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Food and Chemical Toxicology 42 (2004) 1877–1883

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Dithiocarbamates residues in Brazilian food and the potential risk for consumers

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Received 6 March 2004; accepted 16 July 2004

Abstract

Dithiocarbamates are a non-systemic group of pesticides widely used to protect crops from fungal diseases. The current methodology used by monitoring laboratories to determine dithiocarbamates in food involves the analysis of CS_2 generated after hydrolysis of the compound present in the sample. This method does not identify the origin of the CS_2 detected, which may or may not be related to the presence of pesticides leading to a potential overestimation of the dietary dithiocarbamate intake. In this paper, 520 food samples (papaya, banana, apple, strawberry, orange, potato, tomato, rice and dry beans) collected in the local market of the Federal District, Brazil, were analyzed for dithiocarbamate content. Detectable levels ($\geqslant$0.10 mg/kg CS_2) were found in 60.8% of the samples, with the highest levels (up to 3.8 mg/kg) found in strawberry, papaya and banana. No residues were found in rice (polished) and only one dry bean sample had detectable levels of the fungicides. Detectable residues were found in the pulp of banana, papaya (including the seeds) and orange (50–62% of the analyzed samples). An exposure assessment, based on dithiocarbamate levels detected in the food crops analyzed in this study, confirms that the intake of dithiocarbamates through food consumption in the country does not represent a health risk to consumers, i.e., the estimated daily intake is less than the acceptable daily intake. Furthermore, the implementation of more selective methodologies to individually analyze these compounds in food monitoring programs in Brazil is not necessary.

Keywords: Dithiocarbamate fungicides; Food analysis; Chronic dietary risk assessment

1. Introduction

Brazil is the third largest market for pesticide sales in the world, with almost 400 active ingredients registered in the country, including six dithiocarbamate fungicides (Table 1). Based on a previous chronic dietary risk assessment of pesticides, using national maximum residue levels (MRL) as the parameter for residue concentration in crops, the total intake of dithiocarbamates through the daily consumption of treated crops exceeded the acceptable daily intake (Caldas and Souza, 2000). The toxicological significance of ethylene bisdithiocarbamate residue in food is related to the metabolite or its degradation product ethylenethiourea, known to be carcinogenic and teratogenic in rats (WHO, 1994; Belpoggi et al., 2002). Laboratory animals that ingested dithiocarbamates were shown to develop neuropathology, thyroid toxicity, and developmental toxicity to the central nervous system (EPA, 2001; WHO, 1994).

The methodology most commonly used by monitoring laboratories to analyze dithiocarbamates in natural food products relies on the detection of CS_2 generated after acid digestion of any dithiocarbamates present in

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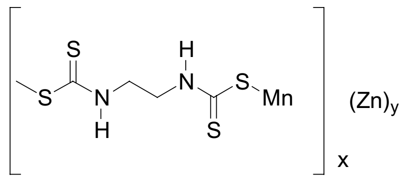
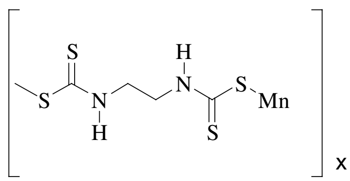
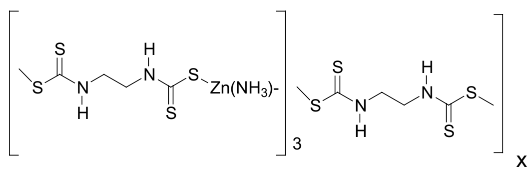
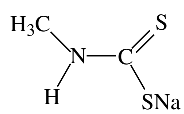
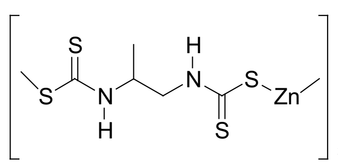
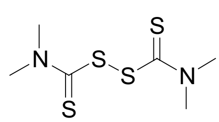
doi:10.1016/j.fct.2004.07.006

Table 1
Dithiocarbamate fungicides registered in Brazil as of January 2004

Dithiocarbamate	Structure	Chemical group
Mancozeb 2.5% zinc and 20% manganese (FAO, 1994)		Ethylene bis-dithiocarbamate (EBDC)
Maneb MW = 265.3 (monomer)		Ethylene bis-dithiocarbamate (EBDC)
Metiram MW = 1088.7 (monomer)		Ethylene bis-dithiocarbamate (EBDC)
Metam sodium MW = 129.2		Sodium methyl dithiocarbamate
Propineb MW = 289.8 (monomer)		Propylene bis-dithiocarbamate
Thiram MW = 240.4		Dimethyl dithiocarbamate

the crop (Ripley et al., 2000; Dogheim et al., 1999; PARA, 2003). Spectrophotometry (Cullen, 1964; Keppel, 1971) or gas chromatography (Hill, 1992; Friedrichs et al., 1995; De Kok and van Bodegraven, 2000) can be used for detection of these compounds, but the origin of the CS_2 generated cannot be determined by either method.

