **contributions** (%) to the cumulative aggregate exposure estimated with the refined scenario of the different sources, routes and substances for 50%, 5% and 1% of the most exposed adults considering three specific neurotoxic effects (motor, sensitivity and autonomic division).

Exposure	Route/Source	Substance	Mean contribution of the 50% exposed individuals*			Mean contribution of the 5% most exposed individuals*			Mean contribution of the 1% most exposed individuals*		
			Motor division	Sensory division	Autonomic division	Motor division	Sensory division	Autonomic division	Motor division	Sensory division	Autonomic division
Cumulative and aggregated exposure	**Total Oral route**	**All substances**	**98**	**99**	**99**	**89**	**94**	**95**	**58**	**75**	**81**
	Dust ingestion	All substances	0.70	0.28	0.26	0.86	0.19	0.18	0.63	0.12	0.11
	Dietary ingestion	All substances	98	99	99	89	94	95	57	75	81
	Total Inhalation route	**All substances**	**0.03**	**0.15**	**0.11**	**0.02**	**0.09**	**0.07**	**0.01**	**0.06**	**0.05**
	Total Dermal route	**All substances**	**1.7**	**0.91**	**0.77**	**11**	**5.5**	**4.9**	**42**	**25**	**19**
	Medicinal dermal source	All substances	0.60	0.50	0.46	6.0	5.0	4.5	30	24	19
	Veterinary dermal source	All substances	0.90	0.32	0.23	4.4	0.53	0.33	12	0.42	0.30
	Air particles dermal source	All substances	0.01	0.04	0.03	0	0.02	0.02	0	0.02	0.01
	Dust dermal source	All substances	0.10	0.05	0.05	0.11	0.03	0.03	0.08	0.02	0.02
Aggregated exposure	**Aggregate exposure**	Cyfluthrin	13	78	57	10	77	59	6.6	62	51
		Cypermethrin	14	9.6	6.0	9.8	7.8	5.0	5.5	5.8	4.0
		Deltamethrin	70	12	36	68	9.0	31	45	7.0	26
		Permethrin	3	1.2	1.0	12	5.8	5.1	43	25	19
	Oral route	Cyfluthrin	13	78	57	10	77	58	6.6	62	51
		Cypermethrin	14	9.6	6.0	10	7.8	5.0	5	5.8	4.0
		Deltamethrin	70	12	36	68	9.0	31	45	7.0	26
		Permethrin	1.3	0.35	0.26	1.3	0.3	0.2	1.0	0.2	0.2
	Inhalation route	Cyfluthrin	0.03	0.15	0.11	0.02	0.09	0.07	0.01	0.06	0.05

	Cypermethrin	0	0	0	0	0	0	0	0	0
	Deltamethrin	0	0	0	0	0	0	0	0	0
	Permethrin	0	0	0	0	0	0	0	0	0
Dermal route	Cyfluthrin	0.01	0.05	0.04	0.01	0.03	0.02	0	0.02	0.02
	Cypermethrin	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0
	Deltamethrin	0.04	0.01	0.02	0.03	0	0.01	0.02	0	0.01
	Permethrin	1.6	0.8	0.7	10	5.5	5	42	25	19

4 Discussion

This study proposed for the first time to estimate the exposure of French adults to four pyrethroids via different routes (oral, inhalation and dermal) and sources (diet, settled dust, indoor and outdoor air, veterinary and medicinal products), and the associated cumulative aggregate risk. Heterogeneous data from the scientific literature, institutional reports, regulatory monitoring and surveys were combined using the methodological approach proposed in Vanacker et al. (2020). We found that diet was the main source of pyrethroid exposure for at least 95% of the population with cyfluthrin and deltamethrin as main contributors to cumulative exposure. For the highest 1% exposed individuals, dermal exposure was also an important route of exposure due to the presence of permethrin in medicinal and veterinary products. For all individuals and considering the three specific neurotoxic effects, 100% of the individual MOE estimated with the three censored scenario were higher than 100, suggesting that no risk associated with the cumulative aggregate exposure to these four pyrethroids is expected for the studied adult population. The closeness of urinary predicted concentrations of pyrethroid metabolites with observed biomonitoring results from the ENNS survey confirmed the relevance of the proposed aggregate exposure modelling, especially for the model using the refined scenario.

