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Probabilistic dietary risk assessment of triazole and dithiocarbamate fungicides for the Brazilian population

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ABSTRACT

Residue data for triazoles (TR) and dithiocarbamates (DT) in 30,786 samples of 30 foods were obtained from mainly two national monitoring programs, and consumption data from a national survey conducted among persons aged 10 years or older. About 16% of the samples contained TR, mainly grape (53.5%), and 16.2% contained DT, mainly apple (59.3%). Flusilazole was the index compound used for the acute effects of TR for women of child-bearing-age (cranium-facial malformation and skeletal variation), cyproconazole for the chronic effects of TR (hepatoxicity), and ethylene-bis-dithiocarbamates (EBDC) for DT (thyroid toxicity). Exposures were estimated using the Monte Carlo Risk Assessment software. Different models were tested, and a Model-Then-Add approach was found to best estimate the chronic exposures to DT and TR. At the 99.9th percentile (P99.9), the cumulative acute TR intakes accounted for up to 0.5% of the flusilazole ARfD, mainly from beans and rice consumption. The chronic TR and DT intakes accounted for 1 and 6.7% of the respective index compound ADIs, with beans and rice accounting for most of the TR intake (~70%), and apple for about 51–56% of the DT intake. The estimated risks from the exposure to TR and DT indicate no health concern for the Brazilian population.

1. Introduction

Food treated with pesticides may contain residues at levels that can pose a health concern to consumers, requiring the conduction of dietary risk assessment studies to assess and guarantee the safety of the food supply (IPCS, 2009). Data from two Brazilian monitoring programs conducted from 2002 to 2010 showed that dithiocarbamates (DT) were the pesticides most detected in the sampled foods, being present in about 20% of the 13,556 samples analyzed (Jardim and Caldas, 2012). DT were also among the most detected pesticides in other monitoring programs worldwide (EFSA, 2016, 2017; DAWR, 2017; Valcke et al., 2017).

Mancozeb and metiram (ethylene-bis-dithiocarbamates; EBDC), and propineb are DT registered for foliar use in about 40 food crops in Brazil (ANVISA, 2018a). Thiram and metam-sodium, also DT, are registered for soil and/or seed treatment uses that are not relevant for dietary exposure as no residues are expected in the food. The toxicological concern of DT is mainly related to their potential of causing thyroid cancer (JMPR, 1994; USEPA, 2001; Belpoggi et al., 2002). Thyroid toxicity induced by the EBDC is attributed to the metabolite ethylenethiourea (ETU), whereas that of propineb is mediated by propylenethiourea (PTU), which is more potent than ETU (JMPR, 1994).

Another important group of pesticides to which people in Brazil can be exposed via food is the triazoles (TR), which were present in 10.2% of the samples analyzed from 2002 to 2010 that contained any residues (Jardim and Caldas, 2012). This group is one of the largest fungicide class in the world market with 11 compounds registered in Brazil (ANVISA, 2018a). In laboratory animals, TR cause developmental toxicity and hepatoxicity after chronic exposure (EFSA, 2009). To assess the risk of this group of pesticides via the diet, two cumulative assessment groups (CAG) were proposed by the European Food Safety Authority (EFSA), one based on the common cranium-facial malformation acute effect to the fetus, and one based on the common hepatoxicity chronic effect (EFSA, 2009). However, cranium-facial malformation (CM) is not the most critical developmental acute effect of TR, and is caused by only a few compounds belonging to this class. Most TR induce skeletal variations (SV) in the exposed fetus, including supplementary ribs and unossified sternebrae (JMPR, 2007; EFSA, 2009),

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an acute effect on which the acute reference doses (ARfDs) for many of these compounds are based (JMPR, 2018).

To the best of our knowledge, only one dietary cumulative risk assessment study was conducted for TR (Boon et al., 2015), and few studies have estimated the risks of the chronic exposure to DT (Caldas et al., 2006; Jensen et al., 2008; Gimou et al., 2008; Struciński et al., 2015; Valcke et al., 2017; Sieke et al., 2018). The study conducted with DT in Brazil had two major limitations: the residue data were only available for nine fruits and vegetables, rice and beans, and individual consumption was estimated based on household food availability data (Caldas et al., 2006).

The objectives of this work were to update the previous chronic dietary risk assessment of DT, and to conduct a cumulative acute and chronic dietary risk assessment of TR for the Brazilian population. Different intake models were tested to estimate the chronic exposure to both groups of pesticides. Exposures were estimated using residue data for 30 food commodities and individual food consumption data for individuals aged 10 years or older.

2. Materials and methods

2.1. Residue data and processing factors

In total, residue data of 30,786 samples covering 30 foods and analyzed between 2005 and 2015 were available for this study (food-as-analyzed). Residue data for DT and TR were analyzed within the Program on Pesticide Residue Analysis in Food (PARA), coordinated by the National Sanitary Surveillance Agency (ANVISA), and by the National Residue and Contaminant Control Program (PNCRC), coordinated by Ministry of Agriculture, Livestock and Food Supplies (MAPA). Samples were collected in food markets randomly selected in all 26 Brazilian states and the Federal District, and analyzed by private or governmental laboratories complying with the ISO-IEC 17025 requirements (ANVISA, 2018b; MAPA, 2017). In these programs, DT were analyzed as CS_2 by either spectrophotometry or gas chromatography coupled to FPD or MS (after isooctane extraction or headspace), with levels of reporting (LORs) ranging from 0.01 to 0.5 mg/kg. TR were determined using multi-residue methods, based on the Mini Luke (General Inspectorate for Health Protection, 1996) or the QuEChERS method (Anastassiades et al., 2003), using GC-ECD, GC-MS or LC-MS/MS, with LORs ranging from 0.005 to 0.4 mg/kg. Additionally, 238 samples of cashew apple, guava, kaki and peach collected in the food market randomly selected in the Federal District from 2010 to 2012 were analyzed for DT by the Laboratory of Toxicology of the University of Brasilia (LabTox). This laboratory also complies with ISO-IEC 17025. DT were analyzed as CS_2 by the spectrophotometric method (Caldas et al., 2001; Jardim et al., 2014), with LOR of 0.05 mg/kg.

Processing factors (PFs) for the compound/food/processing combinations used in this study were obtained from the German Federal Institute for Risk Assessment (BfR, 2016) and the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) reports. In the BfR database, only PFs from studies classified as acceptable or indicative were considered. In this study, when a PF was reported as below a certain number, that number was taken as the PF. Washing was not considered a relevant processing as the consumption of unwashed foods is likely to occur. Table S1(Supplemental material) shows the PFs used in this study.

2.2. Food consumption data

Consumption data were obtained from the last national survey conducted in Brazil in 2008/2009 (*Pesquisa de Orçamento Familiar*, IBGE, 2012). In total, 34,003 participants (10–104 years old) recorded their food consumption on two non-consecutive days. The participants were mostly female (53.8%), were on average 36 years old and weighed on average 64 kg (19.4–150 kg). Almost all responders (99.96%) reported the consumption of at least one of the 184 foods (food-as-eaten) that contained as an ingredient one of the foods analyzed within the national monitoring programs (PARA and PNCRC) and by the LabTox. To map the foods-as eaten to those analyzed, information on the proportions of the food-as-analyzed in each food-as-eaten (e.g. cabbage and rice as part of a cabbage roll) were used. This information is published elsewhere (Jardim et al., 2018; Table S1).

