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Dietary cumulative acute risk assessment of organophosphorus, carbamates and pyrethroids insecticides for the Brazilian population

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ABSTRACT

Cumulative acute dietary risk assessments of organophosphorus (OPs), carbamates (CBs) and pyrethroids (PYs) were conducted for the Brazilian population. Residue data for 30786 samples of 30 foods were obtained from two national monitoring programs and one University laboratory, and consumption data from a national survey conducted among persons 10 years or older. Acephate and methamidophos were used as index compounds (IC) for OPs, oxamyl for CBs and deltamethrin for PYs. Exposures were estimated using the Monte Carlo Risk Assessment (MCRA 8.2) software. Orange and orange juice (mainly containing methidathion), pasta and salted bread (mainly pirimiphos-methyl) contributed most to the OPs intake. Rice accounted for 80% of the CBs intake (teenagers), mainly due to aldicarb. Pasta, salted bread and beans contributed most to the PYs intake (9–14%), mainly due to bifenthrin. The intake did not exceed the ARfD at the 99.9th percentile for OPs, CBs and PYs, and the risks from the exposure were not considered of health concern. When food consumption data become available for children under age 10, studies in the cumulative exposure should be conducted, as this age group is the most critical among the population, mainly due to their higher food consumption per kg body weight.

1. Introduction

Food consumption is the major source of pesticide exposure for the general population and dietary risk assessment studies are essential to identify exposure scenarios that could pose a potential health concern to humans (IPCS, 2009). Brazil is one of the largest pesticide users worldwide, with 542761 tons of active ingredient used in the country in 2014 (IBAMA, 2017). Results of two national monitoring programs for pesticide residues in food showed that about 50% of the 13556 food samples collected from 2002 to 2010 contained at least one pesticide residue (Jardim and Caldas, 2012).

Among the many classes of pesticides to which humans are exposed to via the diet are the acute neurotoxic insecticides organophosphorus (OPs), carbamates (CBs) and pyrethroids (PYs), which mechanisms of actions to their target organism also occur in human and other mammalians (Casida and Durkin, 2013; Soderlund, 2012). The OPs and CBs inhibit the enzyme acetylcholinesterase (AChE) in the central and peripheral (humans only) nervous systems, by binding to and phosphorylating the AChE (OPs), or by the carbamylation of the serine hydroxyl group in the active site of the enzyme (CBs) (EPA, 2006a, 2007a). The pyrethroids exert their neurotoxic effects by the interaction with the voltage-gated sodium channels (VGSC) leading to delayed repolarization, which is more pronounced in cyano-containing (Type II) pyrethroids than for non-cyano (Type I) pyrethroids (EPA, 2011; Clark and Symington, 2012).

Although human exposure to chemical mixtures has been a concern for decades (EPA, 1986), a cumulative exposure assessment for pesticides mixtures was first conducted by the Environmental Protection Agency of the United States in the beginning of this century (EPA, 2002). Cumulative exposure considers the possibility of simultaneous exposure to a group of compounds that have a common mechanism or mode of action (CMG), such as the organophosphorus, the carbamates and the pyrethroids, through oral (food, water) and/or other exposure pathways (dermal, air) (EPA, 1999; Boobis et al., 2008). The cumulative assessment group (CAG) include the compounds within a CMG for which the exposure assessment is conducted.

The cumulative dietary exposure to pesticides can occur via the consumption of a food portion containing multiple residues (the food was treated with different pesticides from the CMG) and/or different foods that were treated with different pesticide products from the CMG. Dietary exposure to multiple pesticide residues has been the object of various studies around the word (Boon and van Klaveren, 2003; Jensen

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Table 1
Processing factors (PF) applied to organophosphorus (OP), carbamates (CB) and pyrethroids (PY) in the exposure assessment.

Compound	Food-*as*-eaten	PF	Processing	Observation[a]
Bifenthrin (PY)	Wheat bread	0.57	Flour to bread	Median of 10 trials; 2010 JMPR[b]
Carbaryl (CB)	Rice, cooked	0.012	Cooking	Median of 8 trials; Shoeibi et al., 2011; Saka et al., 2008
Carbofuran (CB)	Orange, juice	0.04	Juicing	1 trial
	Lemon, juice	0.04	Juicing	Same as orange
Chlorpyrifos (OP)	Apple and milk	0.01	Juicing	1 trial
	Grape, raisin	0.56	Drying	Mean of 2 trials
	Grape, wine	0.06	Wine making	Median of 8 trials
	Orange, juice	0.006	Juicing	Median of 5 trials
	Lemon, juice	0.006	Juicing	Same as orange
	Tomato sauce	0.54	Sauce/purée	1 trial
Chlorpyrifos-methyl (OP)	Tomato sauce	0.12	Sauce/purée	1 trial
Ethephon (OP)	Grape, raisin	11.63	Drying	1 trial
	Grape, wine	1.2	Wine making	Median of 8 trials
Malathion (OP)	Apple and milk	0.15	Juicing	1 trial
Phosmet (OP)	Apple and milk	0.17	Juicing	Median of 12 trials
	Peach, sweet, canned	0.01	Canned/conserved	1 trial
Pirimicarb (CB)	Rice, cooked	0.64	Cooking	Median of 3 trials; Saka et al., 2008
Pirimiphos- methyl (OP)	Wheat bread	0.65	Flour to bread	Median of 6 trials; EFSA, 2009

[a] BfR, 2016, otherwise indicated.

[b] The JMPR Reports and Evaluations can be found at http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmpr/jmpr-rep/en/.

et al., 2003; Caldas et al., 2006a,b; Boon et al., 2008; Jensen et al., 2003, 2009, 2013; Boon et al., 2015; Li et al., 2016; Blaznik et al., 2016; Quijano et al., 2016; Zentai et al., 2016; Stephenson and Harris, 2016; Li et al., 2017). The probabilistic acute cumulative risk assessment study conducted previously in Brazil for organophosphorus and carbamates had however two major limitations: residue data were only available for nine fruits and vegetables, and consumption was estimated based on the food availability in the household, as no individual consumption data at national level was available at that time (Caldas et al., 2006a).

The objectives of this work were to update the previous cumulative acute dietary risk assessment of organophosphorus and carbamates for the Brazilian population, and to conduct a cumulative acute dietary risk assessment of pyrethroids. Residue data for 30 food commodities and individual consumption data for individuals aged ten years or older were available to estimate the cumulative exposures.

2. Materials and methods

2.1. Residue data and processing factors

Residue data for organophosphorus (OPs), carbamates (CBs) and pyrethroids (PYs) pesticides were provided by the Program on Pesticide Residue Analysis in Food (PARA), coordinated by the National Sanitary Surveillance Agency (ANVISA), the National Residue and Contaminant Control Program (PNCRC), coordinated by Ministry of Agriculture, Livestock and Food Supplies (MAPA), and the Laboratory of Toxicology of the University of Brasilia (LabTox). In total, residue data related to 30786 samples of 30 foods analyzed between 2005 and 2015 were used in this study (food-*as*-analyzed).