4.1 Closeness between predicted and observed urinary metabolite concentrations

Considering internal exposures using a PBPK model (Quindroit et al., 2019) makes it possible to test the plausibility of external scenarios to estimate aggregate pyrethroid exposures by comparing predicted concentrations to the biomonitoring results from the ENNS survey and the literature. We observed that the predicted metabolite concentrations were in the same range of magnitude as those from the ENNS survey for general adult population.

Concentrations were also close to those reported by Dereumeaux et al. (2018) for 3-PBA and DBCA metabolites in pregnant women. More specifically, the urinary concentrations of metabolites predicted with the refined scenario were the closest to those of the ENNS survey, compared to the values in the optimistic and pessimistic scenarios.

The less accurate predictions for F-PBA and *cis*-DCCA can be explained by the fact that these two metabolites were only quantified in 30% and 56% of the population, respectively. Moreover, it was observed that cyfluthrin, which is metabolized into these metabolites, was quantified in only 23% of samples in settled dust, and only in 0.04% in food, which is significantly lower than the other substances (e.g. 97% of quantified permethrin in settled dust, 0.66% of quantified cypermethrin in food).

Some specific metabolites were found to be correlated to the parent compound from which they are thought not to not bio-transformed. This can be explained by the fact that individuals exposed to one substance are probably also exposed to other pyrethroids due to their usage (ANSES, 2019), and thus high correlations were observed between pyrethroid exposures. Regardless of the exposure scenario assumed and the metabolites considered, the model underestimates the overall variability observed in urinary concentrations. This is probably due to the fact that pyrethroids are non-persistent compounds whose urinary concentrations are expected to greatly vary over the day according to the contact with the chemical and the time of sampling (Aylward et al., 2017). However, our predictions assumed constant exposure throughout the day, which probably does not reflect real-life diet exposure to pyrethroids. This may also be due to an underestimation of the variability of the PBPK model parameters, which was limited to 30%.

4.2 Diet, medicinal and veterinary products as the main sources of pyrethroid cumulative exposure

Previous work on pyrethroid exposure determinants conducted in France found that diet was the main exposure source to pyrethroids (Darney et al., 2018; Dereumeaux et al., 2018; Fortes et al., 2013; Glorennec et al., 2017; Lu et al., 2009; Morgan, 2012; Saillenfait et al., 2015; Ye et al., 2015). For example, Darney et al. (2018) identified for permethrin that exposure is at 87% from diet, 11% from dust, 1.5% from the dermal route, and 0.5% from inhalation. Certain previous studies also highlighted that other sources can affect overall urinary concentrations of pyrethroid metabolites (Dereumeaux et al., 2018; Fréry et al., 2013; Lu et al., 2006; Morgan, 2012). In the ENNS study, Fréry et al. (2013) made the hypothesis that the high concentrations of pyrethroid metabolites in urine was related to the veterinary treatment of domestic animals, as 38% of individuals in the ENNS population used pesticides as flea treatments on their animals. This source of exposure was also studied in the United States, where individuals who use shampoos or sprays that contain pyrethroids for their pets were observed to be more likely exposed than persons without pets (ATSDR, 2003).

Even when introducing veterinary and medical usages to estimate aggregate exposure to pyrethroids, the results still showed that diet is the major source of exposure for the whole population. However, dermal route due to permethrin in medicinal and veterinary products was the second ranking route of exposure before inhalation. For the most exposed individuals, its contributions to cumulative exposure can reach important percentage. These results confirmed that dermal exposure to permethrin via veterinary and medicinal usages was an important source of exposure and may be one of the reasons why higher metabolite concentrations of pyrethroids were observed in France. However, in the absence of individual data, the estimation of permethrin exposure through veterinary and medicinal products was conducted in using single values instead of distribution for several variables used in the