2.3. Relative potency factors (RPF) for triazoles

To estimate the acute and chronic cumulative exposure to TR, the relative potency factor (RPF) approach was used (EFSA, 2009). RPFs for acute exposure to TR were estimated from the NOAELs (no observed adverse effect level) of two effects on the fetus that occur possibly via a common mechanism of toxicity: cranium-facial malformation (CM) and skeletal variations (SV). Fluzilazole was selected as the index compound (IC) in both cases. For chronic exposure to TR, RPFs were estimated from NOAELs for hepatoxicity effects with cyproconazole as IC. NOAELs were obtained primarily from EFSA (2009), but also from JMPR toxicological evaluations (JMPR, 2018) and from the USA Environmental Protection Agency (USEPA, 2006). All TR detected in the samples were included in the two CAGs, except azaconazole (three positive samples) and imibenconazole (one positive sample), for which no toxicological data was found. Table 1 shows the RPFs for the 15 TR considered in this study, for both acute (SV and CM) and chronic (hepatoxicity) common effects, and the NOAELs used for the calculation ($RPF = NOAEL_{IC}/NOAEL_{pesticide}$). The cumulated residue in a sample was calculated by adding up each detected residue of a given CAG multiplied by its RPF.

2.4. Monte Carlo Risk Assessment (MCRA)

The exposures to TR and DT were calculated using the Monte Carlo Risk Assessment (MCRA) software, version 8.2 (de Boer et al., 2016; van der Voet et al., 2015), using the EFSA optimistic approach, in which it is assumed that residues below the LOR are equal to 0 mg/kg (EFSA, 2012). In this approach, fixed PF values are used and no unit variability is considered in case of acute exposure, i.e. the available monitoring data from composite samples are assumed to be representative of pesticide concentrations in single units of the food. The calculations resulted in a distribution of acute (TR) or chronic exposure levels (DT and TR), describing the variation in exposure levels within the Brazilian population due to individual differences in food consumption and differences in cumulative residue levels (see sections 2.5 and 2.6). The exposures were expressed as percentiles (P) of these intake distributions.

The uncertainties in the exposure estimates due to the limited size of the residue and consumption databases were calculated using the empirical bootstrap approach, in which both databases were resampled 100 times with replacement. These resampled databases were then used to generate 100 exposure distributions from which the exposure percentiles were derived. The uncertainty was subsequently expressed as the lower (LL; P2.5) and upper (UL; P97.5) limits (therefore 95% confidence limits) per exposure percentile resulting from these 100 exposure distributions.

2.5. Cumulative acute exposure to triazoles

The acute cumulative exposures to TR were estimated for women of child-bearing-age (from 12 to 45 years old), which is the relevant population for the two acute CAGs (CM and SV effects to the fetus). The exposures were estimated with the Monte Carlo sampling approach. In this approach, daily consumption patterns of food on a specific per person-day are selected randomly and multiplied by a randomly selected cumulated residue level per consumed food. The exposures for each randomly selected person-day were summed over the foods,

Table 1
Relative Potency Factors (RPF) used for acute and chronic effects of triazoles[a].

Compound	Acute; IC = flusilazole				Chronic; IC = cyproconazole	
	Skeletal variation		Cranium-facial malformation		Hepatotoxicity	
	RPF	NOAEL mg/kg bw/day	RPF	NOAEL mg/kg bw/day	RPF	NOAEL mg/kg bw/day
Flusilazole	1	2 (JMPR, 2007)	1	50 (EFSA, 2009)	1	2 (JMPR, 2007; EFSA, 2009)
Cyproconazole	0.16	12 (JMPR, 2010)	4.2	12 (EFSA, 2009)	1	2 (JMPR, 2010)
Flutriafol	0.6	3.3 (JMPR, 2011)[b]	5	10 (JMPR, 2011)	2	1 (JMPR, 2011)
Epoxiconazole	0.12	15 (EFSA, 2009)	0.8	60 (EFSA, 2009)	2.5	0.8 (EFSA, 2009)[c]
Propiconazole	0.08	30 (JMPR, 2004; EFSA, 2009)	1.7	30 (EFSA, 2009)	0.6	3.6 (EFSA, 2009)
Bromuconazole	0.2	10 (EFSA, 2009)	–	–	2	1 (EFSA, 2009)
Difenconazole	0.02	100 (JMPR, 2007; EFSA, 2009)	–	–	2	1 (EFSA, 2009)
Fluquinconazole	1	2 (EFSA, 2009)	–	–	4.5	0.44 (EFSA, 2009)
Hexaconazole	0.8	2.5 (EFSA, 2009)	–	–	4.2	0.47 (EFSA, 2009)
Metconazole	0.16	12 (USEPA, 2006)	–	–	0.43	4.6 (EFSA, 2009)
Myclobutanil	0.08	94 (JMPR, 1993; EFSA, 2009)	–	–	0.05	39 (EFSA, 2009)
Penconazole	0.02	100 (EFSA, 2009; JMPR, 2015)	–	–	0.13	15 (EFSA, 2009)
Tebuconazole	0.28	30 (EFSA, 2009; JMPR, 2010)	–	–	0.1	16 (JMPR, 2010)
Tetraconazole	0.08	22.5 (EFSA, 2009)	–	–	5	0.4 (EFSA, 2009)
Triadimenol	0.12	15 (EFSA, 2009)	–	–	0.4	5 (EFSA, 2009)

IC: index compound; NOAEL: no-observed adverse effect level; [a] NOAELs were based on rat studies, unless indicated otherwise; [b] based on a lowest observed adverse effect level (LOAEL) of 10 mg/kg bw; [c] mouse study.

resulting in daily cumulative acute exposures per person-day. This process was repeated 100,000 times. To assess the uncertainty due to the limited size of the databases (section 2.4), the resampled databases were sampled 10,000 times.

To express the potential health risk related to the cumulative acute exposure to TR for the CM and SV CAGs, the cumulative exposure percentiles were expressed as % ARfD of flusilazole with ARfDs of 500 μg/kg bw (EFSA, 2009) and 20 μg/kg bw (JMPR, 2007), respectively.

2.6. Modeling the cumulative chronic exposure to triazoles and to dithiocarbamates

Various models are available in MCRA 8.2 for modeling chronic (usual) intake based on incidental consumption patterns. The BetaBinomial Normal (BBN) and the LogisticNormal-Normal (LNN) models are similar as they distinguish variation between individuals from variation between days of the same individual and assume normality at an appropriate transformed scale of the between-individual term to derive usual intake percentiles. If the criterion of normality is violated (e.g. in the case of a multimodal distribution), these models may result in erroneous intake estimates. In this case, two approaches can be taken. One option is the Observed Individual Means (OIM), in which the intakes calculated for the different days of a person are just averaged to obtain an estimated chronic exposure distribution (EFSA, 2012). The other option, which will be preferred in this work, is the Model-Then-Add (MTA) approach, in which the intake is modelled for separate foods or food groups that may show a better fit to the normal distribution model than when the intake is modelled cumulated over all foods. The issue of a non-normal and possibly multimodal distributions due to the origin of substances from multiple foods was noted in several publications and addressed with the MTA approach (de Boer et al., 2009; Goedhart et al., 2012; Slob et al., 2010; van der Voet et al., 2014). In the Model step of MTA, foods that are responsible for each of the peaks in the multimodal distribution obtained are identified among the foods that most contributed to the intake and separated from the total intake. The intake distribution for each selected food or food group can be modelled using either BBN or LNN and the rest of the foods are modeled using OIM. The Add step adds the person-specific usual exposure estimates per food, taking correlations in consumptions into account. The estimates are back-transformed values from a shrunken version of the transformed OIM distribution, where the shrinkage factor is based on the variance components estimated using the linear mixed model for amounts at the transformed scale (model-assisted approach, van der Voet et al., 2014).

In this study, the chronic intakes of TR and DT were first estimated using the LLN and BBN models, and normality was investigated through the normal quantal-quantal (Q-Q) plot, a graphical display of observed vs. theoretical residuals (de Boer et al., 2009). To use MTA, various food and food groups were selected to model the intakes of TR and DT separately using LLN. For those meeting the normality criterion using the normal Q-Q plot, the exposure was modelled using this model. The intake via the remainder of the foods was modeled using OIM (van der Voet et al., 2014). OIM was also used to assess the chronic exposure via all foods for reasons of comparison.

The chronic exposures were estimated for the total population (10 year and over) and for teenagers (from 12 to 18 years old). The potential health risks related to the calculated cumulative chronic exposure to TR were estimated by expressing the percentiles of exposure as % of the ADI, which is 20 μg/kg bw/day for cyproconazole, the IC for chronic effects of TR (EFSA, 2009).

For the chronic exposure to DT (see further, section 2.6.1), the ADI of 30 μg/kg bw established by the JMPR for the EBDC group (JMPR, 1994), which corresponds to 16.9 μg CS_2/kg bw/day, was used to express the percentiles of exposure as % of the ADI.

2.6.1. Total dithiocarbamate chronic exposure and risk characterization

Currently, the analytical methods used in monitoring programs to determine the levels of DT in food measure the CS_2 generated after acid hydrolysis of the fungicide present in the sample, not allowing the identification of the compound applied to the crop (JMPR, 1994; Caldas et al., 2001; Valcke et al., 2017). Hence, the potential source of CS_2 found in the sample needs to be considered to not underestimate (assuming that the detected CS_2 was generated from the DT with the lowest toxicity) or overestimate the risk (assuming that residues were generated from the most toxic DT). In this study, the approach taken by Caldas et al. (2006) was applied to estimate the source of CS_2 using updated DT use and market information in Brazil. Mancozeb is registered in 38 food crops and represents about 78% of the DT volume commercialized in the country for foliar application; metiram is registered in 19 crops, representing about 15% of the market, and propineb is registered in 8 crops, representing about 7% of the market (Pires, 2013; ANVISA, 2018a; IBAMA, 2018). Based on this information, it was assumed that 93% (78 + 15%) of the CS_2 found in the samples originated from the use of the EBDCs (mancozeb or metiram), and 7% from the use of propineb.

Although the mechanism of actions for the thyroid effects of EBDC and propineb involve different metabolites (ETU and PTU, respectively), a pragmatic approach was taken in this study to consider propineb as a partial source of CS_2 detected in the samples. A RPF for propineb related to EBDC of 1.92 was estimated based on the NOAELs of 2.5 and 4.8 mg/kg bw of propineb and mancozeb, respectively, for effects on the thyroid after long-term studies in rats (JMPR, 1994).

Finally, the parameters considered (93% of EBDC and 7% of propineb, and a RPF of 1.92) were applied to the DT intake estimated via the chronic intake model to estimate the total DT chronic exposure, as CS_2, according to the following equation:

$$\begin{aligned} \textit{Total DT exposure} = {} & \textit{modelled intake} \times 0.93 \\ & + [\textit{modelled intake} \times 0.07 \times 1.92] \end{aligned}$$

3. Results

3.1. Residue and consumption data

Table 2 summarizes the residue data of the 30,786 analyzed samples considered in this study. No residues of TR or DT were found in corn flour and cassava flour samples. About 16% of the samples contained at least one TR, mainly in grape (53.5% of the positive TR samples) and papaya (36.4%). Similarly, DT were found in about 16% of the samples, mainly in apple (59.3%) and kaki (46.3%).

In total, 17 TR were detected in the analyzed samples, mostly tebuconazole and difenoconazole (about 51 and 43% of the positive samples, respectively; Fig. 1). Multiple TR were found in 17.2% of the TR positive samples, mainly in grape (38.2% of the positive grape samples) and papaya (23.8%). Most of the multiple residue samples contained two TR (86.6%), 11.7% contained 3 TR, 1.7% contained 4 TR, and 1 grape sample contained 5 TR.

A summary of the consumption data (as food-as-analyzed) for the general population, teenagers and women of child-bearing-age is shown in Table 3. The consumption of all foods-as-eaten is included in these data. Beans and rice, reported by over 70% of all three populations, were consumed at the highest mean levels when all surveyed days were considered (146–181 g/day; Table 3); considering only the consumption days (when consumption was reported), the means ranged from 169 to 241 g/day. Consumption of grape was not frequently reported by the surveyed populations (0.7–1.2% of the consumer days), with a low mean consumption (all days; 1.9 to 3.5 g/day; Table 3). However, when only the consumption days were considered, the mean consumption of grape was the second highest among all foods for the general population and teenagers and the highest for women of child-bearing-age (269–292 g/day; Table 3).

Table 2
Summary of residue data for triazoles (TR) and dithiocarbamates (DT) in food samples collected from 2005 to 2015 in Brazil.

Food as analyzed	Total samples	Positive for TR, %	Positive for DT, %
Apple[a,b]	3175	9.7	59.3
Banana[a,b]	1170	3.3	4.5
Bean[a,b]	1570	25.5	0.4
Beet root[a,b]	602	16.8	6.0
Cabbage[a]	908	1.1	na
Carrot[a,b]	1655	27.1	4.5
Cashew apple[c]	43	na	16.3
Cassava flour[a]	470	0	0
Collard green[a]	529	5.7	6.8
Corn flour[a]	729	0	0
Cucumber[a]	1253	2.9	8.4
Grape[a,b]	989	53.5	8.2
Guava[a,c]	464	11.6	2.2
Kaki[c]	67	na	46.3
Lemon[b]	69	5.8	0
Lettuce[a,b]	1483	8.2	14.6
Mango[a,b]	784	3.1	4.8
Melon[b]	55	1.8	0
Orange[a,b]	1899	13.1	3.5
Papaya[a,b]	2681	36.4	37.5
Peach[b,c]	96	11.5	32.3
Pineapple[a,b]	934	5.0	1.8
Potato[a,b]	1700	0.2	0.3
Rice[a,b]	1800	22.8	0.2
Onion[a,b]	936	0	na
Strawberry[a,b]	1178	25.4	11.3
Sweet pepper[a,b]	981	31.2	34.4
Tomato[a,b]	1844	22.6	30.4
Wheat flour[a]	506	0.2	0
Zucchini[a]	216	10.2	0
Total	**30786**	**15.8**	**16.2**

na = not analyzed.
[a] Analyzed within PARA.
[b] Analyzed within PNCRC.
[c] Analyzed by LabTox.