Data from the PARA concerned 26420 samples of 25 foods collected randomly (non-target sampling) from 2005 to 2015 at local supermarkets and food distributors by state sanitary surveillance agencies in all 26 Brazilian states and the Federal District (apple, banana, beans, cabbage, carrot, cassava flour, collard green, corn flour, cucumber, grape, guava, lettuce, mango, onion, orange, papaya, pineapple, potato, rice, strawberry, sugar beet, sweet pepper, tomato, wheat flour and zucchini) (ANVISA, 2017a). Data from the PNCRC concerned 4128 samples of 20 foods collected randomly from July 2006 to July 2015 at packing houses and/or food distributors by federal agriculture inspectors in 20 Brazilian states and the Federal Districts (apple, banana, beans, carrot, grape, lemon, lettuce, mango, melon, onion, orange, papaya, peach, pineapple, potato, rice, strawberry, sugar beet, sweet pepper and tomato).

In both monitoring programs, samples were analyzed either by government laboratories (6 in the PARA and 5 in the PNCRC) or private laboratories (2 in the PARA and 4 in the PNCRC), all complying with the ISO-IEC 17025 requirements (ANVISA, 2017a; MAPA, 2017a). The samples were analyzed using multiresidue methods, based on the Mini Luke (the Netherlands, 1996) or the QuEChERS method (Anastassiades et al., 2003), using GC-ECD, GC-MS or LC-MS/MS. In the PARA, the level of reporting (LOR) was the limit of detection (LOD) of the method, which ranged from 0.001 to 0.25 mg/kg. In the PNCRC, the LOR equaled the limit of quantification (LOQ), which ranged from 0.005 to 0.4 mg/kg, but was mostly 0.01 mg/kg. The raw residue data from the PARA and the PNCRC were provided by the program managers for the conduction of this study.

Data from the LabTox, which also comply with ISO-IEC 17025, were related to 238 samples of cashew apple, guava, kaki and peach collected randomly in food stores in the Federal District during the period of 2010–2012. The samples were analyzed using a modified QuEChERS extraction method and quantification by GC-FPD, GC-μECD or LC-MS/MS, with LOQs (LORs) ranging from 0.001 to 0.008 mg/kg (Jardim et al., 2014).

Over 200 pesticide compounds (and metabolites) of various classes were analyzed in the national monitoring programs (PARA and PNCRC) and by the LabTox, of which 177 were detected in at least one of the 30786 samples analyzed.

Processing factor (PFs) for the compound/food/processing combinations were obtained primarily from a PF database of the Federal Institute for Risk Assessment of Germany (BfR, 2016). In this database, only PFs coming from studies classified as acceptable or indicative were considered, and when a PF was reported as below a certain number, that number was taken as the PF. PFs for washing were not considered, as consumption of unwashed foods is likely to occur. Additional PFs were obtained from published data. Table 1 shows the PFs used in this study.

2.2. Food consumption data

Consumption data were obtained from the Brazilian Household Budget Survey (HBS; POF 7) performed by the Brazilian Institute of Statistics and Geography in 2008/2009 (IBGE, 2012), which was the last national survey conducted in the country. The raw public data were exported to Microsoft Access for this study. In this survey, 34003 participants (10–104 years old) recorded their food consumption on two non-consecutive days; 33,991 respondents reported the consumption of at least one of the 184 foods (food-*as*-eaten) that contained one of the foods-*as*-analyzed as an ingredient for which residue data were available. The participants were, on average, 36 years old, weighed on average 64 kg (19.4–150 kg) and 53.8% were female. Information of the composition of food-*as*-eaten (e.g. wheat flour as part of a pizza) were taken from different published sources (Fisberg and Villar, 2002; Araújo and Guerra, 2007; Pinheiro et al., 2004), and the proportions of the food-*as*-analyzed in each food-*as*-eaten are shown in Table S1 (Supplementary material).

2.3. Relative potency factors (RPF)

One way to cumulate the exposure to residues of a CAG is to normalize the residues of each compound present in the food to equivalent residues of an index compound (IC), by applying a relative potency factor (RPF) to each component in relation to the IC, assuming a dose-addition interaction (EPA, 2002; Boobis et al., 2008). In this study, RPFs for OPs and CBs were obtained primarily from the US EPA (2006a; 2007a), which were estimated using benchmark doses (BMD_{10}) associated with a 10% rat brain AChE inhibition using methamidophos and oxamyl as index compounds (IC), respectively. RPFs for OPs were also calculated using acephate as IC and BMD_{10} (female rat) reported by US EPA (2006a). RPF for PYs (types I and II) using deltamethrin as IC were obtained from US EPA (2011), which were estimated using a BMD_{20} associated to the neurotoxicity in rats, indicated by 5 endpoints of a functional observational battery (tremors, clonic convulsion, salivation, mobility and body temperature). RPFs for compounds for which a BMD_{10} (OPs and CBs) or BMD_{20} (PYs) was not available were estimated using the NOAEL (No Observed Adverse Effect Level) from studies with dogs, rats or humans, published by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR), the European Commission (EC) or the European Food Safety Authority (EFSA) (Table S2; Supplementary material). In this study, all compounds belonging to a CGM that were detected in the samples were included in the CAG (Table 2), except those for which toxicological data were not available to estimate a RPF: chlortiofos (1 positive sample), etoprophos (3 samples), heptonofos (1 sample), pirimiphos-ethyl (6 samples), protiophos (11 samples); pyridaphention (1 sample). Table 2 shows the RPFs for the compounds in each CAG as used in this study.

2.4. Modelling acute cumulative exposure assessment

The acute cumulative exposure was calculated using the probabilistic Monte Carlo Risk Assessment (MCRA 8.2) software, developed by Biometris, Wageningen University and Research Centre and the National Institute for Public Health and the Environment (RIVM) (de Boer et al., 2016; Boon and van der Voet, 2015; van der Voet et al., 2015). The exposure was calculated assuming that samples with residues < LOR did not contain the residue, by using a fixed PF value, when available, and without considering unit variability. This approach is in accordance with the optimistic model, a concept introduced in the EFSA guidance on probabilistic modelling (EFSA, 2012) and included in the MCRA model. The acute cumulative exposures for the three CAGs (OPs, CBs and PYs) were estimated by selecting randomly a person-day from the food consumption database. The daily consumption amounts of relevant foods on this specific person-day were multiplied with a randomly selected cumulated residue for those foods. These exposures per food were subsequently summed over the foods, resulting in a daily cumulative acute exposure on that person-day. This was repeated 100,000 times resulting in an acute cumulative exposure distribution for the CAG. The exposures were expressed as the 50^{th}, 90^{th}, 99th and 99.9th percentiles of the intake distribution (P50, P90, P95, P99 and P99.9, respectively).