Methods of detection for each specific dithiocarbamate compound are available (Verma et al., 1984; van Lishaut and Schwack, 2000). For each of these methods, non-homogenized plant material is washed with an EDTA solution and the relevant ligand anion (or its derivative) is quantified by HPLC. The applicability of these methods in a large-scale monitoring program, however, may not be justified or practical. Moreover, these methods are not in compliance with established regulatory rules relating to dithiocarbamate MRL in most countries, where the residue is defined as CS_2.

This paper presents the results of a dithiocarbamate monitoring study conducted for several crops consumed in the Federal District area of Brazil. A chronic dietary risk assessment of these compounds using Brazilian food consumption data was performed, and is discussed in light of the currently available methodologies.

2. Material and methods

2.1. Chemicals and samples

All chemicals were analytical grade, obtained from Vetec or E. Merck. The samples (1–2 kg) were collected at local markets in the Federal District area during the period of August 1998–July 2003. Strawberries were collected from 1994 to 1999. After arriving in the laboratory, samples were frozen and then manually cut in to

~0.5 cm pieces immediately before analysis. Samples with inedible portions were peeled before freezing. Polished rice and dry beans were stored (maximum of 15 days) at room temperature and analyzed without any prior processing.

2.2. Methodology

Dithiocarbamate fungicides were determined by the spectrophotometric determination of the cupric complex formed with the CS_2 evolved from the acid decomposition of dithiocarbamates in the presence of stannous chloride as a reducing agent using either the in-series-2 trap reaction system (Cullen, 1964; Keppel, 1971) or a vertical reaction system (Caldas et al., 2001). The solution of the complex formed from the reaction between CS_2 and the copper (II) acetate monohydrate was measured at 435 nm in a continuous flow Gilford Stasar III spectrophotometer (Gilford Instruments, Oberlin, OH). The results are expressed in mg CS_2/kg. The limit of quantification (LOQ) of the method was 0.10 mg/kg CS_2. Recovery levels, from samples fortified with mancozeb, ziram or thiram, at the LOQ or higher, were >70%, with a RSD <20%.

The Theoretical Maximum Daily Intake (TMDI) was calculated using the Brazilian MRL, in mg CS_2/kg, for dithiocarbamates (ANVISA, 2004) and the Federal District or the national food consumption (average in 10 capitals and the Federal District) data, *C*, in kg/day/body weight (IBGE, 1999), based on a 60 kg person (WHO, 1997). All crops with labeled registrations for each fungicide were included in the risk assessment. The ethylene bis-dithiocarbamates mancozeb, maneb and metiram (EBDC) were grouped for the assessment. A molecular weight factor (*F*) of 1.77 was used to transform the intake as CS_2 to EBDC (average of the factors of 1.78, 1.74 and 1.79 for mancozeb, maneb and metiram, respectively). Factors for metam sodium, propineb and thiram were 1.69, 1.9 and 1.58, respectively. The calculated TMDI (as dithiocarbamate) was compared with the acceptable daily intake for the compounds, ADI (ANVISA, 2004), and expressed as %ADI.

$$\mathrm{TMDI} = \left[\sum(\mathrm{MRL}_i \times C_i)\right] \times F$$

$$\%\mathrm{ADI} = \frac{\mathrm{TMDI} \times 100}{\mathrm{ADI}}$$

A refinement in the TMDI in the Federal District was made by substituting the MRL with the mean residue levels found in the crops analyzed in this study. A refinement of the TMDI at the national level (average food consumption data in the country) was conducted using residue data from the Brazilian National Pesticide Monitoring Program (PARA, 2003).

3. Results and discussion

3.1. Residues of dithiocarbamates in food commodities

Table 2 shows the levels of dithiocarbamates, as CS_2, found in the 520 food samples collected in the Federal District area of Brazil. Dithiocarbamates were detected (>0.10 mg/kg) in 60.8% of the samples, with the higher levels (3.3–3.8 mg/kg) found in strawberry, papaya and banana. No residues were found in rice (polished) and only one bean sample had detectable levels of the fungicides. No residue in rice is expected as processing husked rice to polished rice has been shown to decrease the level of many pesticides by up to 95% (Holland et al., 1994).