3.2. Cumulative acute exposure to triazoles and the risk characterization

Table 4 shows the cumulative acute intakes of TR by women of child-bearing-age at the 90[th] percentile (P90) or higher of the intake distribution for the CM and SV effects (CAGs). The lower and upper limits of the confidence interval around the percentiles are also reported. The intakes expressed as flusilazole equivalents for CM were about 10 times higher than those related to SV. Still, for both effects the P99.9 exposure estimates were less than 1% of the fluzilazole ARfD. The consumption of beans and rice accounted for 74 and 89% of the upper 2.5% tail of the cumulative intake distribution for CM and SV, respectively (Fig. 2A and B). Flutriafol in beans was the main risk driver for both acute effects, followed by tebuconazole in rice for SV, and propiconazole and cyproconazole in rice for CM.

3.3. Chronic exposures to triazoles and dithiocarbamates and the risk characterizations using the model-then-add approach

As indicated by a non-linear normal Q-Q plot of observed residues in Fig. 3A–B, the intake distributions of DT and TR using LLN showed to be not normal. BBN modelling gave similar profiles (data not shown). The foods contributing most to the exposure to TR and DT were used as a starting point. Although the chronic intakes at different percentiles may change according to the model applied (see discussion), the contribution of the foods to the total intake distributions remains the same. The five foods (as-analyzed) that contributed most to the TR cumulative chronic intake are shown in Fig. 4A–B for the general population and teenagers. In both cases, beans and rice were the major intake contributors, accounting for 46–50% and 21–23% of the total intake, respectively. Grape, papaya and lettuce were also important contributors to the total intake for the general population (18%), while grape, guava and banana contributed together for 12% in teenagers. Apple was the major contributor for the DT chronic cumulative intake (51–56%, Fig. 4C–D). Papaya, lettuce, tomato and banana accounted together for 34 and 27% of the total intake for the general population and teenagers, respectively.

MTA models using different combinations of the five major foods for both pesticide groups in both populations were tested, looking for a mono-modal distribution and the best fit of the normal Q-Q plots of the residuals, which should show linearity at least in the range between the standardized residuals −2 and 2 (i.e., within the 2.5 to the 97.5% range of the distribution).

For the general population, a MTA model that showed a good fit of the Q-Q plots of TR exposure was obtained after splitting three groups, i.e. grape, rice and the combined [lettuce, papaya, beans] group, from the total intake distribution to be modelled separately with LNN

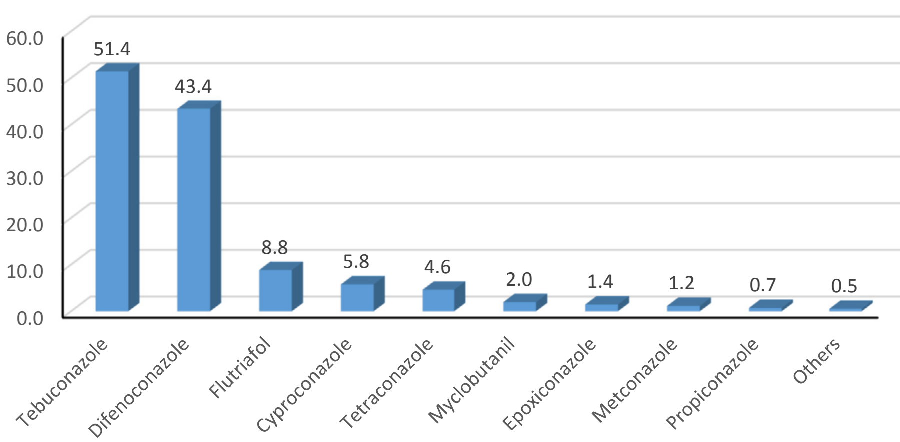

Fig. 1. Triazoles (TR) found in the samples analyzed within the Brazilian monitoring programs (PARA and PNCRC) between 2005 and 2015, in % of the samples containing at least the specified TR. Others: bromuconazole (9 samples), haxaconazole (5), triadimenol (3), azaconazole (3), fluquinconazole (2), flusilazole (1), penconazole (1) and imibenconazole (1).

Table 3
Summary of Brazilian individual consumption data (*Pesquisa de Orçamento Familiar*, 2008/2009 IBGE, 2012).

Food	Mean consumption (gram per day) all days[a]/consumption days[b]		
	General population (10 years and older)	Teenagers (12–18 years)	Women (12–45 years)
Apple	9.9/169	8.9/172	118/165
Banana	18.4/119	16.8/128	15.9/108
Bean	181/241	174/239	46/206
Beet root	0.6/52.8	0.3/46.6	0.6/50.6
Cabbage	0.81/52.7	0.6/59.7	0.74/49.3
Carrot	1.45/33.7	1.0/32	1.5/32.1
Cashew apple	1.64/116	2.2/137	[d]
Collard green	0.84/52.8	0.5/46	0.76/53.1
Cucumber	0.45/51.9	0.2/48.4	0.49/52.8
Grape	3.4/292	1.9/269	3.5/291
Guava	3.66/118	4.8/147	4.2/116
Kaki	0.33/139	0.12/150	[d]
Lemon	0.84/63.5	0.84/60.1	0.82/60.3
Lettuce	2.7/38.7	1.7/36.6	2.7/39
Mango	7.1//193	8.5/266	1.3/181
Melon	0.67/132	0.21/137	0.73/137
Orange	42.1/298	37.4/302	4.1/280
Papaya	6.4/210	2.8/235	5.8/211
Peach	0.58/132	0.47/139	0.6/123
Pineapple	4.5/143	4.1/137	4.9/134
Potato	9.6/96.1	9.5/102	9.6/91.3
Rice[c]	171/195	169/194	147/169
Strawberry	0.83/140	1.0/149	1/140
Sweet pepper	0.1/16.5	0.1/32.2	0.1/14.8
Tomato	6.2/70	4.4/66.5	5.8/64.7
Wheat flour	76.2/95.3	86.6/105	76/91.5
Zucchini	0.8/96.3	0.3/81.8	0.79/6.7

[a] Mean consumption of all person-days.
[b] Mean consumption of the person-days at which the consumption of the food was reported.
[c] Include polished, parboiled and bran.
[d] not analyzed for triazoles.

Table 4
Percentiles (P) of acute cumulative exposures to triazoles of Brazilian women of child-bearing-age (12–45 years old), and risk characterization related to the index compound (fluzilazole).

P	Skeletal variation ARfD = 20 μg/kg bw/day		Cranium-facial malformation ARfD = 500 μg/kg bw/day	
	Intake (CI)	%ARfD. median/UL	Intake (CI)	%ARfD median/UL
90	0 (0.000–0.000)	0.0/0.0	0 (0.000–0.000)	0.0/0.0
97.5	0.0035 (0.002–0.004)	0.0/0.0	0.05 (0.031–0.067)	0.0/0.0
99	0.015 (0.012–0.017)	0.1/0.1	0.195 (0.158–0.235)	0.0/0.0
99.9	0.09 (0.068–0.112)	0.5/0.6	0.909 (0.744–1.34)	0.2/0.3

ARfD: acute reference dose; CI: lower (LL 2.5%) - upper (UL 97.5%) limits of the 95% confidence interval.

(Fig. 3C). For teenagers, rice and the combined [beans + grape + guava + banana] group were modelled separately with LNN (Fig. S2, Supplemental Material). In both cases, the intake of the remaining 20 crops that contained TR was estimated with OIM. For DT, a MTA model that showed a good fit of the Q-Q plots for the general population was to split the intake via apple, papaya and lettuce from the total intake (Fig. 3D). For teenagers, a good option was to model the intake separately for apple, lettuce and tomato (Fig. S4).