The uncertainty due to the limited sample size of the residue and food consumption databases was calculated using the empirical bootstrap approach, in which a dataset is resampled with replacement to obtain a resampled set (or bootstrap sample) of the same size as the original. Both databases were resampled 100 times and the resulting 100 food consumption and concentration databases were used to assess the cumulative acute exposure as described above. From the resulting 100 exposure distributions, the 95% confidence intervals, defined by a lower (LL; P2.5) and upper (P97.5) limit (UL), for the different percentiles were calculated. The intakes and uncertainties were assessed for the general population (10–104 years) and teenagers (12–18 years old).

The potential health risks related to the calculated cumulative acute

Table 2
Compounds included in the cumulative assessment groups (organophosphorus, carbamates and pyrethroids) and their respective Relative Potency factors (RPF).

Compound	RPF	Reference[a]
Organophosphorus, IC = acephate/methamidophos		
Acephate	1/0.08	EPA, 2006a,b,c; BMD_{10}
Azinphos-methyl	1.2/0.10	EPA, 2006a,b,c; BMD_{10}
Caduzafos	19.3/2.2	2009 JMPR; NOAEL
Chlorfenvinphos	11.6/1.34	1994 JMPR; NOAEL
Chlorpyrifos	0.67/0.06	EPA, 2006a,b,c; BMD_{10}
Chlorpyrifos-methyl	0.06/0.005	EPA, 2006a,b,c; BMD_{10}
Diazinon	0.16/0.01	EPA, 2006a,b,c; BMD_{10}
Dichlorvos	5.8/0.67	2011 JMPR; NOAEL
Dimethoate	3.96/0.32	EPA, 2006a,b,c; BMD_{10}
Disulfoton	14.1/1.26	EPA, 2006a,b,c; BMD_{10}
Ethion	4.5/1.0	1990 JMPR; NOAEL
Ethephon	0.50/0.06	2002 JMPR; NOAEL
Fenitrothion	0.69/0.083	2007 JMPR; NOAEL
Fenthion	4.1/0.33	EPA, 2006a,b,c; BMD_{10}
Malathion, malaoxon	0.003/0.000	EPA, 2006a,b,c; BMD_{10}
Methamidophos	12.4/1	EPA, 2006a,b,c; BMD_{10}
Methidathion	3.96/0.32	EPA, 2006a,b,c; BMD_{10}
Mevinphos	9.0/0.76	EPA, 2006a,b,c; BMD_{10}
Monocrotophos	41.7/5	1993 JMPR; NOAEL
Omethoate	11/0.93	EPA, 2006a,b,c; BMD_{10}
Parathion-methyl, paraoxon-methyl	1.5/0.12	EPA, 2006a,b,c; BMD_{10}
Parathion-ethyl	12/0.3	1995 JMPR; NOAEL
Phenthoate	0.25/0.1	1984 JMPR; NOAEL
Phorate	4.7/0.39	EPA, 2006a,b,c; BMD_{10}
Phosalone	0.14/0.01	EPA, 2006a,b,c; BMD_{10}
Phosmet	0.28/0.02	EPA, 2006a,b,c; BMD_{10}
Pirimiphos-methyl	0.44/0.04	EPA, 2006a,b,c; BMD_{10}
Profenofos	0.05/0.004	EPA, 2006a,b,c; BMD_{10}
Pyrazophos	0.10/0.040	1992 JMPR; NOAEL
Triazophos	20/2.4	2002 JMPR; NOAEL
Trichlorfon	0.03/0.003	EPA, 2006a,b,c; BMD_{10}
Carbamates, IC = oxamyl		
Oxamyl	1	EPA, 2007a; BMD_{10}
Aldicarb	4	EPA, 2007a; BMD_{10}
Carbaryl	0.15	EPA, 2007a; BMD_{10}
Carbofuran	2.4	EPA, 2007a; BMD_{10}
Carbosulfan	0.2	2004 JMPR; NOAEL
Methiocarb	0.18	EPA, 2007a; BMD_{10}
Methomyl	0.67	EPA, 2007a; BMD_{10}
Pirimicarb	0.02	EPA, 2007a; BMD_{10}
Propamocarb	0.000	2005 JMPR; NOAEL
Pyrethroids, IC = deltamethrin		
Deltamethrin	1	EPA, 2011; BMD_{20}
Alethrin	0.11	EPA, 2011; BMD_{20}
Beta-cyfluthrin	1.15	EPA, 2011; BMD_{20}
Beta-cypermethrin	0.19	EPA, 2011; BMD_{20}
Bifenthrin	1.01	EPA, 2011; BMD_{20}
Cyflutrin	1.15	EPA, 2011; BMD_{20}
Cypermethrin	0.19	EPA, 2011; BMD_{20}
Etofenprox	0.002	EFSA, 2008; NOAEL
Esfenvalerate + fenvalerate	0.36	EPA, 2011; BMD_{20}
Fenpropathrin	0.5	EPA, 2011; BMD_{20}
Lambda-cyalothrin	1.63	EPA, 2011; BMD_{20}
Permethrin	0.09	EPA, 2011; BMD_{20}

IC = index compound.

[a] The JMPR Toxicological Evaluations can be found at http://www.who.int/foodsafety/publications/jmpr-monographs/en/.

exposures were estimated by comparing each percentile with the ARfD of the ICs. In this study, the lowest ARfD among those published by the US EPA, EC/EFSA and JMPR were used: 5 μg/kg bw for acephate (EPA, 2006b), 1 μg/kg bw for methamidophos (EPA, 2006c) and 1 μg/kg bw for oxamyl (EPA, 2007b), all based on brain and plasma cholinesterase inhibition in rats, and 10 μg/kg bw for deltamethrin, based on neurological effects in rats (EC, 2002).

3. Results

3.1. *Pesticide residues*

Table 3 summarizes the residue data obtained by the national monitoring programs and the LabTox. About 60% of the samples were positive (≥LOR) for at least one of the compounds (18533 samples), with over 80% of sweet pepper, apple, papaya, grape, strawberry, peach, zucchini and tomato samples containing one of the pesticides analyzed. In total, 38 OP compounds, 10 CB compounds, and 14 PY compounds were detected in the samples. OP residues were detected in all foods analyzed, and in 40.2% of the 18533 positive samples, mainly corn flour, wheat flour, onion and potato (> 70%) (Table 3). CB residues were present mainly in sweet pepper (29.2%) and orange (19.9%), and those of PYs (17.1% of positive samples) were found mainly in sweet pepper and kaki (> 50% of positive samples) (Table 3).

Chlorpyriphos, acephate and methamidophos were the most detected OP compounds, methomyl the most detected CB compound and lambda-cyalothrin the most detected PY compound (Fig. 1). Multiple residues (2 or more) of OP compounds were found in 30.3% of the positive samples for this class, mostly with 2 residues (76%), with samples containing up to 7 residues. Only melon and banana did not have multiple OP residues. About 3% of all samples with a positive CB concentration contained 2 residues of this class, mainly tomato (19.7% of tomato positive CB samples) and collard green (16.7%). About 20% of the positive PY samples contained multiple residues of this class (up to 5 residues), mainly sweet pepper and tomato (34% of the PY positive samples each). All three pesticide classes were present simultaneously in 3% of all positive samples.

3.2. *Consumption data*

The 30 foods-*as*-analyzed for which residue data were available can

Table 3
Summary of the pesticide residue data (2005–2015) obtained by the Program on Pesticide Residue Analysis in Food (PARA), the National Residue and Contaminant Control Program (PNCRC) and the Laboratory of Toxicology of the University of Brasilia (LabTox), Brazil.

Food	Total	Positives samples, %[a]	Positive for OP, %[b]	Positive for CB, %[b]	Positive for PY, %[b]
Apple[c,d]	3175	88.8	59.4	3.7	3.5
Banana[c,d]	1170	18.9	4.1	8.1	5.4
Bean[c,d]	1570	71.5	15.0	2.0	2.5
Cabbage[c]	908	23.1	48.1	2.9	3.8
Carrot[c,d]	1655	57.2	45.0	5.8	1.2
Cashew apple [e]	43	27.9	33.3	0	25
Cassava flour[c]	470	3.2	66.7	13.3	26.7
Collard green[c]	529	45.4	25.8	2.5	42.1
Corn flour[c]	729	46.9	99.1	0.6	0.6
Cucumber[c]	1253	60.4	40.4	11.6	12.4
Grape[c,d]	989	87.7	30.3	2.0	10.8
Guava[c,e]	464	55.2	62.1	5.1	13.7
Kaki[e]	67	76.1	35.3	0	62.7
Lemon[d]	69	62.3	18.6	2.3	4.7
Lettuce[c,d]	1483	40.5	19.3	5.5	19.5
Mango[c,d]	784	40.9	10.9	0.6	5.3
Melon[d]	55	29.1	25	0	18.8
Onion[c,d]	936	11.8	73.6	4.5	0
Orange[c,d]	1899	65.2	60.2	19.9	34.7
Papaya[c,d]	2681	88.8	3.9	1.6	14.8
Peach[d,e]	96	82.3	57.0	1.3	40.5
Pineapple[c,d]	934	53.2	30.4	3.0	21.7
Potato[c,d]	1700	35.8	72.6	2	0
Rice, polished[c,d]	1800	38.6	34.7	5.3	12.2
Strawberry[c,d]	1178	86.2	18.9	2.1	33.2
Sugar beet[c,d]	602	39.2	41.5	0.4	10.6
Sweet pepper[c,d]	981	93.8	65.3	29.2	57.0
Tomato[c,d]	1844	80.6	51.9	4.8	33.9
Wheat flour[c]	506	51.0	78.3	0.8	43.8
Zucchini[c]	216	81.0	54.9	12	0
Total	**30786**	**60.2**	**40.2**	**5.5**	**17.1**

[a] Samples that contained at least one pesticide investigated at a level at or above the limit of reporting (LOR).
[b] Related to the positive samples.
[c] Analyzed by the PARA.
[d] Analyzed by the PNCRC.
[e] Analyzed by the LabTox.

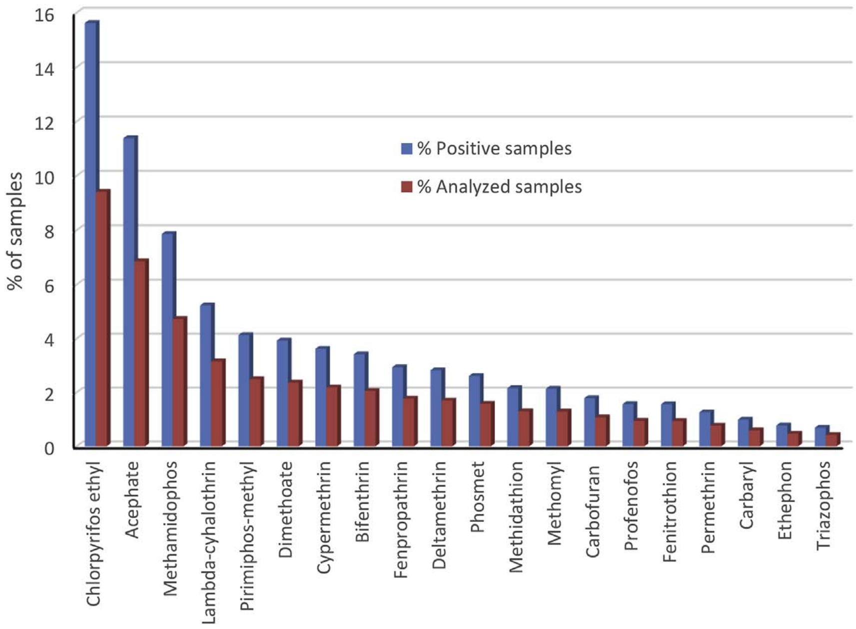


Fig. 1. Most detected organophosphorus, carbamates and pyrethroids pesticides by the Program on Pesticide Residue Analysis in Food (PARA), the National Residue and Contaminant Control Program (PNCRC) and the Laboratory of Toxicology of the University of Brasilia, Brazil, between 2005 and 2015. Analyzed samples: all 30786 samples analyzed; Positive samples: samples that contained at least one pesticide investigated at a level equal or above the limit of reporting (LOR).

Table 4
Summary of Brazilian individual consumption data, obtained from the Brazilian Household Budget Survey (2008/2009 HBS) with individuals from 10 to 104 years old.

Food (number of foods-*as*-eaten[a])	Consumption days, %	Grams/consumption days, mean[b]	Main food-*as*-eaten
Apple (2)	5.8	169	Apple
Banana (7)	15.5	119	Banana
Bean (17)	74.9	241	Cooked
Cabbage (4)	1.5	52.7	Cabbage
Carrot (6)	4.3	33.7	Carrot
Cashew apple (4)	1.4	116	Cashew apple juice
Cassava flour (5)	17.8	71.9	Cassava flour
Collard green (3)	1.6	52.8	Cooked
Corn flour (5)	13.7	137	Couscous
Cucumber (2)	0.9	51.9	Cucumber
Grape (3)	1.2	292	Grape
Guava (3)	3.1	118	Guava juice
Kaki (1)	0.2	139	Kaki
Lemon (2)	1.3	63.5	Lemon juice
Lettuce (1)	7.0	38.7	Lettuce
Mango (2)	3.7	193	Mango
Melon (2)	0.5	132	Melon
Onion (3)	0.6	27.9	Cooked
Orange (8)	14.1	298	Orange juice
Papaya (3)	3.0	210	Papaya
Peach (4)	0.4	132	Peach
Pineapple (2)	3.2	143	Pineapple juice
Potato (9)	10.0	96.1	Cooked otato
Rice[c] (22)	87.9	195	Rice
Strawberry (3)	0.6	140	Strawberry juice
Sugar beet (5)	1.1	52.8	Sugar beet
Sweet pepper (2)	0.1	38.5	Sweet pepper
Tomato (6)	8.8	70.0	Tomato
Wheat flour (70)	80.0	271	Salted bread[d]
Zuchinni (2)	0.9	96.3	Cooked

[a] The foods-*as*-eaten are listed in Table S1 (Supplemental Material).
[b] Mean consumption of the person-days at which the consumption of the food was reported.
[c] Include polished, parboiled and bran.
[d] Reported as *pão de sal*.

be consumed as 184 foods-*as*-eaten in Brazil, including most of the foods-*as*-analyzed themselves (Table S1, Supplemental material).

