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Dietary exposure of Brazilian consumers to dithiocarbamate pesticides—A probabilistic approach

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Abstract

A probabilistic estimation of the exposure of the Brazilian population to the dithiocarbamate pesticides was performed using the Monte Carlo Risk Assessment program (MCRA 3.5). Residue data, as CS_2, for 3821 samples were obtained from the Brazilian national monitoring program on pesticide residues and from the monitoring program conducted in the Distrito Federal on rice, beans and nine fruits and vegetables. Food consumption data were obtained from a Brazilian household budget survey conducted between 2002 and 2003. Processing factors for washing, peeling or cooking were applied to the residues found in the crops. Daily intakes at the highest percentiles for the general population reached a maximum of 2.0 μg CS_2/kg body weight per day (upper band of the 95% confidence interval at P99.99). Tomato, rice, apple and lettuce were the commodities which contributed most to the intake. Based on the registered uses and the toxicological profile of dithiocarbamates, the risk from exposure was evaluated assuming that all residues came from the use of ethylene-bis-dithiocarbamate (EBDC) or that a fraction of it came from the use of propineb. For this last scenario, a cumulative risk assessment was conducted. In the first scenario, the highest intake reached up to 11.9% EBDC ADI for the general population and up to 31.1% ADI for children. When 30% of the residues were considered as coming from propineb use, the values were 15.2% and 39.7% ADI, respectively.

Keywords: Dithiocarbamates; Chronic exposure; Food; Probabilistic exposure assessment

1. Introduction

Dithiocarbamates are one of the most commonly used pesticides around the world, including Brazil, where five compounds are registered for use in 39 crops of human consumption (ANVISA, 2005). These compounds are also the most frequently detected pesticides in monitoring programs worldwide (EU, 2003; Dogheim et al., 2002). In the Brazilian national monitoring program on pesticide residues (Programa de Análise de Resíduos de Agrotóxicos em Alimentos) (PARA, 2005), 21.6% of the samples analyzed contained detectable residue levels of dithiocarbamates, followed by the organophosphorus and carbamates, with 13.1% of positive samples.

Dithiocarbamates can result in neuropathology, thyroid toxicity and developmental toxicity to the central nervous system of laboratory animals (EPA, 2001a; IPCS, 1993). The ethylene-bis-dithiocarbamate (EBDC) mancozeb was considered to be a multipotent carcinogenic agent in a long-term rat study (Belpoggi et al., 2002). Ethylenethiourea (ETU), formed by the degradation and metabolism of EBDCs present in foods, inhibits thyroid peroxidase and thus induces thyroid cancer in laboratory animals (Doerge and Takazawa, 1990). Deterministic estimations of the chronic dietary exposure of the Brazilian population to these compounds have shown that the intake of dithiocarbamates can be of health concern (Caldas and Souza, 2004; Caldas et al., 2004).

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Although the deterministic method of assessing the dietary exposure is easy to perform and understand, the estimates can be unrealistic and little information can be obtained from the resulting exposure estimate. Another approach to calculate the exposure is the probabilistic method (Cullen and Frey, 1999). In this method, the variation in pesticide residue levels, in food consumption and body weight levels of the population addressed are taken into account. Furthermore, the outcomes give information on the likelihood at which a certain exposure level will occur, as well as the uncertainties associated with it.

In the present work, a probabilistic estimation of the exposure to dithiocarbamates in the Brazilian population was performed, using recent residue data generated by the PARA program and food consumption data obtained from a recent Brazilian household budget survey.

2. Material and methods

2.1. Dithiocarbamate residue data

Dithiocarbamate residue data were obtained from the Brazilian national monitoring program on pesticide residues (PARA, 2005) and from the monitoring program conducted by the Pesticide Residue Laboratory of the Central Laboratory of Public Health of the Distrito Federal (LACEN-DF). The PARA program analyzed 3,301 samples of tomato, potato, carrot, lettuce, orange, apple, banana, papaya and strawberry collected at the local market from 2001 to 2004 in ten Brazilian state capitals, representing five Brazilian regions (those presented in Fig. 1). Data from LACEN-DF concern 520 food samples of rice, beans, tomato, potato, orange, apple, banana, papaya and strawberry collected at the local market from 1998 to 2003 in the Distrito Federal (DF) (Caldas et al., 2004). The PARA program does not include samples collected in the DF area, which is located in the central west region of the country (Fig. 1). The analytical methodology used in both programs analyzed the CS_2 evolved from the acid decomposition of the dithiocarbamate(s) present in the sample. CS_2 levels were quantified either by spectrophotometry (LACEN-DF) and/or gas chromatography (PARA). The methodologies were fully validated for each crop in all laboratories that performed the analyses, with limit of quantification (LOQ) ranging from 0.05 to 0.2 mg CS_2/kg (Table 1). The residue data obtained from the two programs were combined for the exposure calculations.

Table 1
Dithiocarbamate residue data

Crop	Samples		LOQ, mg CS_2/kg	Mean concentration[b], mg CS_2/kg
	Analyzed	Detected[a], %		
Apple	406	56.7	0.08 or 0.2	0.309
Tomato	603	44.9	0.08 or 0.1	0.202
Papaya	323	38.4	0.08 or 0.1	0.198
Lettuce	297	34.0	0.08 or 0.1	0.361
Strawberry	482	32.0	0.08 or 0.1	0.154
Banana	267	13.9	0.08 or 0.1	0.099
Orange	541	7.2	0.05, 0.08 or 0.1	0.065
Carrot	435	9.7	0.08 or 0.2	0.040
Potato	396	4.8	0.08 or 0.1	0.052
Beans	32	3.1	0.1	0.052
Rice	39	0	0.1	0.050

[a] $\geqslant$LOQ.
[b] Levels at < LOQ were considered at 1/2 LOQ.

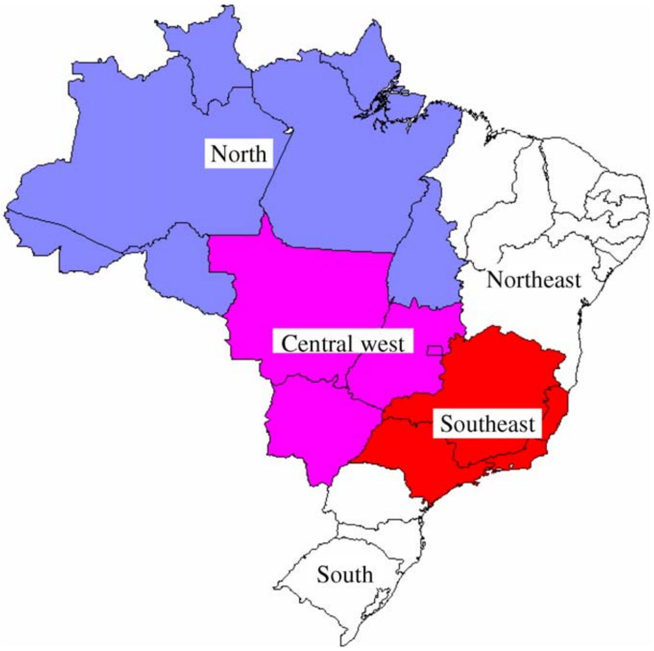

Fig. 1. Brazilian regions and states. *North:* Amazonas, Pará, Acre, Rondônia, Roraima, Amapá and Tocantins; *Northeast:* Maranhão, Ceará, Piauí, Rio Grande do Norte, Pernambuco, Alagoas, Paraíba, Sergipe and Bahia, *Central west:* Mato Grosso, Mato Grosso do Sul, Goiás and Distrito Federal; *Southwest:* Minas Gerais, São Paulo, Espirito Santo and Rio de Janeiro: *South:* Santa Catarina, Paraná and Rio Grande do Sul.

2.2. Food consumption data

The food consumption data were obtained from a Household Budget Survey (HBS) conducted by the Brazilian Institute of Geography and Statistics (IBGE, 2005) from July 2002 to June 2003, including 48,470 households covering the urban and rural areas of all 27 Brazilian states. For 45,348 households, information on the amount of food entering the household was recorded in a diary over 7 consecutive days, and included acquisition using monetary or non-monetary sources. The diary allowed multiple entries for any food during the period of one week. Characteristics of the household members, including age, sex and weights (for individuals older than 20 years) were obtained through questionnaires. The weights of individuals aged less than 20 years were estimated using the US National Health and Nutrition Examination Survey (CDC, 2000).

For the underlying study, the relevant information of the HBS survey was extracted. A total of 5442 food descriptions were reported. Food descriptions concerning the same commodity were grouped (e.g. 108 descriptions for banana, 131 descriptions for dry beans), as well as foods from larger groups (e.g. chicken meat, cow edible offal, sea fish, tomato sauce, soda). A total of 244 food commodities or groups were generated. Only food commodities for which pesticide residue data were available were considered in the present study (see previous section). For the purpose of this study, the amount of food acquired by each household was considered as food consumed.

The 27 Brazilian states are grouped by IBGE (2005) into large regions (Fig. 1), named North (N), Northeast (NE), Central west (CW), Southeast (SE) and South (S), according to their economical, social, political and geographical characteristics. The data obtained from the survey were treated separately for the populations of each region. Due to the limitation of the MCRA program to process very large data sets, the northeast region data was divided into two sub-regions. The results of these two sub-regions were averaged and presented as one figure for the whole northeast region.

For each household, the total week consumption of each food obtained from the HBS data was divided by the household size to generate weekly consumptions per individual. In order to convert these weekly consumptions per individual into daily consumption patterns per individual, as necessary to model chronic exposure, consumption frequencies over the 7 days of the week (WCF) were estimated based on the frequency in which a food was reported in the food diaries as obtained in the HBS study. WCF is the number of days within a week that a food is consumed. The consumption patterns over 7 days for each individual were generated in a SAS System for Windows (Release 8.02 TS level 02MO. SAS Institute Inc. Cary, NC 1999–2001, USA), using WCF and allowing 10% variation among consumed days. For the exposure calculation, WCFs were rounded to 1 significant figure and WCF <1 were considered to be 1.

2.3. Monte Carlo exposure assessment model

The exposure assessment was conducted using the Monte Carlo Risk Assessment (MCRA 3.5) system, an internet-based program developed by RIKILT—Institute of Food Safety in the Netherlands (Boer et al., 2005). For chronic assessment, the program requires a minimum of two consumption days per individual. The distribution of the chronic exposure is calculated by combining the mean residue level of the chemical of interest per food with the empirical distribution of consumption, summed over foods, and expressed per kg body weight per day. In this study, residue levels at <LOQ were considered as 1/2 LOQ for the calculation of the mean concentration.

The resulting distribution of exposure is then analyzed with statistical methods for chronic intake as developed at the Iowa State University (Nusser et al., 1996). The model works by first restricting the statistical analysis to the non-zero intake values, and later recombining the results with the perceived frequencies of zero intakes. The non-normal intake data are transformed to approximate normality using a power transformation. The uncertainties of output statistics were assessed using bootstrap distributions, which characterize the uncertainty of the inference due to the sampling uncertainty of the original dataset. It shows which statistics could have been obtained if random sampling from the population would have generated another sample than the one actually observed (Efron, 1979).