The empirical distributions and the normal Q-Q- plots of the observed residuals of the tested MTA models are shown in Figs. S1–S4 for TR and DT for the general population and teenagers (Supplemental Material). In all cases, there were alternative possibilities to create splits on the foods that showed also very reasonable options for modelling as could be judged from the Q-Q plots. Some models did not show a good fit, such as beans for triazoles in the teenager population (Fig. S2) and grouping banana and apple for dithiocarbamates for general population (Fig. S3).

A comparison of the chronic intakes estimated by the different models (LLN, BBN, OIM and four variations of MTA) was also performed and shown in Table 5 for TR and DT (general population). The BBN and LLN models differ only in the way that exposure frequencies are modelled. They gave similar results at all percentiles for both pesticide classes, indicating that the frequencies of pesticide exposure were equivalently fitted by the two models. As LNN (as well the BBN) models clearly misfit the data (Fig. 3A–B), they gave a very high estimated upper tail percentile and also the largest uncertainty around the estimated mean (UL/LL ratios between 2.4 and 3) compared to the OIM and MTA models (UL/LL between 1.4 and 1.6 for TR and between 1.1 and 1.4 for DT; Table 5). It may be noted that the well-known conservatism (upward bias) of the OIM method (Goedhart et al., 2012; Boon and van der Voet, 2015) shows up at P99.9 for TR and at all three percentiles for DT with percentile estimates, which were as high as the incorrect LNN and BBN estimates. In contrast, the four variations of the TR MTA models gave lower intakes than those from LNN, BBN and, in most cases, OIM. It was reassuring that all four variations of the MTA method led to very similar results, both for TR and DT.

Table 6 shows the exposure estimates for the cumulative chronic exposure to TR and total DT (which considers the source of the detected CS_2 and the RPF of propineb in relation to EBDC) for the MTA models. The P99.9 of chronic cumulative exposure to TR was 0.190 and

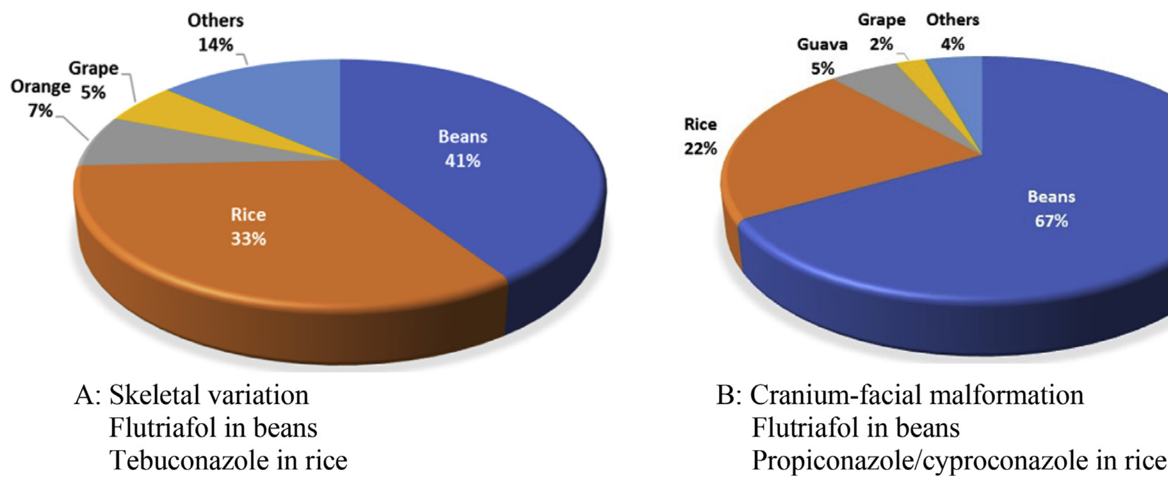

Fig. 2. The foods-as-analyzed and compounds therein that contributed most to the cumulative acute intake of TR for effects on skeletal variation (A) and cranium-facial malformation (B) in the upper 2.5% of the intake distribution. The main risk drivers in beans and rice are also shown.

0.227 μg/kg bw/day for the general and teenager populations, respectively, accounting for about 1% of the ADI of the IC cyproconazole. At this percentile, the total DT intakes, as CS_2, were 0.902 and 1.12 μg/kg bw/day for the general population and teenagers, respectively, corresponding to 5.3 and 6.7% of the EBDC ADI.

4. Discussion

4.1. Pesticide residue and food consumption data

Almost 16% of 30,786 samples of 30 different commodities analyzed within the Brazilian monitoring programs from 2005 to 2015 contained triazoles (TR), a frequency much higher than that found in the 81,417 food samples analyzed in eight European countries from 2007 to 2010 (~1%) (Boon et al., 2015). About 17% of the TR positive samples contained multiple residues of this class. The food with most multiple TR samples was grape (38.2% of the TR positive grape samples). Tebuconazole and difenoconazole were the main TR found in the samples analyzed, present alone or together in 94.8% of the positive samples. These two compounds were also the main TR found in the residue monitoring program conducted by the U.S. Food and Drug Administration in 2015, with tebuconazole being the third pesticide found most among 207 pesticides detected in the food samples (including 14 TR) (USFDA, 2017). Results from the 2014 EU monitoring program showed tebuconazole, difenoconazole and propiconazole as the main TR found in about 9000 plant food samples analyzed (2, 1.8 and 1.5%, respectively; EFSA, 2016).

About 16% of all samples analyzed were positive for DT, as CS_2. This percentage is lower than reported previously for results obtained from the Brazilian monitoring data of 2002–2010 (~20% of the 13,556 samples of 20 crops analyzed; Jardim and Caldas, 2012). In the EU, 12% of the 3639 samples of foods analyzed within the 2015 EU monitoring program were reported to be positive for DT (as CS_2), mainly broccoli (EFSA, 2017). It is well known that brassica (e.g. broccoli and cabbage) and *allium* species (e.g. leek and onion) yield false positive results for DT due to the natural presence of sulfur compounds that release CS_2 under the analysis conditions (Perz et al., 2000). This is the reason why these crops were not analyzed for DT within the Brazilian monitoring programs. Papaya, a crop that has recently been shown to be susceptible for false positive results, was however included in the present, as well as in the previous dataset (Jardim and Caldas, 2012). However, the probability of detecting a false positive result may change according to the method used in the analysis, and was estimated as being 12% for the isooctane method, 55% for the headspace method (in both cases, the CS_2 is determined by GC-FPD), and 94% for the spectrophotometric method (Abakerli et al., 2015). The papaya samples collected within the Brazilian monitoring programs were analyzed by all different methods; however, it was not clear which method was used per sample. Hence, the data for DT in papaya were kept in this study, although false positive results in some samples cannot be excluded.

4.2. Dietary cumulative acute exposure to triazoles

The CAG for the CM acute effect of TR published by EFSA (2009) includes bitertanol, cyproconazole, diniconazole, epoxiconazole, flusilazole, propiconazole and triadimefon, and RPFs were calculated using benchmark dose (BMD) levels with flusilazole as IC (ARfD of 500 μg/kg bw). For the inclusion of a TR in the CAG, EFSA also considered the availability of residue data and registration in the EU by January 2008 (EFSA, 2009).