The levels of dithiocarbamate residues detected in the samples analyzed in this study are within the range of the levels reported by the Brazilian National Pesticide Monitoring Program (PARA, 2003). However, the percentage of samples in this study with detectable levels of dithiocarbamates was much higher than previously reported by the PARA program. From the 1278 samples cited by the PARA program, which included leaf lettuce, banana, potato, carrot, orange, apple, papaya, strawberry and tomato collected in 4 major cities of Brazil (which does not include the Federal District area) between June 2001 and June 2002, 370 (29%) had detectable levels of dithiocarbamates, as CS_2. It is not clear from the report whether the spectrophotometric or GC method was used for the analysis. Only one of 92 banana samples, one of 141 orange samples, and none of the 176 potato samples analyzed were reported to contain detectable residues of dithiocarbamates by the PARA program.

The collection of 180 tomato samples in the Federal District market from 1998 to 2000 was designed to detect any differences that might exist in dithiocarbamates levels in samples collected during the dry season (April–September) compared to the rainy season (October–March). Thirty-two samples collected during the dry season of 1998 showed mean dithiocarbamate levels (0.15 mg/kg CS_2) significantly lower ($p < 0.01$) than the levels found in samples collected during the rainy seasons of 1999 (47 samples, mean of 0.34 mg/kg) and 2000 (57 samples, mean of 0.26 mg/kg). The mean level of dithiocarbamates found in the 44 samples collected during the 1999 dry season (0.23 mg/kg) was also significantly lower than the mean level found in the 47 samples collected during the rainy season of the same year. In addition, the percentage of samples containing detectable residues ($\geqslant$0.10 mg/kg CS_2) was higher in the rainy season. These results reflect the higher demand for fungicide application on crops during wet, humid periods due to the higher incidence of fungal diseases under these environmental conditions.

Table 2
Dithiocarbamates, as CS_2, in various crops consumed in the Federal District, Brazil

Crop	Samples analyzed/ ⩾ LOQ[a]	Residue levels (mg/kg)			MRL[c,d] (mg/kg) (CS_2)
		Higher	Mean[b]	Median	
Apple	37/95%	1.9	0.59	0.45	2 (M/Mt)
Banana fruit[e]	40/75%	3.3	0.48	0.22	1 (M)
Pulp	38/50%	1.3	0.26	0.08	
Pulp/fruit 0.03–1.5; mean = 0.80; median = 0.80					–
Orange fruit[e]	36/64%	1.8	0.30	0.18	2 (M)[f]
Pulp	33/58%	1.2	0.26	0.20	
[Pulp/fruit] 0.59–1.3; mean = 0.94; median = 0.93					–
Papaya fruit[e]	36/100%	2.0	0.52	0.35	3 (M)
Pulp + seeds	35/63%	1.9	0.27	0.12	
[Pulp/fruit] 0.14–1.6; mean = 0.68; median = 0.70					–
Strawberry	47/55%	3.8	0.46	0.18	0.2 (MS)
Potato	35/60%	0.86	0.18	0.11	0.3 (P)
Tomato	218/64%	3.3	0.31	0.22	2 (M)
Dry beans	32/3%	0.13	<0.10	<0.10	0.3 (M/T)
Rice	39/0%	<0.10	<0.10	<0.10	3 (M)

[a] LOQ of 0.10 mg/kg CS_2.
[b] To calculate the mean, samples at <LOQ were considered being at 1/2 LOQ.
[c] ANVISA (2004).
[d] Coming from the use of mancozeb (M), maneb (Mb), metiram (Mt), metam sodium (MS), propineb (P) or thiram (T).
[e] Residues in fruit calculated from results in skin and pulp.
[f] Value for citrus.

Dithiocarbamates are non-systemic fungicides and only very small amounts of pesticide are expected to translocate from the surface to the inner portion of the treated fruit after foliar application (FAO, 1994). In this study, however, detectable residues, as CS_2, were found in the pulp of banana, papaya (including the seeds) and orange (50–62% of the analyzed samples) (Table 2). The mean and median pulp/fruit residue ratio, R, detected in these fruits were within the same range (0.68–0.94). All five orange samples and four banana samples with $R > 1$ had higher residue levels in the pulp compared to the skin.

Although care was taken and no surgical gloves or other rubber material was used during sample handling, the probability of contamination of the fruit pulp from the skin during the peeling process cannot be disregarded. However, even if contamination occurs in some cases, it does not justify the high CS_2 residue levels found in the pulp in the present study. Some authors have raised the hypothesis that CS_2 residues in non-treated papaya fruit come from the sulfur compounds present in the seeds. In one study conducted by De Kok and van Bodegraven (2000), skin, pulp and seeds of treated and non-treated papaya were analyzed by gas chromatography. All four untreated papaya samples (3 skin samples, and 1 seed sample) had detectable levels of CS_2 (0.02–0.10 mg/kg). Average residues in the two treated samples were 2.6 mg/kg in the skin, 0.7 mg/kg in the pulp and 3.1 in the seeds, indicating that the levels found in the pulp and seeds are much higher than what would be expected to occur naturally.