An iteration represents a random selection of one consumption day from the food consumption database combined with the mean residue level of each of the products consumed during that day and which contain the residue of interest. Experiments conducted with 5000–20,000 iterations per bootstrap and 100–500 bootstraps showed that the intakes at the higher percentiles (>90) and their uncertainties varied only at the second or third decimal digit. As a higher number of iterations and/or bootstraps took longer to be processed, the optimal parameters to be used in each simulation were found to be 200 bootstraps of 10,000 iterations each. The simulation for the larger data set took approximately 40 hours to be completed. The outputs from the intake distribution generated after the simulations were specified at percentiles P90, P95, P97.5, P99, P99.9 and P99.99. The uncertainties for each percentile were given at 2.5%, 25%, 75% and 97.5% confidence levels. To calculate the contribution of the different products to the chronic dithiocarbamate intake, we calculated the intake by multiplying randomly drawn consumption patterns from the food consumption database with randomly selected residue data from the concentration database per product (20,000 iterations and 200 bootstraps). The resulting set of intakes was used to assess the contribution. Also here, non-detects were assigned levels equal to 1/2LOQ.

2.4. Processing factors

We did not find typical default processing factor (PF) values for dithiocarbamates in the literature. However some studies have given some indication of the impact of processing on residue levels of individual dithiocarbamate pesticides. Kontou et al. (2001) showed that residues of maneb in tomato were drastically reduced after cooking, with a PF of 0.26. Data submitted to the 2003 JMPR showed that washing tomato and peeling citrus fruits reduced the residues, as CS_2, with average PFs of 0.3 and 0.08, respectively (FAO, 1993). To make the exposure calculations more realistic we therefore included the following PFs in the exposure calculations and assumed that all consumers consumed the products after the form of processing indicated: PF of 0.26 to residues in beans, rice and potato (cooking), of 0.3 to residues in apple, strawberry, carrot, lettuce and tomato (washing) and of 0.08 to residues in orange, banana and papaya (peeling).

3. Results and discussion

3.1. Dithiocarbamate residue data

Table 1 summarizes the results of the 3821 samples of fruits, vegetables, beans (dry, without pods) and rice (polished) analyzed for dithiocarbamate residues. Apple and tomato had the highest frequency of samples containing residues at or above the LOQ, while lettuce and apple presented the highest mean concentrations. Strawberry had the highest number of samples (90 or 18.7% of the samples analyzed) with residues above the maximum residue level (MRL) established by the Brazilian legislation for dithiocarbamates ($MRL = 0.2$ mg CS_2/kg) (ANVISA, 2005). Apple and lettuce had one sample above the MRL (2 and 6 mg CS_2/kg, respectively), while 7 potato samples were above the MRL (0.3 mg CS_2/kg).

Only one bean sample contained detectable residues and no rice (polished) samples showed residues above the LOQ. Although very few samples of bean and rice were analyzed, it is most likely that these results reflect the real residue situation for these commodities. Dithiocarbamates are non-systemic fungicides and most of the residues are expected to be removed during the process from husk rice to polished rice and of removing the pods from the bean vines (FAO, 1993).

3.2. Food consumption data

For this study, only the 45,348 households (93.6% from the total surveyed) which reported data using food diaries were considered. The population of these households, named *total survey* population, was composed of 174,378 individuals (Table 2). From the households with consumption data, 34,038 (75.1%) reported data on the 11 relevant foods for this study (Table 1). The population concerning

Table 2
Characteristics of the Brazilian population considered for dietary exposure

Region	Total survey population[a]		Consumers[b]	
	Individuals	Male/children ⩽ 6 years, %	Individuals	Male/children ⩽ 6 years, %
North	27,928	50.6/13.9	21,562	50.8/14.0
Northeast	72,426	48.6/11.9	60,361	48.8/11.9
Central west	26,093	49.3/10.9	17,566	49.3/10.4
Southeast	28,668	49.5/9.7	20,222	49.5/9.4
South	19,263	49.1/9.6	14,329	49.0/9.3
Brazil	**174,378**	**49.2/11.5**	**134,040**	**49.3/11.4**

[a] Reported food consumption data.

[b] Reported consumption data on the 11 relevant foods.

these households, named *consumers*, defined as those consuming at least one of the 11 foods, was composed of 134,040 individuals. In Table 2, the number of individuals and the percentage male and children aged ⩽6 years are shown for each region. Age ranged from less than 1 year (newborn) up to 110 years (mean of 28 years) and body weight from 3 kg up to 200 kg (mean of 53.1 kg). With the exception of the north region, the majority of the surveyed population was female. Children up to 6 years of age represented a maximum of 13.9% of the total survey population.

In all regions, rice was the most frequent food reported in the diaries, and a WCF of 7 was assigned for this crop, meaning that it is consumed daily by the total survey population. This frequency of consumption agrees well with the fact that rice is a staple food in the Brazilian diet (Sichieri et al., 2003). Beans was the second most frequently consumed food (mean WCF among the regions of 6.0), what also agrees with the dietary pattern normally found in the country. For tomato, the mean WCF was 4.6, followed by 3.9 for banana, 3.2 for potato, 2.0 for orange, 1.8 for apple, lettuce and carrot, 1.1 for papaya and 0.1 for strawberry. The WCF of fruits and vegetables considered in this study were lower in the northern and northeast regions and higher in the southern and southeast regions of the country. For beans, the WCF coefficient of variation among the regions was 9.5%. For the other commodities, much larger variations were found (from 20% for tomato to 106% for strawberry), indicating a higher variability in dietary patterns among the regions for these crops.

Table 3 shows a summary of the food consumption data. In this study, we assumed that the food acquired during a week is consumed during this period, and is distributed over the days of the week as determined by the WCF. Although this might not be totally true for non-perishable crops like rice, this could approach reality for the fruits and vegetables considered in this work. For each commodity, the percentage of positive days is proportional to the WCF. Except for rice and beans, the north and northeast regions showed, in general, the lowest % of positive days. The standard variation (s.d.) of the daily consumption was at least 2.8 times the mean, reaching over 45 times the mean for papaya and over 100 for strawberry, meaning that a large range of consumption values exists for these crops. The raw data showed that very low (<5 g/household/week) or extremely high (e.g. 10 kg/household/week of papaya) levels of consumption were reported for all commodities. Although these values might be considered outliers, they were not removed from the data set, and their impact on the intake calculations is discussed later in this paper.

The Brazilian household budget food survey (HBS) used in this study is the most recent and most complete HBS conducted in the country. However, the use of HBS data for conducting intake assessment has limitations (Byrd-Bredbenner et al., 2000; Serra-Majem et al., 2003). In particular, HBS data do not account for outside household consumption (underestimates the consumption), and for wasted food and food consumed by visitors (overestimates the consumption). The Brazilian HBS allowed for the recording of any food entering the household and was not limited to what was bought. Extremely high consumption values calculated for all foods were probably due, for example, to storage or self production. Serra-Majem et al. (2003) found that, in general, results from HBS studies in Canada and Europe agreed well with the individual dietary data, but underestimated consumption of fish, meat, pulses and vegetables and overestimated that of sugar, honey and cereals.

Another weakness of the HBS data is that it is currently not possible to extrapolate the data to individual food consumption levels within the household. This is particularly important when a subpopulation is to be considered, e.g. children, for which the amount consumed, per kg body weight, can be overestimated in some cases. Chesher (1997) proposed a semi parametric approach to solve this problem, by taking into account the relationship between age, sex and intakes of energy and nutrients to decompose

Table 3
Summary of estimated consumption data[a], in g/person/day

	North			Northeast			Central west			Southeast			South		
	% pos	Mean	s.d.	% pos	Mean	s.d.	% pos	Mean	s.d.	% pos	Mean	s.d.	% pos	Mean	s.d.
Apple	1.0	2.6	54.9	1.1	2.0	35.3	2.8	5.0	58.2	5.6	5.9	56.8	6.6	8.4	68.8
Tomato	11.4	9.0	42.3	23.7	14.2	50.7	18.2	14.1	47.1	23.4	14.3	81.6	22.1	13.9	50.9
Papaya	0.7	2.7	121	0.9	4.3	82.1	0.6	3.1	125	2.8	6.6	123.2	2.4	5.4	146
Lettuce	1.0	2.4	18.8	1.0	0.8	11.7	6.9	1.8	19.0	11.2	1.7	46.6	15.3	3.2	22.5
Strawb.	0.0	0.0	14.0	0.0	0.0	8.7	0.1	0.2	14.6	0.2	0.3	14.2	0.2	0.5	17.6
Banana	9.8	20.4	78.5	14.2	16.2	71.3	11.2	15.0	74.3	22.8	23.1	98.3	25.3	33.7	96.8
Orange	1.1	5.2	127	4.2	9.8	92.3	3.1	11.3	134	9.1	14.5	46.7	9.5	30.0	168
Carrot	1.0	2.4	45.2	3.0	4.4	34.7	3.3	4.7	48.0	6.3	5.3	132.1	5.1	5.0	55.1
Potato	4.5	7.4	48.1	7.2	8.3	42.0	10.6	13.0	54.2	24.2	22.6	67.1	32.4	35.4	81.8
Beans	29.9	30.7	87.8	48.5	46.3	140	25.6	31.9	89.6	24.4	41.1	18.2	24.8	26.2	93.0
Rice	55.4	95.9	293	58.4	98.1	300	36.2	141	328	32.0	104	298	32.5	69.0	322

[a] % pos = % of days with non-zero consumption related to the total survey population; mean and standard deviation (s.d.) for the total survey population.

the British HBS data into individual intake data. A similar approach is currently being developed at the National Institute for Agricultural Research in France (INRA) However, the method is rather laborious and is not yet available for use on a routinely basis.

3.3. Exposure assessment

Percentiles of chronic exposure and their uncertainties were calculated for three different scenarios: total survey days, consumers and consumer-days-only. For the *total survey days* scenario, all the individuals in the survey (including those consuming none or at least one of the 11 foods containing dithiocarbamates) (Table 2) and all the 7 survey days were taken into account. For the *consumers*, only the survey days are included of those individuals who consume at least one of the relevant foods on at least one of the 7 weekdays (Table 2). The number of zero intake days which can be simulated in the *consumers* will therefore be smaller than those simulated for the *total survey days* scenario, as the *consumers* do not include individuals who do not consume any of the relevant foods on any of the 7 weekdays. In both scenarios, the total number of non-zero intake days and zero intake days vary among the commodities and depend on the WCF. It is important, however, to realize that any individual has a positive intake probability of any food on any day, and days with zero intakes for a certain food actually reflect non-zero usual intake. For *consumer-days-only*, only non-zero consumption survey days are considered in the distribution, resulting in the simulation of non-zero intake days.

Table 4 shows the percentiles of dithiocarbamate chronic exposure via the consumption of the 11 foods considered. In principle, the intakes for the total survey days should be below those for consumers, and these should be below those simulated for consumer-days-only, as described above. For all regions, the intakes at the highest percentiles (P99.9 and P99.99) were similar for the scenarios of total survey days and consumers (maximum of 1.37 and 1.84 μg CS_2/kg body weight per day, respectively, for the central west region). In general, the difference between the intakes for these two scenarios increased as the percentile decreased. At P90, the ratio between the two intakes reached a maximum of 1.27 (central west region), with the highest level simulated for the group consumers. These results are expected as the exposures at higher percentiles are driven by individuals actually consuming foods containing dithiocarbamates.

When only non-zero consumption days are considered (consumer-days-only), the intake was considerably higher, and the difference related to the other scenarios increased as the percentile increased. This was true for all regions. At P99.99, the intake for consumer-days-only was about 1.8 times higher than the intake found in the other scenarios.

Table 4
Exposure to dithiocarbamate fungicides, as CS_2, at various percentiles in all scenarios in the Brazilian regions

Percentile	North	NE	CW	SE	South
Total survey days, in μg CS_2/kg body weight/day					
50	0.022	0.040	0.030	0.033	0.034
90	0.160	0.182	0.237	0.224	0.210
95	0.249	0.267	0.352	0.340	0.319
97.5	0.363	0.367	0.485	0.477	0.449
99	0.559	0.541	0.689	0.707	0.656
99.9	1.14	0.957	1.37	1.32	1.22
99.99	1.64	1.32	1.84	1.81	1.68
Consumers, in μg CS_2/kg body weight/day					
90	0.187	0.210	0.301	0.284	0.254
95	0.282	0.289	0.427	0.415	0.368
97.5	0.396	0.397	0.580	0.566	0.508
99	0.602	0.549	0.811	0.814	0.746
99.9	1.14	0.957	1.37	1.32	1.22
99.99	1.64	1.32	1.84	1.81	1.68
Consumer-days-only, in μg CS_2/kg body weight/day					
90	0.215	0.216	0.337	0.297	0.268
95	0.324	0.311	0.480	0.432	0.392
97.5	0.461	0.427	0.650	0.595	0.543
99	0.697	0.617	0.917	0.859	0.788
99.9	1.64	1.32	1.84	1.81	1.68
99.99	3.33	2.48	3.21	3.28	3.08

No significant differences were detectable between the intakes in the north, central west, southeast and south regions for the tree scenarios at P99.99 (Fig. 2). However, these intakes were significantly higher compared to those found in the northeast region. These results can be explained by investigating the input data used in the exposure estimates. Apple and lettuce were the commodities with the highest mean concentrations found in the analyzed samples (Table 1). The mean consumption of these two crops in the northwest region, however, were the lowest within Brazil (2.0 ± 35.3 and 0.8 ± 11.7 g/person/day, respectively, Table 3).

On average, tomato contributed 24.6% to the total intake, followed by rice (20.1%), apple (19.2%), lettuce (8.8%) and beans (8.0%). Strawberry was the commodity which contributed least to the intake (0.3%) (Fig. 3). Indeed, contribution of apple to the total intake in the northeast region was the lowest among the regions, and of lettuce it was the third lowest among the regions (23). The significant contribution of rice to the total intake, even though no residues were detected in rice samples, was due to the relatively high LOQ (0.1 mg CS_2/kg) and the high consumption frequency of this crop by the Brazilian population.

The relatively high LOQs shown in Table 1 are typical of the spectrophotometric method used by most of the laboratories to analyze CS_2. To evaluate the impact of assigning 1/2 LOQ to samples with residue levels <LOQ, as used in this study, we repeated the assessment for the southern region by assigning zero to these samples. The intakes at $\geqslant$P90 were, on average, 57% of the values listed in Table 4 for this region (data not shown), indicating a relatively high impact of the level assigned to the non-detect samples on the exposure assessment. This was very likely

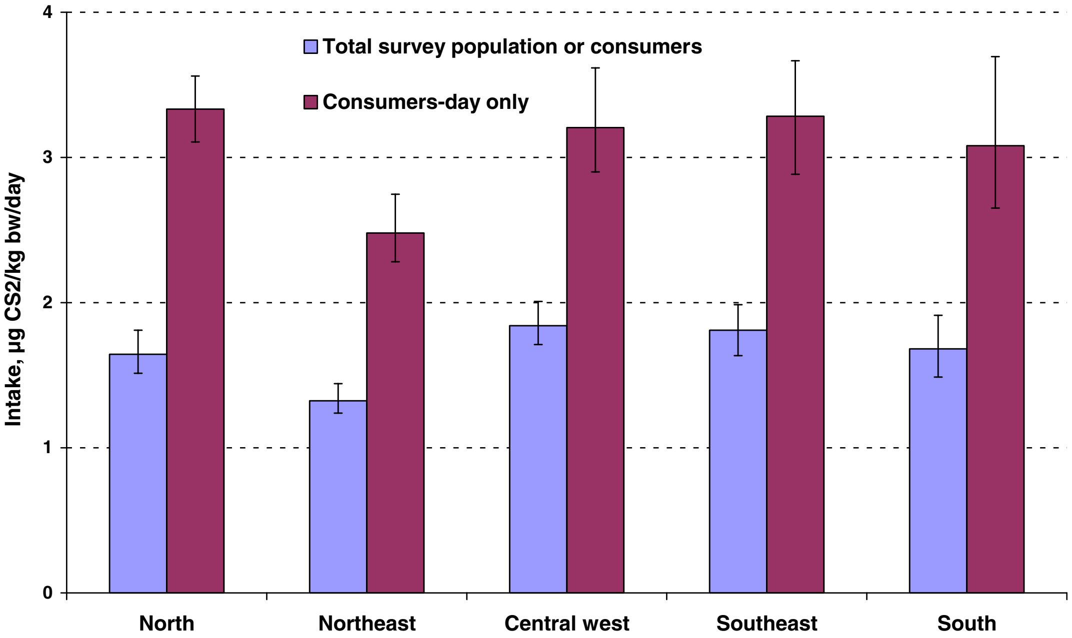

Fig. 2. Chronic dietary exposure to dithiocarbamate in Brazilian regions through the consumption of beans, fruits and vegetables at P99.99. The uncertainties shown represent confidence levels at 2.5% and 97.5%.