Of the seven compounds included in the CM CAG, residue data in Brazil was available only for four TR. In the present study, flutriafol was also included in the CAG, based on toxicological data reported by the JMPR (2011). However, the most critical acute effect produced by TR is SV, which was the basis for the ARfD of 20 μg/kg bw set for flusilazole by the JMPR (2007). Similar to CM, it is reasonable to assume that the skeletal variations observed in fetus exposed to TR share the same mechanism of toxicity, and a CAG for this common effect was formed for this study. This CAG included all 15 TR for which Brazilian residue data and toxicological data were available (Table 2). In this study, the RPF for both acute effects were estimated using NOAELs. Although the best approach to derive RPFs is to use BMD levels, the estimation of these levels requires the use of BMD modelling and data that are mostly included in the original reports of the developmental studies. These reports were not available to this study. EFSA also calculated RPFs for the CM CAG using NOAELs, which were similar to those calculated using the BMD, with exception of propiconazole, for which the estimated BMD was considered to be unreliable (EFSA, 2009).

The TR acute cumulative exposure assessment for women of child-bearing-age population showed that the intake for the SV CAG was about 10 times lower than that for the CM CAG. RPFs for all five compounds included in the CM CAG were higher than those for the same compounds in the SV CAG. Furthermore, the RPFs for the other ten compounds in the SV CAG were mostly below 1, including for the two compounds most detected, difenoconazole (0.02) and tebuconazole (0.28). The %ARfD, however, was about twice as high at the 99.9th percentile (P99.9) for the SV CAG, as the ARfD for this effect is much lower. In both cases, the risks for the exposed fetus were negligible, representing less than 1% of the respective ARfD, even at the upper level of the 95% confidence intervals of the P99.9 intakes. The

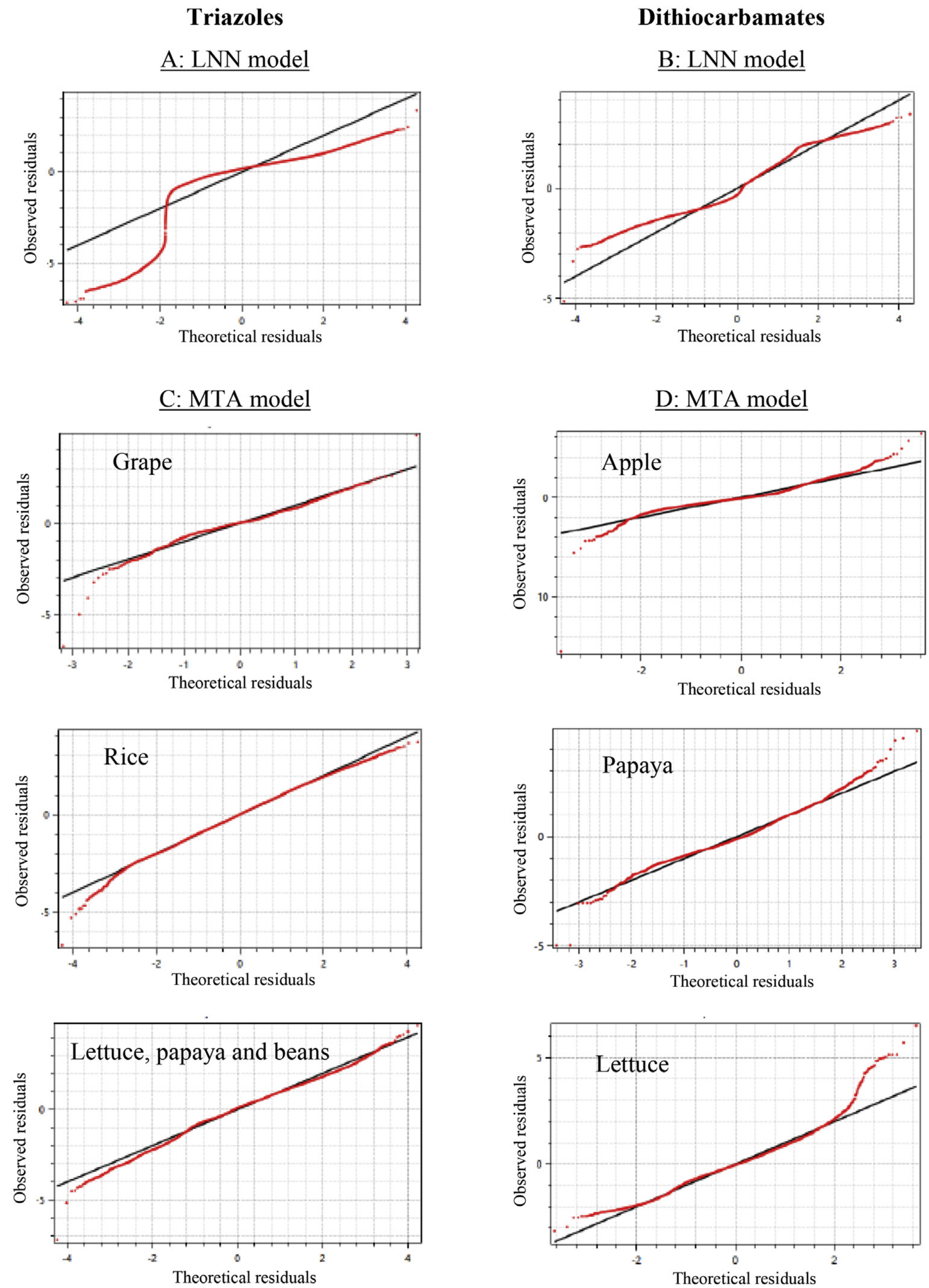

Fig. 3. Q-Q-plots of observed vs. expected residuals of LogisticNormal-Normal (LNN) models for TR and dithiocarbamates (A and B), and the LNN modeling (logarithmic transformation) of the Model-then-Add (MTA) (C and D), for the general population. The Q-Q plots for the BetaBinominal Normal (BBN) models were very similar to those for LNN in A and B.

consumption of rice and beans (including all food preparations) contributed most to total TR intake in the upper 2.5% of the cumulative exposure distribution for both acute effects (71 and 81%). For CM, the consumption of beans alone contributed for about 64% to the total cumulative intake, mainly via the intake of flutriafol. Beans and rice form the basis of the Brazilian diet, consumption being reported by over 70% of individuals belonging to the populations considered in this study. Rice and beans were included as an ingredient in 22 of the 184 food preparations reported in the dietary survey (Jardim et al., 2018).

Boon et al. (2015) estimated the acute cumulative exposure to TR for the CM effect (EFSA, 2009) using the two approaches for non-detect residues suggested by the EFSA (2012) – the pessimistic approach (which includes setting the non-detects at the LOR for authorized pesticides) and the optimistic approach as used in the present study (non-detects set at a concentration of 0 mg/kg). The authors estimated the cumulative acute TR intakes for adolescents and adults in eight European countries. At P99.9, the intakes ranged from 0.34 to 7.6 μg/kg bw using the optimistic approach, which were higher than those for the CM CAG estimated in the present study for women-of-child bearing age, the relevant population for this common effect. In Boon et al. (2015), the intake of bitertanol and triadimefon were the main risk drivers for the acute cumulative exposure in most countries, compounds not included in the present study. Using the pessimistic approach, the intakes ranged from 9.4 up to 137 μg/kg bw. The authors recognized however