Table 4 summarizes the consumption data for the Brazilian population, aged 10 years or older. Rice was the food most reported by the participants (87.9% of consumption days), mainly reported as such, with a mean consumption of 195 g/day (consumption days only). Consumption of wheat flour preparations (70 preparations) was the second most frequently reported (80% of consumption days), with a mean of 271 g/day, mainly as salted bread (plain white flour bread, reported as *pão de sal*). Consumption of beans, which forms the basis of most of the Brazilian daily meals together with rice, including 16 bean preparations, was reported on about 75% of the consumption days (241 g/day). Of the fruits, banana and orange were the most reported (15.5 and 14.1%), with orange being the fruit with the highest mean consumption (298 g/day), mainly as juice. Grape had the second highest mean consumption (292 g/day), although it was rarely reported (1.2%); no consumption of grape juice was reported in the database. Corn flour and cassava flour were reported in 13.7 and 17.8% of the consumption days, respectively, and tomato, the most reported among the vegetables, in 8.8% of the consumption days (70 g/day).

3.3. Acute cumulative exposure and risk assessment

The mean intakes and the upper limit of the 95% confidence interval (UL) at P50 were 0 μg/kg bw per day for all CAGs. Table 5 shows therefore the cumulative intakes at percentiles equal to or higher than P95, and the corresponding percentage of the ARfD of the respective ICs. Highest exposures were calculated for the OPs with acephate as IC, reaching 1.8 μg/kg bw per day in the general population at the P99.9 of exposure. Considering the uncertainty in the sample size of the databases, the ULs of this percentile were 2.95, 0.265 and 0.354 μg/kg bw per day for OPs, CBs and PYs, respectively; all in teenagers.

Fig. 2 shows the foods-*as*-eaten that contributed most to the cumulative acute intake of OP at the upper 2.5% tail of the intake distribution. When acephate was used as IC (Fig. 2A), orange and orange juice were the main contributors to the exposure for the general population (37% of the total intake), and orange juice and salted bread (*pão de sal*) the main contributors for teenagers (30% of the total intake). Similar results were found with methamidophos as IC (Fig. 2B). The compounds contributing most to the OP acute cumulative exposure (20–30%) were pirimiphos-methyl in wheat flour and methidathion in orange, both for the general population and teenagers, using either IC (Fig. 2).

The consumption of rice accounted for 62 and 80% of the cumulative intake of CBs at the upper 2.5% tail of the exposure distribution for general population and teenagers, respectively, mainly due to the presence of aldicarb (59.9 and 78.8%, respectively) (Fig. 3A). Carbofuran was a driver for the CB cumulative intake via the consumption of orange and orange products. No foods contributed more than 15% to the total cumulative intake of PYs, with pasta, salted bread and beans being the main foods (9–14%). The intake of PYs was mainly driven by the presence of bifenthrin in wheat flour and beans (Fig. 3B).

The percentages of ARfD of the cumulative acute intake of OPs were below 100 at all percentiles, but were higher with acephate as IC (up to 33% of the ARfD; Table 5). The cumulative acute intakes for CBs and PYs were also below the ARfDs, reaching 17% of the oxamyl ARfD and 3% of the deltamethrin ARfD at the P99.9 for teenagers (Table 5).

4. Discussions

4.1. Pesticide residue and food consumption data

Chlorpyriphos, methamidophos, dimethoate and acephate were the organophosphorus (OPs) compounds most detected in the PARA program from 2001 to 2004 (4001 samples; Caldas et al., 2006a). They were also the main OPs found in the current data, which included a much larger residue dataset (30786 samples).

In addition to a larger residue dataset, this study included residue data for 30 foods, much more than in the previous study in which only 9 fruits and vegetables were included (Caldas et al., 2006a). Most important was the inclusion of residue data for rice, beans and wheat flour, which are part of 109 of the 184 Brazilian foods-*as*-eaten considered in this study, and their consumption was reported by most individuals in the consumption survey. About 48% of the rice samples, almost all of the wheat flour samples (98.8%) and 17.5% of the bean samples were positive for at least one pesticide relevant for this study. Furthermore, samples of rice, beans and wheat flour had multiple residues of OPs (4.6, 24.3 and 16.8% of positive samples for this CAG, respectively), and while bean samples had no multiple residues of PYs, two samples contained 2 CB residues.

There were many individuals in the consumption survey that reported the consumption of unspecified foods, which could not be considered in this study. For example, there were 17 different descriptions of unspecified fruits and vegetables, reported at least once by most of the surveyed individuals (52.1%), and in 37.7% of the surveyed days, mainly raw vegetables, juice, vegetable soup and cooked vegetables. This limitation of the food consumption data will be discussed later.

4.2. Dietary cumulative acute exposure

Cumulative acute exposure to pesticides was first conducted by US EPA, which defined the OPs as a CMG, established the CAG and methamidophos as the index compound (EPA, 2002). In 2005, the US EPA

Table 5
Percentiles of acute cumulative exposure (intake, µg/kg bw/day) to organophosphorus. Carbamates and pyrethroid pesticides in the Brazilian population.