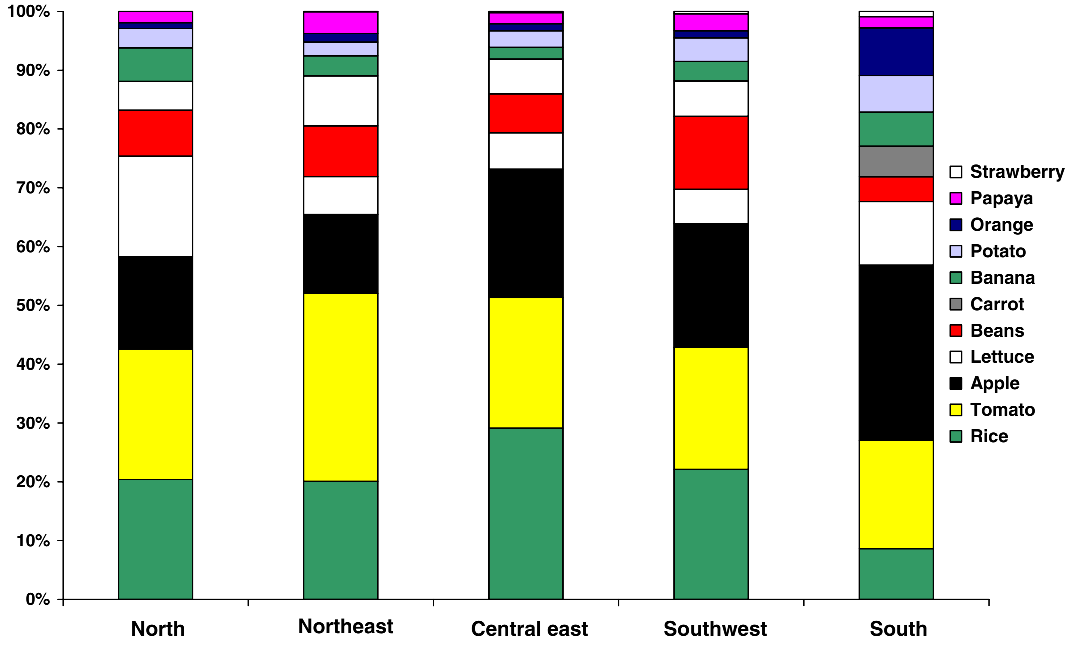

Fig. 3. Contribution (%) of the foods to the dietary exposure to dithiocarbamate in the Brazilian regional populations.

due to the large number of non-detect samples in the whole residue database addressed here. However, assuming samples with levels <LOQ to be equal to zero is probably not conservative enough to assess the chronic exposure to dithiocarbamates in this study. As all crops considered have registered use of at least one compound of the group, we assumed that all crops are likely that to be treated. No data on percentage of crop treated in Brazil are available.

Fig. 4 shows the calculated intakes for children up to 6 years of age (total survey days of children). As children have higher food consumption levels per kg body weight, the intake at any percentile was higher than those found in the general population, reaching up to 5.3 µg/kg body weight in the northern and southern regions (at the upper band of the 95% confidence interval at the P99.99). Again, the intakes in the northern region were the lowest within the country. It is possible that these exposures are