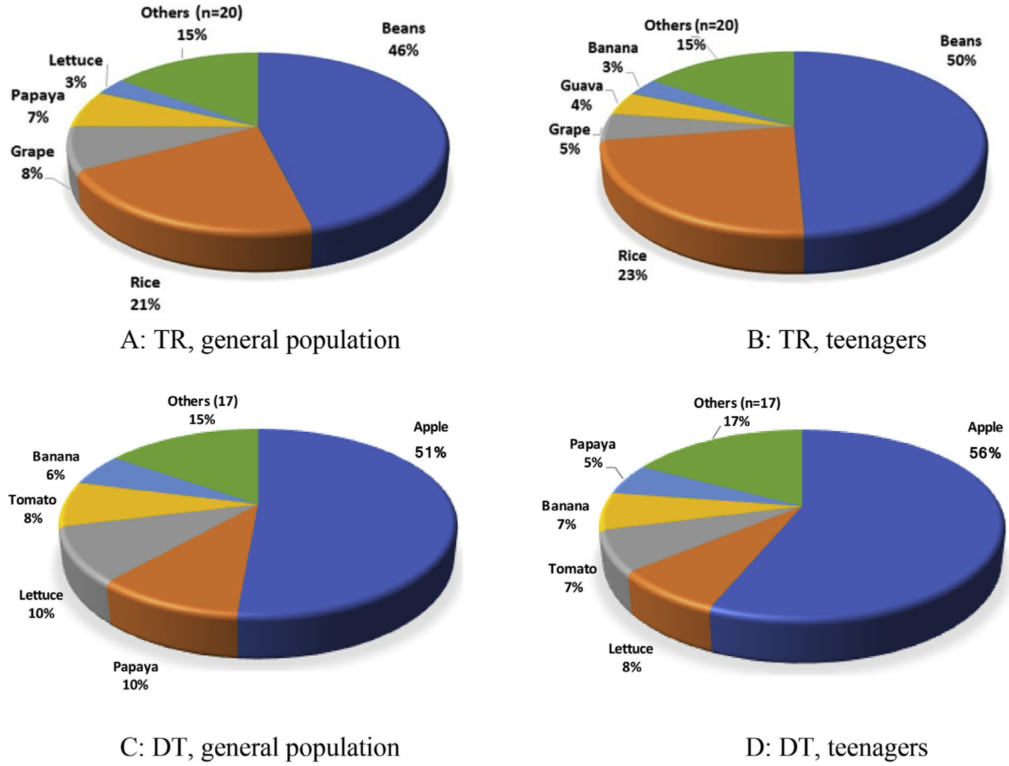

Fig. 4. The foods-as-analyzed that contributed most to the chronic intake of triazoles (TR, A and B) and dithiocarbamates (DT, C and D), in % of the total intake distribution.

Table 5
Percentiles (P) of the cumulative chronic exposure to triazoles and dithiocarbamates for the Brazilian general population using different chronic intake models.

Model	P90	P95	P99.9
TR, μg/kg bw/day (CI)			
BBN	0.117 (0.047–0.144)	0.137 (0.057–0.169)	0.384 (0.173–0.449)
LLN	0.117 (0.047–0.144)	0.137 (0.057–0.169)	0.384 (0.173–0.446)
OIM	0.054 (0.046–0.068)	0.071 (0.061–0.088)	0.386 (0.300–0.469)
MTA1[a]	0.050 (0.043–0.063)	0.061 (0.053–0.076)	0.190 (0.160–0.239)
MTA2[b]	0.049 (0.042–0.063)	0.062 (0.053–0.077)	0.227 (0.194–0.281)
MTA3[c]	0.049 (0.041–0.062)	0.060 (0.051–0.075)	0.186 (0.155–0.226)
MTA4[d]	0.050 (0.044–0.063)	0.062 (0.055–0.077)	0.227 (0.196–0.278)
DT, μg CS_2/kg bw/day (CI)			
BBN	0.239 (0.204–0.487)	0.403 (0.342–0.836)	1.56 (1.28–3.23)
LLN	0.239 (0.203–0.477)	0.493 (0.308–0.822)	1.56 (1.23–3.26)
OIM	0.297 (0.285–0.311)	0.456 (0.438–0.481)	1.72 (1.57–1.84)
MTA2[e]	0.183 (0.173–0.193)	0.259 (0.243–0.278)	0.848 (0.788–1.02)
MTA1[f]	0.180 (0.169–0.190)	0.252 (0.238–0.269)	0.840 (0.772–1.03)
MYA3[g]	0.175 (0.167–0.185)	0.246 (0.233–0.261)	0.836 (0.759–0.981)
MTA4[h]	0.177 (0.167–0.189)	0.248 (0.233–0.267)	0.840 (0.766–1.04)

BBN:; CI = lower (LL. 2.5%) - upper (UL. 97.5%) limits at 95% of confidence interval; LNN:; MTA: model-then-add.
[a] Split of grape, rice and [lettuce, papaya, beans].
[b] Split rice and [grape, lettuce, papaya, beans].
[c] Split rice, grape, lettuce, papaya and beans.
[d] Lettuce and [grape, rice, papaya, beans].
[e] Split of apple, papaya and lettuce.
[f] Split of apple, banana and [lettuce, tomato, papaya].
[g] Split of apple, banana, lettuce, tomato, papaya.
[h] Split of apple, banana, tomato, and [lettuce, papaya].

the conservativeness of this approach, which include also the use of maximum residue limits (MRLs) of animal commodities, the main contributors for the total acute intake in this scenario (Boon et al., 2015).

Table 6
Percentiles (P) of the cumulative chronic exposure to TR and total DT to the Brazilian population, and the risk characterization related to the index compounds (IC). Intakes were estimated with the Model-then-Add model.

P	General population (10–104 years)		Teenagers (12–18 years)	
	Intake, μg/kg bw/day (CI)	% IDA median/UL*	Intake, μg/kg bw/day (CI)	% IDA, median/UL*
Triazoles; IC: cyproconazole, ADI = 20 μg/kg bw/day				
90	0.050 (0.043–0.063)	0.2/0.3	0.052 (0.044–0.068)	0.2/0.3
95	0.061 (0.053–0.076)	0.3/0.4	0.067 (0.056–0.084)	0.3/0.4
99	0.096 (0.086–0.119)	0.5/0.6	0.105 (0.090–0.136)	0.5/0.7
99.9	0.190 (0.16–0.24)	0.9/1.2	0.227 (0.176–0.298)	1.0/1.5
Total dithiocarbamates, as CS_2; IC: EBDC, ADI = 16.9 μg CS_2/kg bw/day**				
90	0.194 (0.184–0.206)	1.2/1.2	0.186 (0.167–0.209)	1.1/1.2
95	0.275 (0.259–0.296)	1.6/1.8	0.267 (0.243–0.299)	1.6/1.8
99	0.512 (0.478–0.565)	3.0/3.3	0.532 (0.451–0.614)	3.1/3.6
99.9	0.902 (0.839–1.09)	5.3/6.4	1.12 (0.774–1.52)	6.7/9.0

CI = lower (LL. 2.5%) - upper (UL. 97.5%) limits at 95% of confidence interval; EBCD: ethylene-bis-dithiocarbamates; ADI: accepted daily intake.
*rounded to up 2 significant figures; **total intake = [intake x 0.93 + (intake x 0.07 × 1.92)].

4.3. Dietary cumulative chronic exposure to triazoles and dithiocarbamates

Various models are available in the MCRA computational tool for modeling chronic intake based on incidental consumption patterns. Which to choose should be determined on a case by-case basis (de Boer et al., 2009). If the criterion of normality is not met with BBN or LLN (e.g. in the case of a multimodal distribution), as shown in this study for the chronic exposure to TR and DT, these models result in erroneous intake estimates. In that case, either OIM or the MTA approach can be used. OIM is known to overestimate the exposure in the right tail of the exposure distribution (Goedhart et al., 2012; Boon and van der Voet, 2015). MTA can be used to model the chronic exposure if different foods and/or food groups with high exposure can be identified, and for which the intake distribution on its own meets the normality criterion, as shown in this study for different combinations of foods/food groups.

The intake percentiles P90, P95 and P99.9 did not differ much between the MTA models tested, and were all lower than the estimates from BBN, LLN or OIM. Although finding the best MTA model was not trivial, demanding expert judgement regarding the selection of food groups to be modelled separately with an exposure model based on normality, this is the best and most refined approach for estimating usual intake when the normality criterion for the distribution of the positive intakes across all foods is not met. This is even more relevant when the exposure approaches or exceeds the ADI.

At P99.9, the cumulative chronic intakes of TR (hepatotoxic common effect) were 0.19 and 0.23 μg/kg bw/day for the general population (10 years or older) and teenagers (12–18 years old), respectively, accounting for about 1% of the cyproconazole ADI. Similar cumulative intakes were found by Boon et al. (2015) using the optimistic approach and OIM for the Danish and Italian populations (0.17 and 0.27 μg/kg bw/day); in the pessimistic approach (also based on OIM), the P99.9 of chronic exposure exceeded the cyproconazole ADI in both countries (by 2.7 and 4.4 times).

The dietary intake assessment of DT was limited by the residue data, which was obtained by non-specific methods that measure the CS_2 generated by the compounds under acid conditions (JMPR, 1994; Caldas et al., 2001), with a potential to produce false positive results in crops containing sulfur compounds (Perz et al., 2000; Abakerli et al., 2015). Struciński et al. (2015) applied the worst-case scenario to estimate the acute exposure of DT in the Polish population, assuming that all CS_2 quantified in the samples originated from the compound with the lowest ARfD among the DT listed in the EU MRL legislation. Similar approach was taken by Jensen et al. (2008), who compared the acute intake in Denmark with the ARfD of maneb, which is three times lower than the ARfD of mancozeb. For the chronic assessment, the authors compared the intake with the mancozeb/maneb ADI, as they are the most frequently used DT in the EU. Similar approach was taken by Gimou et al. (2008) in Cameroon. Conservative approaches were also taken by Valcke et al. (2017) for estimating the chronic risk quotient for the Canadian population using the toxicological reference value for propineb and by Sieke et al. (2018), who used the ADI of ziram, the most toxic DT (ADI of 6 μg/kg bw/day), to characterize the chronic dietary risk for the German population.

In the present study, a more realistic approach was taken. Based on information on agriculture uses (foliar application) and the market share of DT in Brazil, it was assumed that 93% of the analyzed CS_2 originated from the use of EBDC (mancozeb and metiram) and 7% from the use of propineb. A RPF of propineb in relation to EBDC was used to estimate the total DT intake. The total intake represented less than 7% of the EBDC ADI in both the general population and teenagers, mainly due to the consumption of apple (51–56%), which was the food with the highest percentage of positive samples for DT. If a conservative approach was assumed in the present study (that all CS_2 were from the use of propineb), the total intake at P99.9 would represent about 12% of the ADI for propineb (7 μg/kg bw/day), still not representing a risk to consumers.

The previous chronic exposure assessment conducted for the Brazilian population was based on a limited residue database (rice, beans and nine fruits and vegetables) and food availability at the household level as a proxy for individual food consumption, and did not consider prepared food (Caldas et al., 2006). The usual intake was estimated using BBN (MCRA 3.0), which showed normality due to the large consumption database used. Over 48,000 households were included in the survey (covering seven days), leading to over one million person-days (Caldas et al., 2006). Three scenarios were considered: 100% of the CS_2 originated from the use of mancozeb, or that 10, 20 or 30% from the use of propineb. For the general population (2–104 years old), the total intake at P99.9 accounted for 7.5 to 10.4% of the mancozeb ADI, and for children (up to 6 years old) it reached 40% of the ADI. The present study is a refinement of the previous one, mainly due to a larger residue database and the use of individual food consumption data that includes prepared food. However, the assessment for children under 10 years was not possible in this study due to the lack of consumption data.

4.4. Uncertainties and limitations

Uncertainty in dietary exposure assessment can be estimated qualitatively and/or quantitatively, arising mainly from insufficient knowledge about exposure scenarios, but also from the models used and their parameters (Kettler et al., 2015; Tennant et al., 2017). In the present study, uncertainties due to limitations in the available concentration data and/or consumption data were quantified by the bootstrap approach, as recommended by EFSA (2012), and reported as 95% confidence intervals (between the 2.5% and 97.5% percentiles of the uncertainty interval) around the different percentiles of exposure. Among the models that estimated usual intake (BBN, LLN and MTA), the calculated uncertainty was smaller when the MTA model was used, with an UL/LL ratio of about 1.1–1.4, against 2.6 to 3 for BBN and LLN. This was expected as the normality criterion was not met with BBN and LLN, leading to a high uncertainty.

Uncertainties in the residue data are mainly related to sampling, the method of analysis, the approach used to include samples with residue levels below the LOR and the applied processing factors (EFSA, 2012). In the present study, samples were collected in all Brazilian states and the Federal District, giving a high geographic representativeness; however, the sampling procedure used by the monitoring programs may not be statistically representive of the residue situation in the food available in the market. Additional uncertainty in the residue data was inherent to the method of analysis, which was critical for DT, as discussed above. In this study, censored data (< LOR) was considered to have residues at 0 mg/kg (optimistic approach), which may have underestimated the intake. On the other hand, assuming a PF reported as below a certain number as the nominal PF may have led to an overestimation of the intake.

Although the consumption data used in this study included 184 food-as-eaten prepared with the 30 foods-as-analyzed, some consumption data could not be used as the data was reported as "unspecified food" (e.g. fruit, vegetable), as discussed by Jardim et al. (2018). This might have led also to an underestimation of the cumulative intakes, mainly of DT for which fruits and vegetables were the most important foods for the total intake. On the other hand, the lack of processing factors for cooking of rice and beans might be a source of overestimation of the TR intake, for which these foods contributed most for the acute and chronic cumulative intakes.

5. Conclusions

This study is a refinement of the previous one conducted in Brazil for the dietary exposure to DT, and the first conducted on TR in the country. The cumulative acute exposure of TR accounted for up to 0.5% of the ARfD at the P99.9 of the intake distribution for both common effects considered (cranium-facial malformation and skeletal variation) and did therefore not represent a health concern for the relevant population (women of child-bearing-age). The same conclusion was true for the cumulative chronic exposure to TR and DT for individuals from 10 years or older (up to 1 and 6.7% of the respective ADIs). Although laborious and time consuming, the MTA approach proved to be efficient when typical usual intake models do not show a normal distribution, and results are likely to be closer to the true intake, mainly at the highest percentiles.

The current Brazilian individual consumption data did not include children under 10 years, a population that has a higher consumption per kg body weight of certain foods than adults, mainly fruits and vegetables. When this data becomes available, dietary risk assessments for TR, DT and other pesticides present in the Brazilian food supply should also be conducted for this age group.

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.2018.05.002.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2018.05.002.

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