Percentile	Organophosphorus				Carbamates		Pyrethroids	
	Acephate (ARfD = 5 µg/kg bw/day[a])		Methamidophos (ARfD = 1 µg/kg bw/day[b])		Oxamyl (ARfD = 1 µg/kg bw/day[c])		Deltamethrin (ARfD = 10 µg/kg bw/day[d])	
	Intake (CI)	%ARfD[e], mean/UL	Intake (CI)	%ARfD[e], mean/UL	Intake (CI)	%ARfD[e], mean/UL	Intake (CI)	%ARfD[e] mean/UL
General population (10 to 104 years)								
95	0.000 (0.000–0.000)	0/0	0.000 (0.000–0.000)	0/0	0.000 (0.000–0.000)	0/0	0.000 (0.000–0.002)	0/0
99	0.129 (0.096–0.140)	3/3	0.012 (0.009–0.012)	12/12	0.000 (0.000–0.000)	0/0	0.035 (0.026–0.040)	0.4/0.4
99.9	1.80 (1.33–2.18)	36/44	0.162 (0.116–0.191)	16/19	0.090 (0.069–0.150)	9/15	0.228 (0.168–0.270)	2/3
Teenagers (12 to 18 years)								
95	0.000 (0.000–0.000)	0/0	0.000 (0.000–0.000)	0/0	0.000 (0.000–0.000)	0/0	0.001 (0.000–0.002)	0/0
99	0.131 (0.099–0.188)	3/4	0.012 (0.009–0.017)	12/17	0.000 (0.000–0.000)	0/0	0.042 (0.028–0.052)	0.4/0.5
99.9	1.64 (1.12–2.95)	33/59	0.151 (0.099–0.252)	15/25	0.174 (0.131–0.265)	17/26	0.274 (0.177–0.354)	3/4

CI = lower (LL, 2.5%) - upper (UL, 97.5%) limits at 95% confidence interval.

[a] EPA, 2006b.

[b] EPA, 2006c.

[c] EPA, 2007a.

[d] EC, 2002.

[e] Rounded to 2 significant figures.

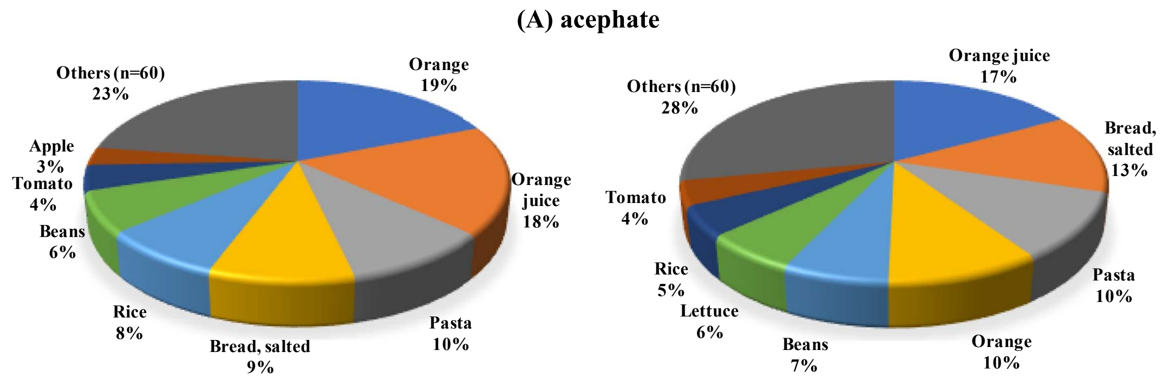
published its first cumulative assessment for CBs, with oxamyl as IC (EPA, 2007a), and more recently the cumulative assessment of PYs (EPA, 2011). Currently, only the United States include cumulative exposure assessments in the pesticide registration process (aggregate and probabilistic; EPA, 2016), but many research groups conducted these studies worldwide using different approaches and ICs.

Boon and van Klaveren (2003) used acephate or phosmet as IC for the combined probabilistic cumulative acute exposure to OPs and CBs for the Dutch population. This combined approach was also used by Jensen et al. (2003, 2009) in Denmark (chlorpyriphos or methamidophos as IC), using a deterministic and probabilistic models, respectively, by our research group using the MCRA software for the Brazilian population (acephate or methamidophos as IC (Caldas et al., 2006a), and more recently by Blaznik et al. (2016) in Slovenia (acephate as IC) and by Li et al. (2017) in China (chlorpyriphos or methamidophos as IC), both using the MCRA software. However, although exposure to OPs and CBs leads to a common neurotoxic effect (inhibition of AChE), they are not structurally related and have a dissimilar mechanism of action, the first group acting as a phosphorylating agent, and the latter as a carbamylating agent of the enzyme (EPA, 2006a, 2007a). As an additive effect is assumed in the cumulative exposure assessment when using the RPF approach to cumulate concentrations of compounds belonging to a CAG per sample, considering the AChE inhibitors (OPs and CBs) combined in a single CAG may overestimate the cumulative exposure and result in unrealistic risk estimations. In the present study, OPs and CBs were therefore considered as separate CAGs, following the approach proposed by the US EPA (2006a; 2007a), and similar as used in Boon et al. (2008).

An important decision to be made when conducting a chemical exposure assessment to chemicals is how to treat the censored data, which are concentrations reported as below the LOR. When estimating the exposure to a single compound, a common approach is to replace the censored data for a value equal or ½ LOR (EPA, 2000), to demonstrate worst case situations. However, in cumulative exposure assessment this approach would imply multiple simultaneous worst cases situations that do not occur in real life, mainly for chemicals with a large proportion of samples < LOR, which is the case of many pesticide/food combinations. Indeed, Boon et al. (2015) tested the two EFSA (European Food Safety Agency) models to perform probabilistic exposure assessments of pesticides, the "pessimistic" (censored data are equal to the LOR for registered pesticides) and the "optimistic" (censored data equal to 0 mg/kg) model, as used in the present study. The authors concluded that the pessimistic model was over-conservative and indicated the need to develop an intermediate approach that could reflect a more realistic estimation, keeping a certain degree of conservativism. On the other hand, the US EPA (2007a) showed that replacing censored data by a value different from 0 mg/kg had little impact on the upper end of the cumulative CB exposure distribution, which was mainly driven by the consumers with a high consumption of foods containing high cumulative pesticide levels.