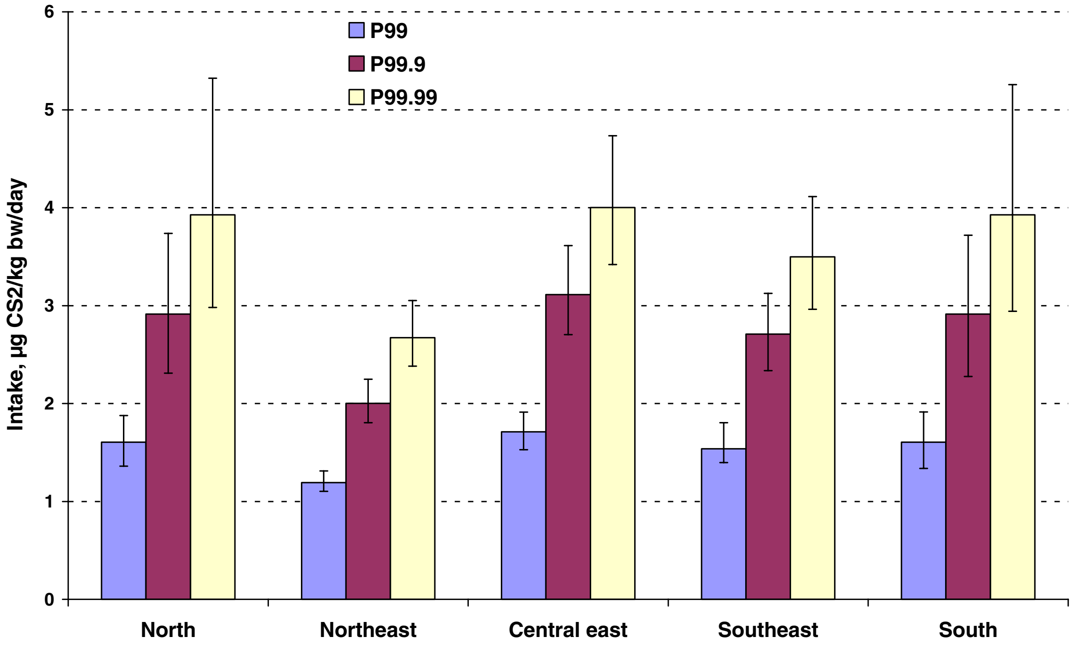

Fig. 4. Chronic dietary exposure to dithiocarbamates for children up to 6 years old (total survey population) at the highest percentiles. The uncertainties shown represent the confidence levels at 2.5% and 97.5%.

overestimated due to limitation of the HBS to discriminate between consumption profiles of individuals within a household, assuming the same consumption level for children and adults.

While the results for the total survey days and consumers scenarios might underestimate the consumption for individuals (household) who did not report acquiring the food during the week of the survey, extremely high levels of consumption reported by others might have overestimated the exposure, e.g. due to buying food for the whole week, or longer. In any case, it is possible that the intakes at higher percentiles were driven by the very high consumption values found for all crops in all regions. Indeed, for example, papaya consumption of >3000 g/person/day was among the top 10 consumptions at the highest intakes in the simulations.

3.4. Dietary risk assessment of dithiocarbamates

The analytical methodology currently applied in most laboratories to analyze dithiocarbamates in food does not discriminate among the compounds used in the crops. The results are therefore expressed as CS_2 derived from any dithiocarbamate present (EU, 2003; Dogheim et al., 2002; Caldas et al., 2004). To evaluate the potential risk of dietary exposure to dithiocarbamates, the estimated intakes need to be compared to a toxicological reference value of one compound within the dithiocarbamate class or to a group of compounds with the same mechanism of toxicity, assumed to have been present in the food analyzed. According to the Compendium of Pesticide Common Names (CPCN, 2005), 21 compounds belong to the dithiocarbamate class of pesticides, of which six have been registered for use in Brazil as of December 2004: maneb, mancozeb, metiram, metam sodium (metam), propineb and thiram. The use of maneb was canceled in 2005 (ANVISA, 2005). Of these compounds, maneb, mancozeb and metiram belong to the group of ethylene-bis-dithiocarbamates (EBDC).

Although all dithiocarbamates produce carbon disulfide (CS_2) *in vivo*, which is a known inducer of chronic distal peripheral neuropathy in laboratory animals, only the EBDCs, ziram (a dithiocarbamate not registered in Brazil) and thiram were found to act by a common mechanism of toxicity for distal peripheral neuropathy via this metabolite (EPA, 2001a). However, no accepted daily intake (ADI) has been assigned to reflect this toxicity. The EBDCs can also induce thyroid cancer in laboratory animals through another common metabolite, ethylenothiourea (FAO, 1993; EPA, 2001b). Based on this toxicological profile, an EBDC group ADI of 30 µg/kg bw/day (16.9 µg CS_2/kg bw per day) was established in 1993 by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) based on the non-observable-effect-level (NOAEL) found on long term studies for thyroid effects in dog for metiram (2.5 mg/kg bw/day) and in rat for mancozeb and maneb (4.8 and 5 mg/kg bw/day, respectively) (FAO, 1993).

Propineb has the same mechanism of action as the EBDCs, but through the metabolite propylenethiourea, having an ADI of 7 µg/kg bw/day (3.7 µg CS_2/kg bw/day) established by the JMPR, based on the NOAEL of 0.74 mg/kg bw/day found on short-term study (62 days) for thyroid effects in rat (FAO, 1993). A NOAEL of 2.5 mg/kg bw/day was also found on a long term study for the same effects.

Thiran has an ADI of 0.01 mg/kg bw/day (FAO, 1992). No ADI has been established for metam by either the JMPR or the Brazilian government. An ADI of 10 μg/kg bw/day (5.9 μg/kg bw CS_2/day) has been established by the German authorities (BgVV, 2001).

According to the toxicological profile of the compounds, three exposure scenarios to dithiocarbamate pesticides can be visualized: the CS_2 residues detected in the samples are derived from the use of: (1) thiram, metam or propineb alone; (2) of at least one compound within the EBDC group; or (3) of any EBDC and propineb.

The first exposure scenario, meaning that none of the EBDCs was the source of the residues found in the samples, is unlikely to occur. At least one EBDC compound was allowed for use in 36 out of the 39 commodities registered for dithiocarbamates during the period of the PARA program, including all crops relevant for this study, except strawberry (ANVISA, 2005). The EBDC mancozeb is by far the most used dithiocarbamate in the country, with 15 commercial products on the market as of December 2003 (SINDAG, 2004). The use of mancozeb determined most of the MRLs set for the dithiocarbamates, as CS_2, by the Brazilian authorities (ANVISA, 2005). In addition, thiram is registered in Brazil only for seed treatment (ANVISA, 2005), and, although metam is the only product registered for strawberry, the contribution of this food to the total intake was not significant (maximum of 0.9%; Fig. 3).

In the second exposure scenario, all the CS_2 analyzed in the crops relevant for this study were assumed to have come from the use of any EBDC. In this case, the intake estimates (in μg CS_2/kg bw/day) should be compared with the EBDC ADI (16.9 μg CS_2/kg bw/day). Table 5 shows the contribution of the exposure at national level (mean of all regions) and for the highest exposure region for the general population and children up to 6 years at the highest percentiles (total survey days or consumers), in % of ADI. For the general population, the exposure contributed to a maximum of 11.9% ADI, and for children, to a maximum of 31.1% ADI. This risk from the exposure for children was probably overestimated, as the food consumption for children obtained from HBS data might be overestimated, as it was discussed previously. For the consumer-days-only (data not shown), the intake could contribute to 21.8% of the ADI (southern region, upper band of the 95% confidence interval at P99.99) for the general population. However, this risk level is unlikely to occur over a long term period, as both zero and non-zero consumption days are expected to occur over a life time.

When we consider the third exposure scenario, in which propineb, in addition to any EBDC, was also the source of the CS_2 detected in the samples, the registered use of this compound should be investigated in detail. Propineb is registered for foliar application in potato, beans, apple and tomato, and only one product containing this compound is commercialized in the country (ANVISA, 2005). In addition, only the lettuce MRL was driven by the use of propineb. When this profile is compared with the EBDC registration profile discussed earlier, we find that the fraction of crops treated with propineb is probably small compared with that of the EBDCs, mainly of mancozeb.

To calculate the total CS_2 intake in the third scenario, the concept of cumulative exposure from compounds with the same mechanism of toxicity has to be applied (Wilkinson et al., 2000). In the toxicity equivalence factor (TEF) cumulative approach, exposures to a group of common mechanism chemicals with different potencies are normalized to yield a total equivalent exposure to one of the chemicals, called the index compound (IC). This approach has been applied for the cumulative exposure of organophosphorous and carbamates pesticides (EPA, 2001c; Boon and Klaveren, 2003). Hamilton (1998) also considered the common thyroid toxicity of the EBDCs and probineb to estimate the dietary intake of these compounds. In the present study, the different potencies among the EBDCs were not taken into account and mancozeb, the main EBDCs used in Brazil, was considered the IC for the group. The TEF for propineb (equal to 1.92) was calculated as the ratio between the NOAEL found on long term studies for thyroid effects in rats for mancozeb and propineb (shown previously).

To calculate total equivalent exposure, as mancozeb, the TEF was applied to the intake fraction coming from the use of propineb (intake * % of residues as propineb) and

Table 5

Risk assessment of the exposure of the Brazilian population to the dithiocarbamate pesticides, in % ADI, for general population and children up to 6 years old, at the highest intake percentiles, considering that 100% of the residues come from the use of any ethylene-bis-dithiocarbamate (EBDC) or that a fraction (%) comes from the use of propineb (PB)

	National[a]	Highest[b]	National[a]			Highest[b]		
	100% EBDC	100% EBDC	10% PB	20% PB	30% PB	10% PB	20% PB	30% PB
General population								
P99.9	6.9 (6.4–7.4)	8.1 (7.6–8.7)	7.5 (7.0–8.1)	8.1 (7.6–8.8)	8.8 (8.2–9.5)	8.9 (8.4–9.5)	9.6 (9.0–10.3)	10.4 (9.7–11.1)
P99.99	9.5 (8.7–10.4)	10.9 (10.1–11.9)	10.4 (9.5–11.3)	11.2 (10.4–12.3)	12.1 (11.2–13.2)	11.9 (11.1–13.0)	12.9 (12.0–14.1)	13.9 (12.9–15.2)
Children								
P99.9	13.5 (11.3–16.2)	17.2 (13.5–22.1)	14.7 (12.3–17.7)	15.9 (13.3–19.2)	17.2 (14.4–20.7)	18.8 (14.7–24.0)	20.4 (16.0–26.1)	22.0 (17.2–28.1)
P99.99	17.8 (14.5–22.2)	23.2 (17.4–31.1)	19.4 (15.8–24.2)	21.0 (17.2–26.2)	22.7 (18.5–28.3)	25.4 (19.0–33.9)	27.5 (20.6–36.8)	29.6 (22.2–39.7)

[a] Mean of the Brazilian regions.

[b] Highest exposure population among the regions: central west region for the general population and south region for children. The ranges represent the lower (2.5%) and the upper (97.5%) bands of the 95% confidence interval, given by the bootstraps.

the normalized intake added to the intake fraction coming from the use of EBDC (intake * % of residues as EBDC). The calculated intakes for the highest percentiles, expressed as % ADI are shown in Table 5. The national intake, when 10% of the residues were considered to originate from the use of propineb, for the general population and children reached 11.3% and 24.2% ADI, respectively. In the highest exposure populations, those numbers were 13.0% and 33.9% ADI. In general, the impact of the presence of residues from propineb on the exposure scenario was only significant when propineb contributed to 30% of the residues.

The processing factors used in this study were an estimation of the effects of cooking, washing and peeling to the dithiocarbamate residues found in the samples. When these effects are not considered (PF equal to 1), indicating a worst case situation, the intakes were, on average, 4.4 times higher than what was found when processing effects were considered. However, not considering processing effects is unrealistic, particularly in those cases where food needs to be cooked before consumption.

4. Conclusions

This study showed that the chronic dietary intake of dithiocarbamates by the Brazilian population through the consumption of 11 food products did not exceed the toxicological acceptable level. Although the main crops with registered use of dithiocarbamates were considered in the study, it is important to emphasize that another 28 crops of human consumption have registered use of dithiocarbamate pesticides in the country, including cucumber, squash, bell pepper and grapes. Presently, no pesticide residue data is available for these crops at national level. Although the consumption data used here is the most updated available, there is a need for data which reflects real food consumption patterns in Brazil, mainly for children.

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