permethrin dermal exposure estimation. Thus, permethrin exposure through these sources may be refined in collecting individual data. More generally, even though the proposed approach considered part of the uncertainty, such as that related to data combination, some sources of uncertainty were not taken into account. The type of uncertainty differed depending on the source of exposure. For example, for diet exposure, consumed quantities of food came from a representative national survey with a high number of participants and investigated food items, whereas for dust exposure, ingested dust quantities were generated from probabilistic distributions from the Exposure Factor Handbook (U.S. EPA, 2011a). Similarly, pyrethroid concentrations in food came from national monitoring programmes whereas, for example, cyfluthrin and deltamethrin concentrations in the air were simulated from only 8 dwellings in the North of France. Moreover, indoor concentrations, irrespective of the building, were considered similar to those measured in dwellings. Considering censored data, diet which is the main source of pyrethroid exposure had the higher percentage of censored data, with less than 1% of quantified samples. This impacted the refined and pessimistic scenarios, where the limit of detection and quantification were used to replace a part of the censored data. However, regarding the optimistic scenario which replaced censored data by zero, diet still remains the main source of pyrethroid cumulative exposure (Supplementary material S5b). One observed difference was that the cypermethrin contribution increased with this scenario due to a higher percentage of observed values in food compared to cyfluthrin. Finally, other sources of pyrethroids such as smoking and living in the vicinity of crops during pregnancy that were observed as positively associated with urinary levels of pyrethroids (Dereumeaux et al., 2018), must be taken into account to have a comprehensive overview of pyrethroid exposure. Finally, the differences among urinary metabolite concentrations between countries and/or populations such as children, adults, and pregnant women, may be due to variety in agriculture practices related to different types of

crops and climate in the vicinity and different dietary habits. In the present study, all four pyrethroids were mainly found in cow's milk, and depending on the substance, they were also observed in some meats, cereals, fruits and in cauliflower. Importantly, even though permethrin is no longer approved since the year 2000 for agricultural uses, it is still used in biocide products (Regulation (EU) 528/2012). Moreover, it may be found in imported products, as in other countries such as in the United States, permethrin is still used in food/feed crops, livestock and livestock buildings. The results obtained in the present study were similar to those of Glorennec et al. (2017) where exposure of French children was also found to be highly correlated with cereals (pasta, rice, and semolina). In other countries, urinary metabolite concentrations were positively correlated with the intake of vegetables in the adult Italian population (Fortes et al., 2013), in the general Canadian population (Ye et al., 2015), and in the German pediatric population (Becker et al., 2006).

4.3 No potential risk of neurotoxic effect in cumulating and aggregating six sources of pyrethroids

Previous chronic and acute cumulative risk assessments of pyrethroid exposure from diet (Jardim et al., 2018; Li et al., 2016; Quijano et al., 2016) concluded that exposure to pyrethroids was under-control, and the risk was not considered of health concern. However, these studies were only based on pyrethroid residues sampled in food limited to vegetables and/or fruits for two of them and considered other toxicological points of departure. In the present study, MOE were calculated by considering other sources and routes of exposure and NOAELs from 3 specific effects established by EFSA on functional alterations of the motor division, the sensory division and the autonomic division (EFSA 2019b). For the three specific effects, all individual MOEs were higher than 100 reflecting no potential risk for neurotoxic effect in the French adult population irrespectively of the censored scenario under

consideration. Since for each substance the NOAEL values set for the three specific effects were considerably different (Table 2), weighting the exposure by the related RPFs had a significant impact on the risk ranking of the substances and the exposure source. Indeed, considering the alteration of the motor division deltamethrin was the main contributor whereas for the alteration of the sensory and autonomic division it was the cyfluthrin for which the NOAEL was divided by eight.

While some uncertainties linked to data collection and toxicological data assessment as well as limitations in the available data and scientific knowledge have been pointed out by EFSA (EFSA 2019c), the established NOAELs for each specific effects have been considered reliable to perform the cumulative risk assessment to combined exposure of the 4 pyrethroids.

Cyfluthrin, cypermethrin, deltamethrin based plant protection products and permethrin based veterinary products are commonly used in France. However, considering other pyrethroids approved within the EU and those allowed elsewhere in the world that can be found in imported foodstuffs, would provide a more accurate picture of exposure to this compound family, and enable refinement of the cumulative risk assessment associated to their neurotoxic potential. Furthermore, a more comprehensive risk assessment linked to combined aggregate exposure to neurotoxicants should also consider pesticides other than pyrethroids included in EFSA CAGs for their effects on the nervous system as well as any other contaminant known to alter the motor, sensory or autonomic functions.

5 **Conclusion**

The main source of pyrethroid exposure was the consumption of food containing cypermethrin and deltamethrin, followed by dermal source exposure to permethrin via veterinary or medicinal products for the most exposed individuals. The main contributors to dietary exposure were products of animal origin (meat and milk), cereals, fruits and

cauliflower. The cumulative aggregate exposure of the adult population in France was not considered a health concern for neurotoxicity. Further studies aimed at providing more precise results could be carried out by integrating factors such as smoking habits and living near agricultural areas. Other avenues to explore include considering other pyrethroid parent compounds sharing the same specific critical effects, and examining exposure specifically in children.

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Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: