



**HAL**  
open science

## **Aggregate and cumulative chronic risk assessment for pyrethroids in the French adult population**

Marie Vanacker, Paul Quindroit, Karine Angeli, Corinne Mandin, Philippe Glorennec, Céline Brochot, Amélie Crépet

### ► **To cite this version:**

Marie Vanacker, Paul Quindroit, Karine Angeli, Corinne Mandin, Philippe Glorennec, et al.. Aggregate and cumulative chronic risk assessment for pyrethroids in the French adult population. *Food and Chemical Toxicology*, 2020, 143, pp.111519. <10.1016/j.fct.2020.111519>. <hal-02890342>

**HAL Id: hal-02890342**

**<https://ehesp.hal.science/hal-02890342v1>**

Submitted on 16 Jul 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Marie Vanacker: Methodology, Software, Writing - Original Draft, Visualization

Paul Quindroit: Methodology, Software

Karine Angeli: Methodology, Writing - Review & Editing

Corinne Mandin: Writing - Review & Editing

Philippe Glorennec: Methodology, Review & Editing

Céline Brochot: Methodology, Writing - Review & Editing

Amélie Crépet: Conceptualization, Methodology, Writing - Original Draft, Supervision, Project administration, Funding acquisition

Journal Pre-proof

Aggregate and cumulative chronic risk assessment for pyrethroids in the French adult population

Marie Vanacker<sup>a</sup>, Paul Quindroit<sup>b</sup>, Karine Angeli<sup>c</sup>, Corinne Mandin<sup>d</sup>, Philippe Glorennec<sup>e</sup>, Céline Brochot<sup>b</sup>, Amélie Crépet<sup>a</sup>

<sup>a</sup> French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Risk Assessment Department, Methodology and Studies Unit, 947001, Maisons-Alfort, France.

<sup>b</sup> Institut National de l'Environnement Industriel et des Risques (INERIS), Models for Ecotoxicology and Toxicology Unit, Parc ALATA, BP2, 60550 Verneuil-en-Halatte, France

<sup>c</sup> French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Risk Assessment Department, Chemicals Assessment Unit, 947001, Maisons-Alfort, France.

<sup>d</sup> University of Paris-Est, Scientific and Technical Center for Building (CSTB), Health and Comfort Department, French Indoor Air Quality Observatory (OQAI), 84 Avenue Jean Jaurès, Champs-sur-Marne, 77447, Marne-la-Vallée Cedex 2, France.

<sup>e</sup> Univ Rennes, EHESP, INSERM, Research Institute for Environmental and Occupational Health (IRSET) - UMR\_S 1085, F-35000 Rennes, France.

## Abstract

Pyrethroids are commonly used as insecticides in households, in agriculture or in veterinary and medicinal products. This study aimed to assess cumulative aggregate exposure to cyfluthrin, cypermethrin, deltamethrin and permethrin in adults in France and the associated health risk, and to identify major contributions of exposure sources and routes. External chronic exposures were estimated from dietary and several environmental sources for the oral, inhalation and dermal routes. Internal concentrations of five associated metabolites were simulated with a physiologically-based pharmacokinetic model. The predicted urinary concentrations were in same order of magnitude as those of the French ENNS biomonitoring 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.

Aggregate and cumulative chronic risk assessment for pyrethroids in the French adult population

Marie Vanacker<sup>a</sup>, Paul Quindroit<sup>b</sup>, Karine Angeli<sup>c</sup>, Corinne Mandin<sup>d</sup>, Philippe Glorennec<sup>e</sup>, Céline Brochot<sup>b</sup>, Amélie Crépet<sup>a</sup>

<sup>a</sup> French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Risk Assessment Department, Methodology and Studies Unit, 947001, Maisons-Alfort, France.

<sup>b</sup> Institut National de l'Environnement Industriel et des Risques (INERIS), Models for Ecotoxicology and Toxicology Unit, Parc ALATA, BP2, 60550 Verneuil-en-Halatte, France

<sup>c</sup> French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Risk Assessment Department, Chemicals Assessment Unit, 947001, Maisons-Alfort, France.

<sup>d</sup> University of Paris-Est, Scientific and Technical Center for Building (CSTB), Health and Comfort Department, French Indoor Air Quality Observatory (OQAI), 84 Avenue Jean Jaurès, Champs-sur-Marne, 77447, Marne-la-Vallée Cedex 2, France.

<sup>e</sup> Univ Rennes, EHESP, INSERM, Research Institute for Environmental and Occupational Health (IRSET) - UMR\_S 1085, F-35000 Rennes, France.

## Abstract

Pyrethroids are commonly used as insecticides in households, in agriculture or in veterinary and medicinal products. This study aimed to assess cumulative aggregate exposure to cyfluthrin, cypermethrin, deltamethrin and permethrin in adults in France and the associated health risk, and to identify major contributions of exposure sources and routes. External chronic exposures were estimated from dietary and several environmental sources for the oral, inhalation and dermal routes. Internal concentrations of five associated metabolites were simulated with a physiologically-based pharmacokinetic model. The predicted urinary concentrations were in same order of magnitude as those of the French ENNS biomonitoring

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, indoor and 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 null 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

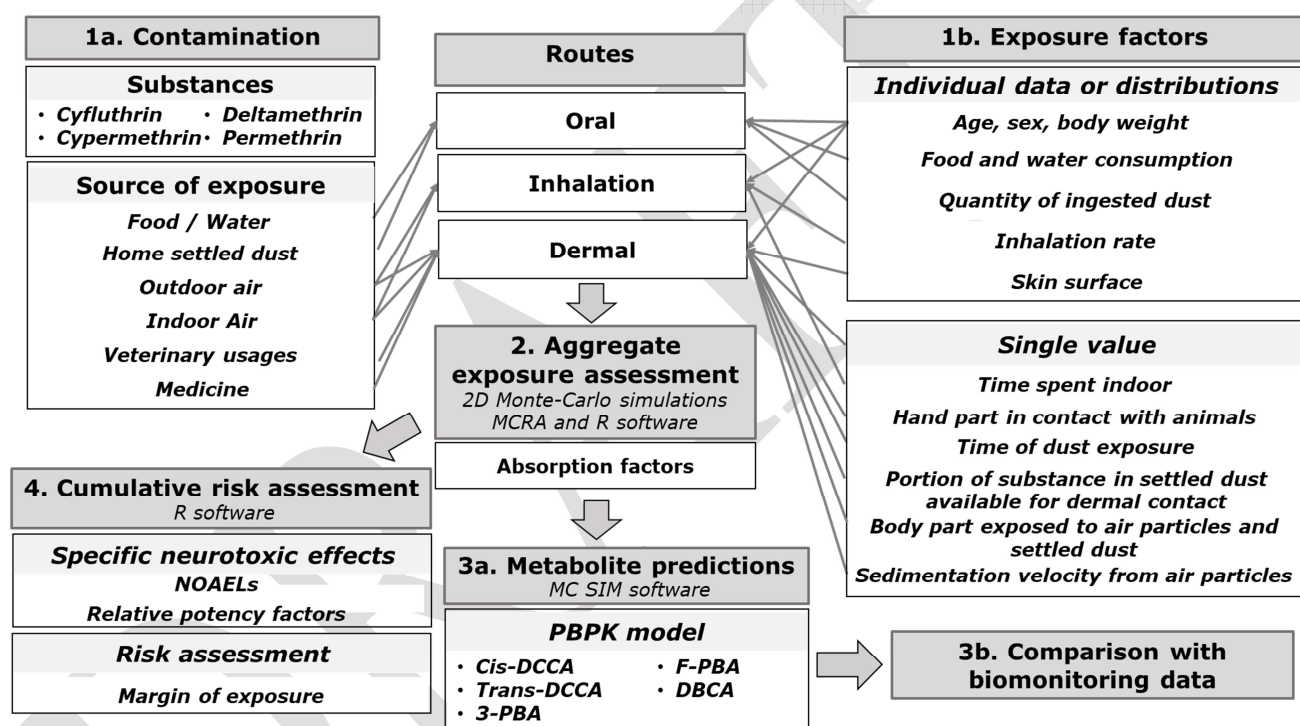
(ANSES, 2019) and present in diet (Darney et al., 2018; Crépet et al., 2019). Cypermethrin and deltamethrin were part of the 15 pesticides which drove the dietary exposure to 144 pesticides with a potential steatosis effect in Europe (Crépet et al., 2019). Moreover, even though its registration was canceled 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,  $C_{\text{food},i}$  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  $C_{\text{dust};i}$  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  $-18\text{ }^{\circ}\text{C}$ . 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  $100\text{ }\mu\text{m}$ . 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  $5.3\text{ ng/g}$  and  $26\text{ ng/g}$  and the LOQs between  $12.3$  and  $66\text{ ng/g}$ . 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  $C_{\text{ind};i}$  ( $\text{ng}/\text{m}^3$ ) were calculated with Eq (1) as the sum of concentrations in the particulate phase ( $\text{PM}_{10;\text{ind};i}$ ) and concentrations in the gas phase ( $\text{Gas}_{\text{ind};i}$ ).

$$C_{\text{ind};i} = \text{PM}_{10;\text{ind};i} + \text{Gas}_{\text{ind};i} \quad \text{Eq (1)}$$

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  $\text{pg/m}^3$ ) and quantified in 54% of samples (LOQ 41.8  $\text{pg/m}^3$ ), 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  $\times$  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  $C_{\text{out},i}$  ( $\text{ng/m}^3$ ) 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  $1.77 \text{ ng/m}^3$  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](http://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 m<sup>2</sup>, the concentration of permethrin considered was 0.867 g/m<sup>2</sup>. 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  $Q_{\text{food}}$  (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  $Q_{\text{dust},j}$  (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  $\text{m}^3/\text{day}$  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  $0.05 \text{ m}^3/\text{MJ}$ , 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):

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

$$\text{BMR}_j = \text{abw}_j + \text{bbs}_j + c \quad \text{Eq (3)}$$

### 2.2.4 Skin surface

The skin surface of the individual  $j$   $S_j$  was estimated directly from INCA2 body weight  $\text{bw}_j$  and body size  $\text{bs}_j$ , with Eq (4) of Dubois and Dubois (1916).

$$S_j = 0.007184 \times \text{bw}_j^{0.425} \times \text{bs}_j^{0.725} \quad \text{Eq (4)}$$

### 2.2.5 Other exposure factors

The time spent in all indoor environments  $T_{\text{ind}}$  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:

$$E_{\text{Aggregate},x} = E_{\text{Oral},ij} \times \text{Abs}_{\text{Oral}} + E_{\text{Inh},ij} \times \text{Abs}_{\text{Inh}} + E_{\text{Cut},ij} \times \text{Abs}_{\text{Cut}} \quad \text{Eq (5)}$$

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  $E_{\text{Oral},ij}$  expressed in ng/kg bw/d was estimated (6) by the addition of the dietary exposure  $E_{\text{Oral}_{\text{Dietary}},ij}$  and the exposure by dust ingestion  $E_{\text{Oral}_{\text{Dust}},ij}$ :

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

### *Dietary exposure*

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

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

where  $C_{\text{food};i}$  is the concentration of the pyrethroid in food  $i$  (ng/g),  $Q_{\text{food};j}$  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  $Q_{\text{dust};j}$  is the quantity of ingested dust (mg/day), and  $C_{\text{dust};i}$  the concentrations in settled dust (ng/g).

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

### *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  $C_{\text{ind};i}$  and outdoor  $C_{\text{out};i}$  (ng/m<sup>3</sup>) air, the time spent indoors  $T_{\text{ind}}$  (%), and the daily inhalation rate  $IR_j$  (m<sup>3</sup>/day).

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

### *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.

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

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.

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

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

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

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

**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 <sup>1</sup>EFSA (2013) and <sup>2</sup>U.S. EPA (2011a).

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

<i>Cyfluthrin</i>			ANSES (2010)	U								0 - 1.6						0.25 (29%)	0.65 (14%)		
<i>Cypermethrin</i>			Blanchard et al. (2014)	U								0 - 0.28							0.2 (3%)		
<i>Deltamethrin</i>	PM10 <sub>ind</sub>	Inhalation /	ANSES (2010)	U								0 - <0.25						0.25 (0%)			
<i>Permethrin</i>		Dermal	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%)	
<b>Concentration in indoor gas phase (ng/m<sup>3</sup>)</b>																					
<i>Cyfluthrin</i>			ANSES (2010)	U															0.25 (29%)	0.65 (14%)	
<i>Cypermethrin</i>			Blanchard et al. (2014)	U																0.6 (0%)	
<i>Deltamethrin</i>	GAS <sub>ind</sub>	Inhalation /	ANSES (2010)	U															0.25 (0%)		
<i>Permethrin</i>		Dermal	Blanchard et al. (2014)	U																0.6 (0%)	
<b>Concentration in outdoor air (gas phase + particles) (ng/m<sup>3</sup>)</b>																					
<i>Cyfluthrin</i>			Regulatory	U																0.071 (7%)	
<i>Cypermethrin</i>		Inhalation	monitoring	U																0.005 (7%)	
<i>Deltamethrin</i>	C <sub>out</sub>	/Dermal	network for air	U																0.016 (0.3%)	
<i>Permethrin</i>			quality	U																0.007 (8%)	0.05 (3%)
<b>Concentration on pets skin after treatment (mg/m<sup>2</sup>)</b>																					
<i>Permethrin</i>	C <sub>animal</sub>	Dermal	ANMV	U																0 - 11,110	
<b>Concentration on human skin after medical treatment (g/m<sup>2</sup>)</b>																					

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

<b>Other factors</b>									
<b>Time spent indoors (%)</b>									
<i>Adult &lt;21 years old</i>	$T_{ins}$	Inhalation / Dermal	U.S. EPA	SV	86.7				
<i>Adult &gt; 21 and &lt; 65 years old</i>			(2011a)	SV	80.5				
<i>Adult &gt; 65 years old</i>				SV	79.3				
<b>Fraction of pyrethroid concentration in home dust available for dermal contact (unitless)</b>									
<b>Quantity of dust adherent to the skin (g/m<sup>2</sup>)</b>	$Mad_{dust}$	Dermal	Beko et al. (2013)	SV	0.15				
<b>Time of home dust exposure (h)</b>			$t_{dust}$	Dermal	Hermant et al. (2017)	SV	24		
<b>Sedimentation velocity from air particles to the skin (m/h)</b>	$vp$	Dermal	Hermant et al. (2017)	SV	2.15				
<b>Fraction of body that is exposed</b>			$f_{skin}$	Dermal	U.S. EPA (2011a)	SV	0.63		
<i>Male</i>				SV	0.67				
<i>Female</i>				SV	0.67				
<b>Time spent for animal care (minutes/day)</b>									
<i>18 to 64 years old</i>	$t_{animal}$	Dermal	U.S. EPA	N	45.9 ± 66.6	1 - 760	30	109	150
<i>&gt; 64 years old</i>			(2011a)	N	54.8 ± 64.5	1 - 383	30	135	180
<b>Mean body surface corresponding to hand size (%)</b>									

<i>&lt; 21 years old</i>				SV	4.5				
<i>Male &gt; 21 years old</i>	$P_{\text{hands}}$	Dermal	U.S. EPA	SV	5.2				
<i>Female &gt; 21 years old</i>			(2011a)	SV	4.8				
<b>Hand surface fraction in contact with animals (unitless)</b>	$f_{\text{hands}}$	Dermal	U.S. EPA	N	0.18	0.02 - 0.27	0.2	0.26	0.26
			(2011a)						
<b>Period of cream application (h)</b>	$t_{\text{scabies}}$	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  $E_{\text{cumulative}}$  was calculated in Eq (15) as the sum of each pyrethroid aggregate exposure multiplied by its RPF:

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

$$\text{with } RPF_x = \text{NOAEL}_{\text{deltamethrin}} / \text{NOAEL}_x \quad \text{Eq (16)}$$

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  $E_{\text{cumulative}}$ :

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

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 RSEspo 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).

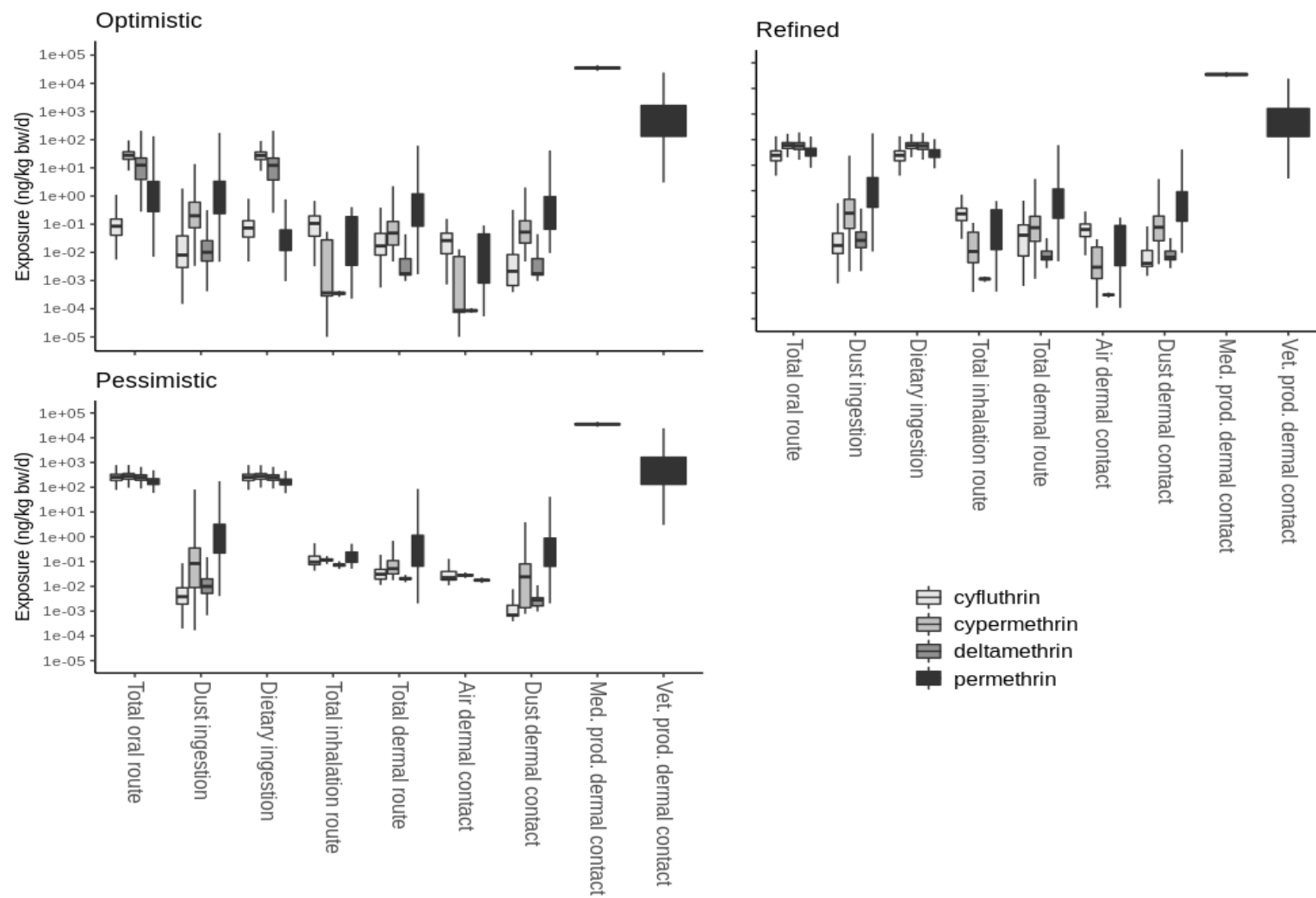
### 3 Results

#### 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 P95<sup>th</sup> 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 P99<sup>th</sup>, 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.

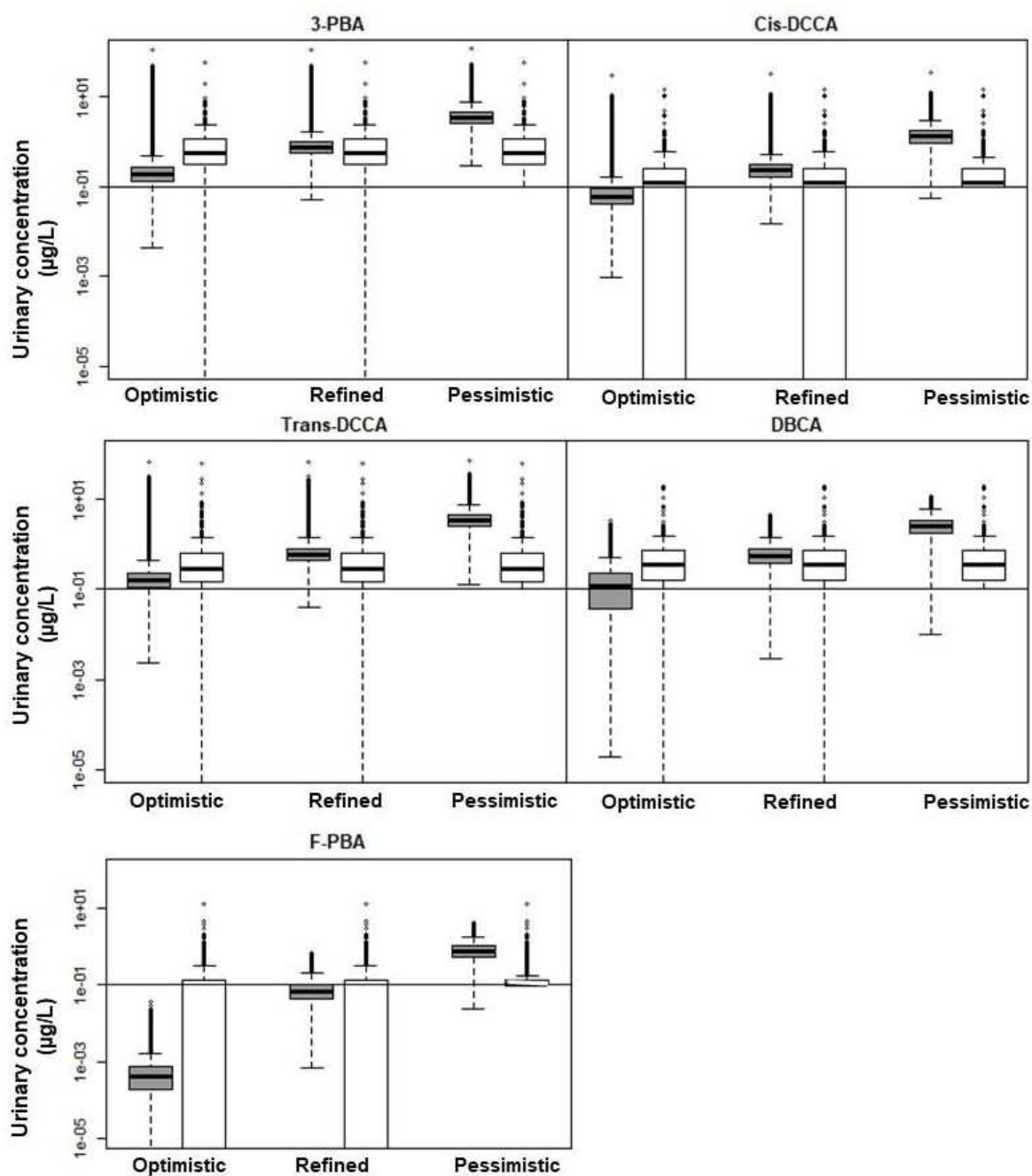


**Figure 2.** Boxplots of exposure (ng/kg bw/d) of the French adult population to pyrethroids according to routes and sources of exposure and to the three censored scenarios

### 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  $\mu\text{g/L}$  for the P5<sup>th</sup>, 0.74  $\mu\text{g/L}$  for the median and 1.5  $\mu\text{g/L}$  for the P95<sup>th</sup>. In comparison, the measured values were 0.14  $\mu\text{g/L}$  for the 5<sup>th</sup> percentile, 0.58  $\mu\text{g/L}$  for the median, and 4.4  $\mu\text{g/L}$  for the P95<sup>th</sup>. 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  $\mu\text{g/L}$  compared to the measured one of 0  $\mu\text{g/L}$  and the predicted P95<sup>th</sup> was 0.18  $\mu\text{g/L}$ , compared to the measured one of 1.09  $\mu\text{g/L}$ .

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 ( $\mu\text{g/L}$ ), according to the censored scenarios. The horizontal black line represents the LOQ of  $0.1 \mu\text{g/L}$  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	<i>cis</i> -DCCA	<i>trans</i> -DCCA	F-PBA
Aggregate exposure	Cyfluthrin	<b>0.624*</b>	0.381	<b>0.676*</b>	<b>0.677*</b>	<b>0.847**</b>
	Cypermethrin	<b>0.602*</b>	0.378	<b>0.632*</b>	<b>0.642*</b>	<b>0.575*</b>
	Deltamethrin	<b>0.634*</b>	<b>0.721**</b>	<b>0.498*</b>	<b>0.507*</b>	<b>0.411*</b>
	Permethrin	<b>0.756**</b>	<b>0.464*</b>	<b>0.670*</b>	<b>0.681*</b>	<b>0.533*</b>
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	<b>0.655*</b>	<b>0.412*</b>	<b>0.703**</b>	<b>0.704**</b>	<b>0.863**</b>
	Cypermethrin	<b>0.622*</b>	<b>0.412*</b>	<b>0.643*</b>	<b>0.654*</b>	<b>0.555*</b>
	Deltamethrin	<b>0.641*</b>	<b>0.746**</b>	<b>0.492*</b>	<b>0.502*</b>	0.376
	Permethrin	<b>0.749*</b>	<b>0.610*</b>	<b>0.668*</b>	<b>0.677*</b>	<b>0.639*</b>
Total oral route	Cyfluthrin	<b>0.624*</b>	0.381	<b>0.676*</b>	<b>0.677*</b>	<b>0.848**</b>
	Cypermethrin	<b>0.602*</b>	0.379	<b>0.633*</b>	<b>0.642*</b>	<b>0.576*</b>
	Deltamethrin	<b>0.634*</b>	<b>0.721**</b>	<b>0.498*</b>	<b>0.507*</b>	<b>0.412*</b>
	Permethrin	<b>0.801**</b>	<b>0.499*</b>	<b>0.711**</b>	<b>0.723*</b>	<b>0.573*</b>
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

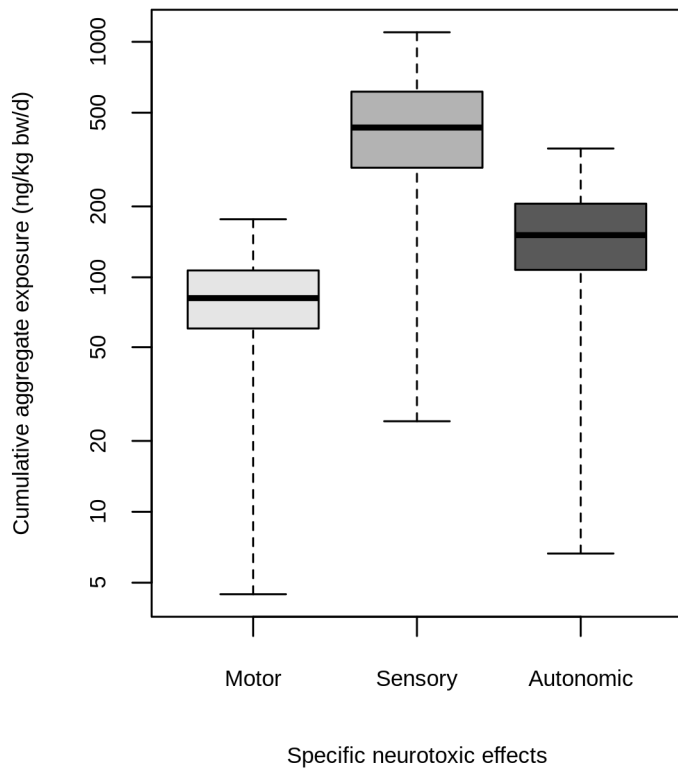
### 3.3 Cumulative aggregate exposure and risk assessment

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/d considering the three specific

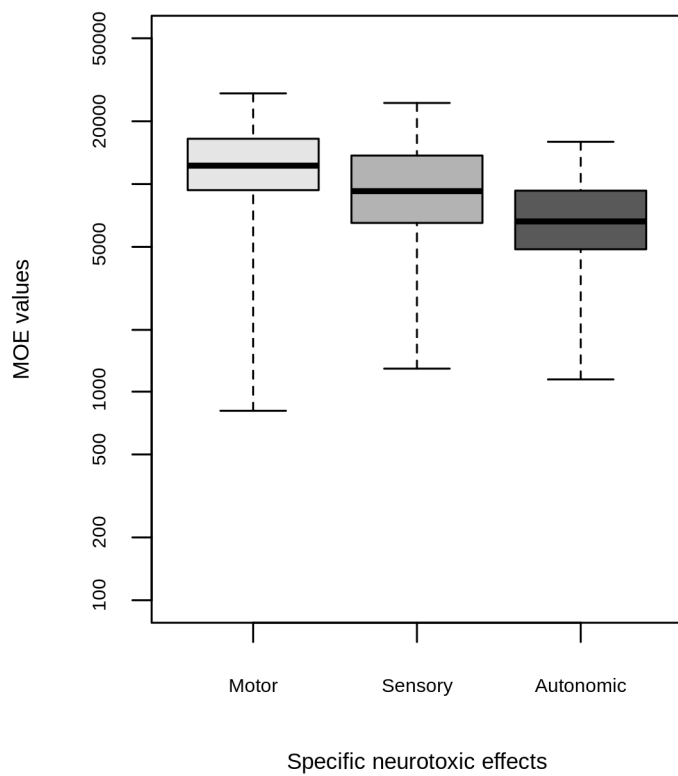
effects (Fig. 4). The individual MOEs estimated from the cumulative aggregate exposure were all higher than 100 for the three censored scenarios and the three specific effects (Fig. 5). The MOEs estimated for the P99.9<sup>th</sup> of the cumulative aggregate exposure with the refined scenario were 995, 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			Mean contribution of the 5% most exposed			Mean contribution of the 1% most exposed		
			individuals*			individuals*			individuals*		
			Motor division	Sensory division	Autonomic division	Motor division	Sensory division	Autonomic division	Motor division	Sensory division	Autonomic division
Cumulative and aggregated exposure	<b>Total Oral route</b>	<b>All substances</b>	<b>98</b>	<b>99</b>	<b>99</b>	<b>89</b>	<b>94</b>	<b>95</b>	<b>58</b>	<b>75</b>	<b>81</b>
	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
	<b>Total Inhalation route</b>	<b>All substances</b>	<b>0.03</b>	<b>0.15</b>	<b>0.11</b>	<b>0.02</b>	<b>0.09</b>	<b>0.07</b>	<b>0.01</b>	<b>0.06</b>	<b>0.05</b>
	<b>Total Dermal route</b>	<b>All substances</b>	<b>1.7</b>	<b>0.91</b>	<b>0.77</b>	<b>11</b>	<b>5.5</b>	<b>4.9</b>	<b>42</b>	<b>25</b>	<b>19</b>
	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
Aggregated exposure	<b>Aggregate exposure</b>	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
	<b>Oral route</b>	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
<b>Inhalation route</b>	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
	Cyfluthrin	0.01	0.05	0.04	0.01	0.03	0.02	0	0.02	0.02
<b>Dermal route</b>	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 be 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.

## 6 Acknowledgments

This study was part of the EuroMix project (No. 633172) funded in the framework of Horizon 2020 (H2020-SFS-2014-21). It has developed approaches and tools for mixture and aggregate risk assessment.

## 7 References

- Air Breizh, 2008. Mesure de pesticides à Mordelles. Résultats de la campagne 2007. Bilan 2005/2006/2007, in: A. Breizh, C. Régional, R. Métropole (Eds.), Rennes, 33p.
- Air Breizh, 2012. Campagne de mesure de pesticides à Mordelles du 7 avril au 20 juillet 2010, in: A. Breizh, C. Régional, R. Métropole (Eds.), Rennes, 29p.
- Air Breizh, 2015. Mesure des pesticides dans l'air à Mordelles - campagne 2014, in: A. Breizh, C. Régional, R. Métropole (Eds.), Rennes, 39p.
- AirPACA, 2015. Observatoire des résidus de pesticides en PACA. 2015 : Résultats. Air PACA Qualité de l'Air, 53p.
- AIRPARIF, 2016. Les pesticides dans l'air francilien - Partie II- Campagne 2013/2014, in: A.-L.O.d.l.a.e. île-de-France (Ed.), Paris, 85p.
- ANSES, 2010. Exposition de la population générale aux résidus de pesticides en France. Synthèse des données d'utilisation, de contamination des milieux et d'imprégnation de la population, in: ANSES (Ed.), Maisons-Alfort, France, 365p.
- ANSES, 2015. Avis de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à la "hiérarchisation des dangers sanitaires toxiques ou présents en France métropolitaine chez les chiens et les chats". ANSES, Maisons-Alfort, 68p.
- ANSES, 2019. Etude Pesti'Home. Enquête nationale sur les utilisations domestiques de pesticides., in: ANSES (Ed.). Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du trava, Maisons-Alfort, 284p.
- ASPA, 2016. Campagne de mesures. Evaluation des produits phytosanitaires dans l'air en Alsace. Année 2015, in: A.p.l.S.e.l.é.d.l.P.A.e. Alsace (Ed.), Schiltigheim, 50p.
- ATSDR, 2003. Toxicological profile for pyrethrins and pyrethroids. Agency for Toxic Substances and Disease Registry  
U.S. Department of Health and Human Services, Atlanta, Georgia, 287p.

- Aylward, L.L., Hays, S.M., Zidek, A., 2017. Variation in urinary spot sample, 24 h samples, and longer-term average urinary concentrations of short-lived environmental chemicals: implications for exposure assessment and reverse dosimetry. *Journal of Exposure Science & Environmental Epidemiology* 27, 582-590, doi: 10.1038/jes.2016.54.
- Becker, K., Seiwert, M., Angerer, J., Kolossa-Gehring, M., Hoppe, H.-W., Ball, M., Schulz, C., Thumulla, J., Seifert, B., 2006. GerES IV Pilot Study: Assessment of the exposure of German children to organophosphorus and pyrethroid pesticides. *International Journal of Hygiene and Environmental Health* 209, 221-233, doi: <https://doi.org/10.1016/j.ijheh.2005.12.002>.
- Béchaux, C., Crépet, A., Cléménçon, S., 2014. Improving Dietary Exposure Models by Imputing Biomonitoring Data through ABC Methods. *The International Journal of Biostatistics* 10, 277-287, doi: <https://doi.org/10.1515/ijb-2013-0062>.
- Beko, G., Weschler, C.J., Langer, S., Callesen, M., Toftum, J., Clausen, G., 2013. Children's phthalate intakes and resultant cumulative exposures estimated from urine compared with estimates from dust ingestion, inhalation and dermal absorption in their homes and daycare centers. *PLoS One* 8, 1-18, doi: 10.1371/journal.pone.0062442.
- Bitar, D., Thiolet, J.-M., Haeghebaert, S., Castor, C., Poujol, I., Coignard, B., Che, D., 2012. Increasing incidence of scabies in France, 1999-2010, and public health implications. *Annales de Dermatologies et de Vénérologie* 139, 428-434, doi: 10.1016/j.annder.2012.01.023.
- Blanchard, O., Glorennec, P., Mercier, F., Bonvallot, N., Chevrier, C., Ramalho, O., Mandin, C., Bot, B.L., 2014. Semivolatile organic compounds in indoor air and settled dust in 30 French dwellings. *Environmental Science and Technology* 48, 3959-3969, doi: 10.1021/es405269q.
- Bois, F.Y., 2009. GNU MCSim: Bayesian statistical inference for SBML-coded systems biology models. *Bioinformatics* 25, 1453-1454, doi: 10.1093/bioinformatics/btp162.
- Bois, F.Y., Brochot, C., 2016. Modeling Pharmacokinetics, in: E. Benfenati (Ed.), *In Silico Methods for Predicting Drug Toxicity*. Springer New York, New York, NY, pp. 37-62.
- Cao, Z., Shafer, T.J., Crofton, K.M., Gennings, C., Murray, T.F., 2011. Additivity of pyrethroid actions on sodium influx in cerebrocortical neurons in primary culture. *Environmental Health Perspectives* 119, 1239-1246, doi: 10.1289/ehp.1003394.
- Clewell, H.J., Tan, Y.M., Campbell, J.L., Andersen, M.E., 2008. Quantitative Interpretation of Human Biomonitoring Data. *Toxicology and Applied Pharmacology* 231, 122-133, doi: <https://doi.org/10.1016/j.taap.2008.04.021>.
- Crépet, A., Vanacker, M., Sprong, C., de Boer, W., Blaznik, U., Kennedy, M., Anagnostopoulos, C., Christodoulou, D.L., Ruprich, J., Rehurkova, I., Domingo, J.L., Hamborg Jensen, B., Metruccio, F., Moretto, A., Jacxsens, L., Spanoghe, P., Senaeve, D., van der Voet, H., van Klaveren, J., 2018. Selecting mixtures on the basis of dietary exposure and hazard data: application to pesticide exposure in the European population in relation to steatosis. *International Journal of Hygiene and Environmental Health*, doi: <https://doi.org/10.1016/j.ijheh.2018.12.002>.
- Darney, K., Bodin, L., Bouchard, M., Cote, J., Volatier, J.L., Desvignes, V., 2018. Aggregate exposure of the adult French population to pyrethroids. *Toxicology and Applied Pharmacology* 351, 21-31, doi: 10.1016/j.taap.2018.05.007.
- DGAL, 2010-2014. National monitoring programs of primary animal and plant production and animal feed (PSPC), <https://agriculture.gouv.fr/plans-de-surveillance-et-de-controle>
- DGCCRF, 2010-2014. National monitoring programs of primary plant production, food of animal and plant origin and animal feed (PSPC), <https://www.economie.gouv.fr/dgccrf/securite/produits-alimentaires>
- DGS, 2010-2014. National monitoring programs on tap and bottled water. <https://www.data.gouv.fr/fr/datasets/resultats-du-controle-sanitaire-de-leau-du-robinet/>

- Dereumeaux, C., Saoudi, A., Gorla, S., Wagner, V., De Crouy-Chanel, P., Pecheux, M., Berat, B., Zaros, C., Guldner, L., 2018. Urinary levels of pyrethroid pesticides and determinants in pregnant French women from the Elfe cohort. *Environment International* 119, 89-99, doi: <https://doi.org/10.1016/j.envint.2018.04.042>.
- Dubois, D., Dubois, E.F., 1916. Nomogramme pour la détermination de la surface cutanée à partir de la taille et du poids. *Archives Internationales de Médecine* 17, 863-871, doi.
- Dubuisson, C., Lioret, S., Touvier, M., Ariane, D., Calamassi-Tran, G., Volatier, J.-L., Lionel, L., 2010. Trends in food and nutritional intakes of French adults from 1999 to 2007: Results from the INCA surveys. *British Journal of Nutrition* 103, 1035-1048, doi: [10.1017/S0007114509992625](https://doi.org/10.1017/S0007114509992625).
- EC, 2000. 2000/817/EC: Commission Decision of 27 December 2000 concerning the non-inclusion of permethrin in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing this active substance (notified under document number C(2000) 4140) (Text with EEA relevance).
- EFSA, 2012. Guidance on the Use of Probabilistic Methodology for modelling Dietary Exposure to Pesticide Residues. *EFSA Journal* 10, doi: [10.2903/j.efsa.2012.2839](https://doi.org/10.2903/j.efsa.2012.2839).
- EFSA, 2013. Scientific opinion on dietary reference values for energy. EFSA panel on dietetic products, nutrition and allergies. *EFSA Journal* 11, 3005, doi.
- EFSA, 2019a. Establishment of cumulative assessment groups of pesticides for their effects on the nervous system. *EFSA Journal* 17, e05800, doi: [10.2903/j.efsa.2019.5800](https://doi.org/10.2903/j.efsa.2019.5800).
- EFSA, 2019b. Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. *EFSA Journal* 17, e05634, doi: [10.2903/j.efsa.2019.5634](https://doi.org/10.2903/j.efsa.2019.5634).
- Fierens, T., Van Holderbeke, M., Standaert, A., Cornelis, C., Brochot, C., Ciffroy, P., Johansson, E., Bierkens, J., 2016. Multimedia & PBPK modelling with MERLIN-Expo versus biomonitoring for assessing Pb exposure of pre-school children in a residential setting. *Science of The Total Environment* 568, 785-793, doi: <https://doi.org/10.1016/j.scitotenv.2016.03.194>.
- Fortes, C., Mastroeni, S., Pilla, M.A., Antonelli, G., Lunghini, L., Aprea, C., 2013. The relation between dietary habits and urinary levels of 3-phenoxybenzoic acid, a pyrethroid metabolite. *Food and Chemical Toxicology* 52, 91-96, doi: <https://doi.org/10.1016/j.fct.2012.10.035>.
- Fox, M.A., Brewer, L.E., Martin, L., 2017. An Overview of Literature Topics Related to Current Concepts, Methods, Tools, and Applications for Cumulative Risk Assessment (2007-2016). *Int J Environ Res Public Health* 14, 389, doi: [10.3390/ijerph14040389](https://doi.org/10.3390/ijerph14040389).
- Fréry, N., Guldner, L., DSaoudi, A., R., G., A., Z., Bidondo, M., 2013. Exposition de la population française aux substances chimiques de l'environnement. Tome 2: Polychlorobiphényles (PCB-NDL) et Pesticides. Insitut de Veille Sanitaire (InVS), Saint-Maurice, 178p.
- Fréry, N., Saoudi, A., Garnier, R., Zeghnoun, A., Falq, G., 2011. Exposition de la population française aux substances chimiques de l'environnement. . Insitut de Veille Sanitaire (InVS), Saint-Maurice, 151p.
- Glennec, P., Serrano, T., Fravallo, M., Warembourg, C., Monfort, C., Cordier, S., Viel, J.F., Le Gleau, F., Le Bot, B., Chevrier, C., 2017. Determinants of children's exposure to pyrethroid insecticides in western France. *Environment International* 104, 76-82, doi: [10.1016/j.envint.2017.04.007](https://doi.org/10.1016/j.envint.2017.04.007).
- Hermant, M., Blanchard, O., Perouel, G., Boulanger, G., Merlo, M., Desvignes, V., 2017. Environmental exposure of the adult French population to permethrin. *Risk Analysis*, doi: [10.1111/risa.12866](https://doi.org/10.1111/risa.12866).

- Jardim, A.N.O., Brito, A.P., van Donkersgoed, G., Boon, P.E., Caldas, E.D., 2018. Dietary cumulative acute risk assessment of organophosphorus, carbamates and pyrethroids insecticides for the Brazilian population. *Food and Chemical Toxicology* 112, 108-117, doi: <https://doi.org/10.1016/j.fct.2017.12.010>.
- Layton, D.W., 1993. Metabolically consistent breathing rates for use in dose assessments. *Health Phys* 64, 23-36, doi: 10.1097/00004032-199301000-00003.
- Li, Z., Nie, J., Lu, Z., Xie, H., Kang, L., Chen, Q., Li, A., Zhao, X., Xu, G., Yan, Z., 2016. Cumulative risk assessment of the exposure to pyrethroids through fruits consumption in China - Based on a 3-year investigation. *Food and Chemical Toxicology* 96, 234-243, doi: 10.1016/j.fct.2016.08.012.
- Lig'Air, 2014. Contamination de l'air par les produits phytosanitaires en région Centre - Année 2013 - Rapport final. Lig'Air, Surveillance de la qualité de l'air en région Centre, Saint-Cyr-En-Val, 36p.
- Lig'Air, 2015. Contamination de l'air par les produits phytosanitaires en région Centre - Val de Loire. Année 2014, in: L.A.-S.d.l.q.d.l.a.e.r. Centre (Ed.), Saint-Cyr-en-Val, 46p.
- Lig'Air, 2016. Contamination de l'air par les produits phytosanitaires en région Centre - Val de Loire. Année 2015, in: L.A.-S.d.l.q.d.l.a.e.r.C.-V.d. Loire (Ed.), Saint-Cyr-en-Val, 43p.
- Lig'Air, 2017. Contamination de l'air par les produits phytosanitaires. région Centre - Val de Loire. Année 2016, in: L.A.S.d.l.q.d.l.a.e.r.C.-V.d. Loire (Ed.), Saint-Cyr-En-Val, 36p.
- Loire, A.P.d.l., 2005. Mesure de produits phytosanitaires en zones viticoles et urbaines de Loire-Atlantique, in: A.P.d.l. Loire (Ed.), Nantes, 37p.
- Loire, A.P.d.l., 2008. Mesures de produits phytosanitaires dans l'air en zone arboricole et en milieu urbain. Campagne de mesure printemps-été 2007, in: A.P.d.l. Loire (Ed.), Nantes, 33p.
- Lu, C., Barr, D.B., Pearson, M., Bartell, S., Bravo, R., 2006. A Longitudinal Approach to Assessing Urban and Suburban Children's Exposure to Pyrethroid Pesticides. *Environmental Health Perspectives* 114, 1419-1423, doi: 10.1289/ehp.9043.
- Lu, C., Barr, D.B., Pearson, M.A., Walker, L.A., Bravo, R., 2009. The attribution of urban and suburban children's exposure to synthetic pyrethroid insecticides: a longitudinal assessment. *Journal Of Exposure Science And Environmental Epidemiology* 19, 69-78, doi: 10.1038/jes.2008.49.
- Mandin, C., Mercier, F., Lucas, J.P., Ramalho, O., Blanchard, O., Bonvallet, N., Raffy, G., Gilles, E., Glorennec, P., Le Bot, B., 2014. ECOS-POUSS: A nationwide survey of semi-volatile organic compounds in home settled dust, Air Conference 2014, July 7-12. International Society of Indoor Air Quality and Climate, Hong-Kong, 143-148.
- Mandin, C., Mercier, F., Ramalho, O., Lucas, J.-P., Gilles, E., Blanchard, O., Bonvallet, N., Glorennec, P., Le Bot, B., 2016. Semi-volatile organic compounds in the particulate phase in dwellings: A nationwide survey in France. *Atmospheric Environment* 136, 82-94, doi: 10.1016/j.atmosenv.2016.04.016.
- Meek, M.E.B., Boobis, A.R., Crofton, K.M., Heinemeyer, G., Van Raaij, M., Vickers, C., 2011. Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. *Regulatory Toxicology and Pharmacology* 60, S1-S14, doi: <https://doi.org/10.1016/j.yrtph.2011.03.010>.
- Mercier, F., Gilles, E., Saramito, G., Glorennec, P., Le Bot, B., 2014. A multi-residue method for the simultaneous analysis in indoor dust of several classes of semi-volatile organic compounds by pressurized liquid extraction and gas chromatography/tandem mass spectrometry. *Journal of Chromatography A* 1336, 101-111, doi: 10.1016/j.chroma.2014.02.004.
- Mercier, F., Glorennec, P., Blanchard, O., Le Bot, B., 2012. Analysis of semi-volatile organic compounds in indoor suspended particulate matter by thermal desorption coupled with gas

- chromatography/mass spectrometry. *Journal of Chromatography A* 1254, 107-114, doi: 10.1016/j.chroma.2012.07.025.
- Morgan, M.K., 2012. Children's exposures to pyrethroid insecticides at home: a review of data collected in published exposure measurement studies conducted in the United States. *Int J Environ Res Public Health* 9, 2964-2985, doi: 10.3390/ijerph9082964.
- Nouvelle-Aquitaine, A., 2017. Mesure des pesticides dans l'air. Campagne 2016, in: A.N.-A.L.o.r.d. l'air (Ed.), Bordeaux, 80p.
- ORAMIP, 2013. Campagne d'évaluation des concentrations en phytosanitaires dans l'air ambiant - 2012 - Commune de Douelle (Lot), in: O.-O.R.d.l.A.e. Midi-Pyrénées (Ed.), Colomiers, 31p.
- ORAMIP, 2014. Campagne d'évaluation des concentrations en phytosanitaires dans l'air ambiant - 2013 - Commune de Douelle (Lot), in: O.-O.R.d.l.A.e. Midi-Pyrénées (Ed.), Colomiers, 25p.
- Özkaynak, H., Xue, J., Zartarian, V.G., Glen, G., Smith, L., 2011. Modeled estimates of soil and dust ingestion rates for children. *Risk Analysis* 31, 592-608, doi: 10.1111/j.1539-6924.2010.01524.x.
- Pas-de-Calais, A.N.-. 2015a. Rapport d'études : Campagne de mesure de la qualité de l'air. Mesure des pesticides en Nord - Pas-de-Calais. Année 2013., in: A.N.-P.-d.-C.P.a.c.é.A.p.l.s.e.l.é.d. l'atmosphère (Ed.), Lille, 45p.
- Pas-de-Calais, A.N.-. 2015b. Rapport d'études : Campagne de mesure de la qualité de l'air. Mesure des pesticides en Nord - Pas-de-Calais. Année 2014., in: A.N.-P.-d.-C.P.a.c.é.A.p.l.s.e.l.é.d. l'atmosphère (Ed.), Lille, 48p.
- Pas-de-Calais, A.N.-. 2016. Rapport d'études : Campagne de mesure de la qualité de l'air. Mesure des pesticides en Nord - Pas-de-Calais. Année 2015., in: A.N.-P.-d.-C.P.a.c.é.A.p.l.s.e.l.é.d. l'atmosphère (Ed.), Lille, 52p.
- Quijano, L., Yus, V., Font, G., Pardo, O., 2016. Chronic cumulative risk assessment of the exposure to organophosphorus, carbamate and pyrethroid and pyrethrin pesticides through fruit and vegetables consumption in the region of Valencia (Spain). *Food and Chemical Toxicology* 89, 39-46, doi: <http://dx.doi.org/10.1016/j.fct.2016.01.004>.
- Quindroit, P., Beaudouin, R., Brochot, C., 2019. Estimating the cumulative human exposures to pyrethroids by combined multi-route PBPK models: Application to the French population. *Toxicology Letters* 312, 125-138, doi: <https://doi.org/10.1016/j.toxlet.2019.05.007>.
- R Core Team, 2017. R: A language and environment for statistical computing., R Foundation for Statistical Computing, Vienna, Austria.
- Ratelle, M., Coté, J., Bouchard, M., 2015. Time profiles and toxicokinetic parameters of key biomarkers of exposure to cypermethrin in orally exposed volunteers compared with previously available kinetic data following permethrin exposure. *Journal of Applied Toxicology* 35, 1586-1593, doi: 10.1002/jat.3124.
- Saillenfait, A.M., Ndiaye, D., Sabate, J.P., 2015. Pyrethroids: exposure and health effects--an update. *International Journal of Hygiene and Environmental Health* 218, 281-292, doi: 10.1016/j.ijheh.2015.01.002.
- Sarigiannis, D.A., Hansen, U., 2012. Considering the cumulative risk of mixtures of chemicals - a challenge for policy makers. *Environ Health* 11 Suppl 1, S18-S18, doi: 10.1186/1476-069X-11-S1-S18.
- Sarigiannis, D.A., Karakitsios, S.P., 2018. Modeling Complex Exposures, in: C.V. Rider, J.E. Simmons (Eds.), *Chemical Mixtures and Combined Chemical and Nonchemical Stressors: Exposure, Toxicity, Analysis, and Risk*. Springer International Publishing, Cham, pp. 81-125.
- Sarigiannis, D.A., Marafante, E., Gotti, A., Reale, G.C., 2009. Reflections on new directions for risk assessment of environmental chemical mixtures. *International Journal of Risk Assessment and Management* 13, 216-241, doi: <https://doi.org/10.1504/IJRAM.2009.030697>.