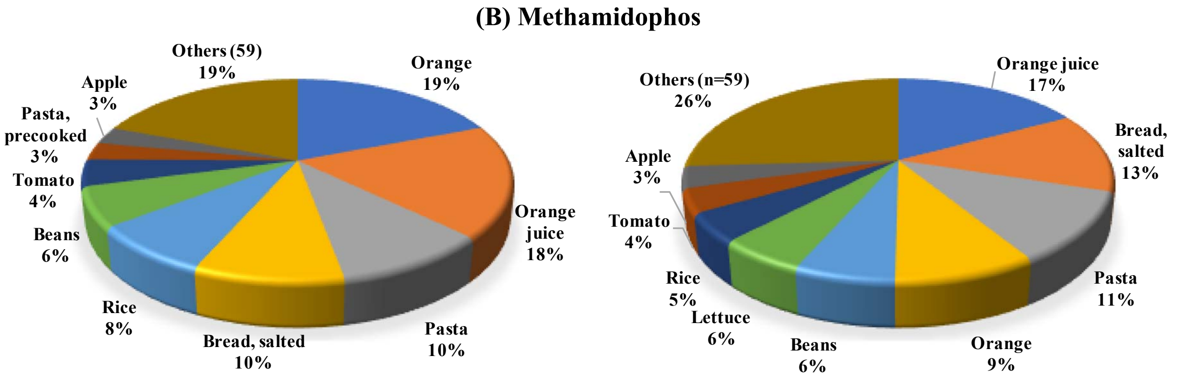
The Brazilian pesticide monitoring programs, as other programs worldwide (EFSA, 2016; Australia, 2017), analyze foods as they are commercialized or traded, as the main purpose is to monitor compliance with good agricultural practices, i.e., the maximum residue level (MRL). Often, the foods to which the MRL applies are not consumed as such, but after processing (Scholz et al., 2017). For most pesticides, food processing decreases the residue levels in the food, mainly through thermal degradation during cooking, dilution (juicing) or removal of inedible peels. Hence, whenever available, a processing factor (PF) should be applied to the residue data to optimize the exposure assessment. In this study, PFs were taken primarily from the BfR database, and were supplemented with data from other sources for wheat flour products and cooked rice, which were important food drivers in the assessments. For the OPs, about 60% of the cumulative intake (upper 2.5% tail) was driven by the presence of methidathion in orange and pirimiphos-methyl in wheat flour. PFs for pirimiphos-methyl/wheat flour→cooked pasta and methidathion/orange→peeling or juicing were however not available. Yet, the application of a PF for pirimiphos-methyl/wheat flour→bread (0.65) and other PFs for OPs had an insignificant impact on the cumulative intake for either population or IC (< 1%; data not shown).

Aldicarb in rice and carbofuran in orange were the main compound/food combinations driving the intake at the 2.5% upper tail of the intake distribution for CBs. The application of a PF for carbofuran/orange →juice (0.04) had an important impact on the intakes at the P99.9 (reduction of about 48%; data not shown). No PF for aldicarb/rice→



General population (≥ 10 years)
Main driving compounds:
Methidathion in orange - 29.1%
Pirimiphos methyl in wheat flour - 21.3%

Teenagers (12 to 18 years)
Main driving compounds:
Methidathion in orange - 21.6%
Pirimiphos methyl in wheat flour - 29.0%



General population (≥ 10 years)
Main driving compounds:
Methidation in orange – 26.3%
Pirimiphos-methyl in wheat flour – 21.6%

Teenagers (12 to 18 years)
Main driving compounds:
Methidation in orange – 19.8%
Pirimiphos-methyl in wheat flour – 29.9%

Fig. 2. The foods-*as*-eaten that contributed most to the cumulative intake (upper 2.5% of the intake distribution) of organophosphorus compounds, expressed as percentage of the total intake, using acephate (A) or methamidophos (B) as index compounds. The main risk driver compounds are also shown.

cooked rice was available to refine the intake. Aldicarb and carbosulfan also had the highest estimated RPF among the compounds belonging to the CB CAG (4 and 2.4, respectively; Table 1). It is important to point out, however, that aldicarb was detected only in two of the 1800 rice samples analyzed, at concentrations of 0.03 and 2.2 mg/kg, collected in 2009 and 2011, respectively, in addition to 17 other food samples (up to 0.01 mg/kg) collected from 2009 to 2015. Although this compound is still authorized for use in coffee, sugar cane and citrus as soil application (ANVISA, 2017b), currently no aldicarb product is commercialized in Brazil (MAPA, 2017b).

The application of a PF for bifenthrin/wheat flour→bread had an insignificant impact on the cumulative intake of PYs (data not shown).

4.3. *Risk characterization of the cumulative acute exposure*

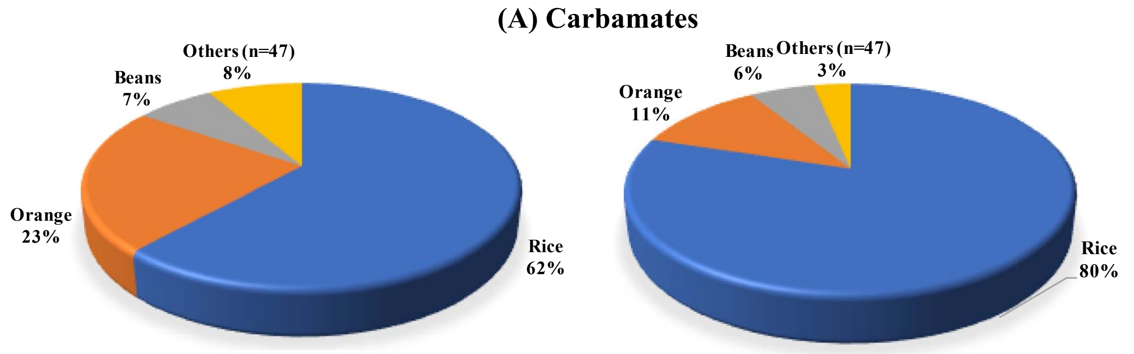
The current assessment is much more refined than the previous work conducted in Brazil (Caldas et al., 2006a), which showed a possible risk for a combined OPs and CBs acute exposure at the UL of the confidence interval of the P99.9, using residue data for only 9 foods (did not include rice or wheat flour) and household food availability data for food consumption. In the present study, no risks were identified for OPs or CBs even at the UL of the confidence interval of the P99.9.

Boon at al. (2008) found a possible risk at the P99.9 of cumulative acute exposure to OPs and CBs for 1–6 year old Dutch children (ARfD of 50 and 9 μg/kg bw for acephate and oxamyl, respectively), mainly from the consumption of spinach and apple (concentration values < LOR considered as 0, unit variability and PF as distributions). In China (Li et al., 2017), a potential for the combined exposure to OPs and CBs exceeding the ARfD of methamidophos (3 μg kg bw) was only found using the pessimistic approach of EFSA (2012) as implemented in the MCRA software, for preschool children (0.029%), school-age children (0.022%) and adults (0.002%). Zentai et al. (2016), using a statistical model and only measured residues, found that the 99.95% of the cumulative organophosphorus intake was below the acephate ARfD of 100 mg/kg bw, indicating no risk to the Hungarian population. The US EPA estimated that the probabilistic dietary cumulative exposures at P99.9 to OPs (metamidophos as IC; EPA, 2006a) or CBs (EPA, 2007a) did not exceed the Agency's level of concern for the American population (margin of exposure, MOE, higher than 100 at P99.9).

In the present study, no risks were found for the Brazilian population from the cumulative acute exposure to PYs, similar to the conclusion for PYs in USA (EPA, 2011; MOE > 100 at P99.9). To the best of our knowledge, no other study evaluated the cumulative acute risk to PYs.

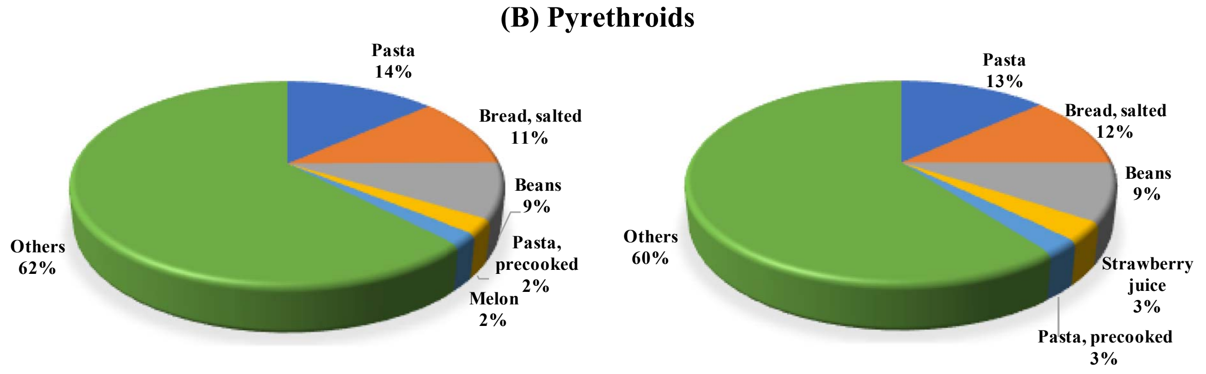
4.4. *Uncertainties and limitations*

Uncertainties in dietary exposure assessments are due to the lack of knowledge of the real world (lack of or insufficient concentration data and/or consumption data) and can be decreased if more data is made available (Kettler et al., 2015). In this study, the uncertainty in the exposure assessment due to the limited sample size of the residue



General population (≥ 10 years)
Main driving compounds:
Aldicarb in rice – 59.9%
Carbofuran in orange – 24.1%

Teenagers (12 to 18 years)
Main driving compounds:
Aldicarb in rice – 78.8%
Carbofuran in orange – 11.6%



General population (≥10 years)
Main driving compounds:
Bifenthrin in wheat flour – 27.1%
Bifenthrin in beans – 8%

Teenagers (12 to 18 years)
Main driving compounds:
Bifenthrin in wheat flour – 27.3%
Bifenthrin in beans – 8.7%

Fig. 3. The foods-*as*-eaten that contributed most to the cumulative intake (upper 2.5% of the intake distribution), expressed as percentage of the total intake for carbamates (A) and pyrethroids (B). The main risk driver compounds are also shown.

concentration and food consumption data was quantified by the bootstrap approach, and reported as 95% confidence intervals (between the 2.5% and 97.5% percentiles of the uncertainty interval) around the percentiles of exposure. The ratio of the confidence intervals (UL/LL) for the P95, P99 and P99.9 intakes shown in Table 5 ranged from 1.3 up to 2.6 (at P99.9, methamidophos as IC, teenagers), and the highest percentile was used to characterize the risks from the exposures. Although high percentiles have larger uncertainties than moderate percentiles, since they are based on fewer data points, the decision to use the P99.9 is supported by the size of the food consumption survey (two days for 34,000 individuals) and concentration database (around 1000 measurements on average for 30 foods). The P99.9 corresponds to 1 in 1000 individual/concentration combinations, a number that was exceeded by far in this study. Furthermore, the underlying food consumption and concentration data used for the simulated individual-days at the P99.9 of the exposure distribution, assessed in the 'drill-down' option at the MCRA (de Boer et al., 2016), showed that the P99.9s were based on realistic estimates of food consumption and concentrations.

However, the residue and food consumption databases have many additional uncertainties that cannot be quantified, and can only be assessed qualitatively. Uncertainties in the residue data are related primarily to the sampling procedure used by the monitoring programs, particularly for foods with high variability in concentrations due to regional or seasonal differences (Kettler et al., 2015), and the uncertainty inherent to the method of analysis. Furthermore, there is an uncertainty related to the PFs applied to the residue data. Regarding the food consumption, the uncertainties in this study were mostly related to the low level of detail included in the food survey, as discussed earlier, from the extrapolation of the food consumption survey (2008–2009) to other years (2005–2015), and the conversion of foods/ingredients (food-*as*-eaten) to their food-*as*-analyzed counterparts, which in this study was obtained mainly from reference books.

Additional uncertainties on the cumulative exposure and on the risk characterization are related to the uncertainties in the toxicological data used to account for the differences in toxicity among the compounds within a CMG to estimate the RPF (EPA, 2006a, 2007a; 2011), and in the establishment of the ARfD of the index compounds, primarily related to the study and the safety factor selected in this process (Solecki et al., 2005). To address this latter uncertainty, we selected the lowest ARfD established to avoid that a potential health risk was not observed. Furthermore, the selected IC, which should preferably have a large body of toxicological data of acceptable quality, will also affect the outcome of the assessment. In this study, the cumulative acute intake of OPs was higher when acephate was used as IC compared to methamidophos (BMD_{10} of 0.99 and 0.08 mg/kg bw, respectively), which was a consequence of the higher RPFs calculated using acephate as IC. Similar results were obtained in the previous study that also used the two ICs (Caldas et al., 2006a). However, the overall conclusion regarding potential health risk related to the cumulative acute exposure to OPs was not affected by the choice of IC.

This study has major advantages compared to the previous work conducted on the cumulative exposure to OPs and CBs of the Brazilian population (Caldas et al., 2006a) – it includes a much larger residue dataset and food consumption data obtained from individual consumption information. Furthermore, converting food-*as*-analyzed to 184 food-*as*-eaten as reported in the food survey allowed the consideration of a larger number of foods included in the Brazilian diet, such as bread, pasta and juice. This number is, however, still limited considering the large Brazilian population and the wide variety of foods consumed within the country, and was likely affected by the large number of reported unspecified food that could not be considered in the study. Furthermore, one major limitation regarding the food consumption is the absence of food consumption data for Brazilian children under 10 years old. Although residue data were not available for foods of animal origin, most likely this information would not impact the intake considerably at the upper tail of the distribution, as very low residues level are expected to remain in these commodities arriving from the dietary exposure of farm animals (FAO/WHO JMPR, 2017).

Overall, based on the overview of the uncertainties presented above, the calculated exposure to OPs, CBs and PYs may be underestimated due to the limited number of foods considered in this study and the high number of unspecified food in the consumption database, which was probably not outweighed by a possible overestimation of the exposure due to the limited information on the PFs. Other uncertainties discussed could either result in an under- or overestimation of the exposure.

5. Conclusions

This study is a refinement of the previous study conducted in Brazil for the cumulative acute exposure to OPs and CBs through the diet, and the first conducted on PYs in Brazil. The cumulative acute exposure did not exceed the ARfD for either CAG at the P99.9 of the intake distribution, and does therefore not represent a health concern for the population under consideration (10 years or older). When consumption data becomes available, further studies should also be conducted for children under 10 years, which is the most critical population to pesticide exposure, mainly due to the consumption of fruits and vegetables and their higher consumption per kg body weight.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.12.010.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.12.010.

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