- Soderlund, D.M., Clark, J.M., Sheets, L.P., Mullin, L.S., Piccirillo, V.J., Sargent, D., Stevens, J.T., Weiner, M.L., 2002. Mechanisms of pyrethroid neurotoxicity: implications for cumulative risk assessment. *Toxicology* 171, 3-59, doi: 10.1016/S0300-483X(01)00569-8.
- Starr, J., Graham, S., Stout, D., 2nd, Andrews, K., Nishioka, M., 2008. Pyrethroid pesticides and their metabolites in vacuum cleaner dust collected from homes and day-care centers. *Environmental Research* 108, 271-279, doi: 10.1016/j.envres.2008.07.022.
- Soderlund, D.M., Clark, J.M., Sheets, L.P., Mullin, L.S., Piccirillo, V.J., Sargent, D., Stevens, J.T., Weiner, M.L., 2002. Mechanisms of pyrethroid neurotoxicity: implications for cumulative risk assessment. *Toxicology* 171, 3-59, doi: 10.1016/S0300-483X(01)00569-8.
- Tornero-Velez, R., Davis, J., Scollon, E.J., Starr, J.M., Setzer, R.W., Goldsmith, M.-R., Chang, D.T., Xue, J., Zartarian, V., De Vito, M.J., Hughes, M.F., 2012. A Pharmacokinetic Model of cis- and trans-Permethrin Disposition in Rats and Humans With Aggregate Exposure Application. *Toxicological Sciences* 130, 33-47, doi: 10.1093/toxsci/kfs236.
- U.S. EPA, 2011a. Exposure Factors Handbook 2011 Edition (final report). U.S. Environmental Protection Agency, Washington, DC, 1436p.
- U.S. EPA, 2011b. Pyrethrins/Pyrethroid cumulative risk assessment. U.S. Environmental Protection Agency; Office of Pesticide Programs, Washington, D.C. 20460, 88.
- Ueyama, J., Saito, I., Kamijima, M., 2010. Analysis and evaluation of pyrethroid exposure in human population based on biological monitoring of urinary pyrethroid metabolites. *Journal of Pesticide Science* 35, 87-98, doi: 10.1584/jpestics.R10-01.
- van der Voet, H., de Boer, W.J., Kruisselbrink, J.W., Goedhart, P.W., van der Heijden, G.W.A.M., Kennedy, M.C., Boon, P.E., van Klaveren, J.D., 2015. The MCRA model for probabilistic single-compound and cumulative risk assessment of pesticides. *Food and Chemical Toxicology* 79, 5-12, doi: 10.1016/j.fct.2014.10.014.
- van Klaveren, J.D., Kruisselbrink, J.W., de Boer, W.J., van Donkersgoed, G., Biesebeek, J.D.t., Sam, M., van der Voet, H., 2019. Cumulative dietary exposure assessment of pesticides that have acute effects on the nervous system using MCRA software. *EFSA Supporting Publications* 16, 1708E, doi: 10.2903/sp.efsa.2019.EN-1708.
- Vanacker, M., Tressou, J., Perouel, G., Glorennec, P., Crepet, A., 2020. Combining data from heterogeneous surveys for aggregate exposure: Application to children exposure to lead in France. *Environmental Research* 182, 109069, doi: 10.1016/j.envres.2019.109069.
- Wei, B., Isukapalli, S.S., Weisel, C.P., 2013. Studying permethrin exposure in flight attendants using a physiologically based pharmacokinetic model. *Journal of Exposure Science & Environmental Epidemiology* 23, 416-427, doi: 10.1038/jes.2013.12.
- Willemin, M.-E., Desmots, S., Le Grand, R., Lestremau, F., Zeman, F.A., Leclerc, E., Moesch, C., Brochot, C., 2016. PBPK modeling of the cis- and trans-permethrin isomers and their major urinary metabolites in rats. *Toxicology and Applied Pharmacology* 294, 65-77, doi: <https://doi.org/10.1016/j.taap.2016.01.011>.
- Willemin, M.E., Kadar, A., de Sousa, G., Leclerc, E., Rahmani, R., Brochot, C., 2015. In vitro human metabolism of permethrin isomers alone or as a mixture and the formation of the major metabolites in cryopreserved primary hepatocytes. *Toxicology in Vitro* 29, 803-812, doi: <https://doi.org/10.1016/j.tiv.2015.03.003>.
- Woollen, B.H., Marsh, J.R., Laird, W.J.D., Lesser, J.E., 1992. The metabolism of cypermethrin in man: differences in urinary metabolite profiles following oral and dermal administration. *Xenobiotica* 22, 983-991, doi: 10.3109/00498259209049904.
- Xue, J., Zartarian, V., Tornero-Velez, R., Tulse, N.S., 2014. EPA's SHEDS-multimedia model: children's cumulative pyrethroid exposure estimates and evaluation against NHANES biomarker data. *Environment International* 73, 304-311, doi: 10.1016/j.envint.2014.08.008.
- Ye, M., Beach, J., Martin, J.W., Senthilselvan, A., 2015. Associations between dietary factors and urinary concentrations of organophosphate and pyrethroid metabolites in a Canadian

general population. *International Journal of Hygiene and Environmental Health* 218, 616-626, doi: <https://doi.org/10.1016/j.ijheh.2015.06.006>.

DRAWN

DRAFT

**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:

A handwritten signature in black ink, appearing to read 'Scrapal', is written over a diagonal line.