The authors (De Kok and van Bodegraven, 2000) also showed that homogenizing papaya samples (peel, seeds and pulp) with a polytron could give false positive results for dithiocarbamates when non-treated samples are analyzed by the spectrophotometric method, but not by the GC method. Cell disruption after the fine homogenization of the sample releases sulfur compounds that are detected spectrophotometricaly. No CS_2 was detected in the untreated samples by either detection method when the samples were processed with minimal cutting, which is how the samples were processed in the present study.

Carbon disulfide and other sulfur compounds can be found naturally in the atmosphere, soil and some vegetables. CS_2 not related to the use of the dithiocarbamate fungicides has been described in the head space atmosphere of lettuce (Batten et al., 1995), in homogenates of fresh mushrooms (Chen and Ho, 1986) and in the volatile oils found in the stems of cabbage, broccoli and cauliflower (Buttery et al., 1976). According to Hill (1992), brussels sprouts are capable of producing postharvest levels of CS_2 up to 2 mg/kg for a few days after picking. CS_2 has been detected in experimental plants treated with mancozeb and maneb according to results submitted to the 1993 JMPR. These results were compiled from experimental trials conducted on various crops including onions, broccoli, cabbage, spinach, asparagus, celery, citrus, pome fruits, cranberries, banana, papaya, grapes, plums, tomato, sugar beet, potato, carrots and cereals (FAO, 1994). Pulp of banana and citrus fruit treated with mancozeb were shown to have residues higher than the non-treated controls in trials conducted in Japan and the USA (FAO, 1994). Either the spectrophotometric or the GC method was used for analysis in the trials.

3.2. Chronic dietary risk assessment

In Brazil, a dithiocarbamate MRL is established for each crop. Because more than one dithiocarbamate fungicide may be labeled for a particular crop, the MRL is set based upon the fungicide that produced the highest residue levels in experimental field trials. A dietary risk assessment was conducted for the EBDC collectively (mancozeb, maneb and metiram), metam sodium, propineb and thiram, and included the estimated dietary intake of all registered crops for each of these compounds. The EBDC have a common mechanism of toxicity (EPA, 2001) and the same ADI (ANVISA, 2004); as such, the intake of these compounds was grouped for the dietary risk assessment.

In the Federal District, the TMDI of dithiocarbamates through the diet ranged from 61% ADI in propineb to 130% ADI in metam sodium (Table 3). Metam sodium is registered in Brazil as a pre-planting soil fumigant in strawberry, potato, carrot and tomato, however, it is unlikely that its use would contribute to dithiocarbamate residues. Metam sodium hydrolyses rapidly in the field into methyl isothiocyanate, the bioactive compound, and the product label recommends the planting only after all the gas is dissipated, 7–21 days after soil treatment (ANVISA, 2004).

Refinements in intake values were calculated by replacing the MRL in the TMDI calculation by the mean dithiocarbamate residue levels found in the crops analyzed in this study (Table 2). Refinement of the residue levels resulted in a significant decrease in the %ADI for all compounds (Table 3). The largest decrease of the %ADI occurred for thiram (98%) and for the EBDC (83%), the only compounds with registered use in rice. As no residues were detected in rice, replacing the MRL (3.0 mg/kg, husked rice) for the 1/2 LOQ in the refined calculation had the greatest impact on the %ADI. Rice is a major food commodity in the Brazilian diet, with a yearly per capita consumption of over 45 kg in the Federal District area, the highest consumption in the country.

In a previous, chronic dietary risk assessment study based on registered pesticides in Brazil, the National Theoretical Maximum Daily Intake (NTMDI) of mancozeb, maneb and metiram represented 850%, 270% and 11% of the ADI, respectively (Caldas and Souza, 2000). Although the EBDCs (mancozeb, maneb, and metiram) should be grouped to calculate total dietary intake (EPA, 2001), the NTMDI calculation was performed separately, as until August 2003, the Brazilian legislation designated a separate MRL for each compound. Table 3 shows the updated dietary risk assessment study for the dithiocarbamates according to the current Brazilian legislation, which establishes a dithiocarbamate MRL, as CS_2 (ANVISA, 2004). The NTMDI for the EBDC contributed to 47% ADI.

Table 3
Summary of risk assessments of chronic dietary intake of dithiocarbamates in Brazil

Dithiocarbamate	ADI[a] (mg/kg) body weight (source)	%ADI				Number of registered food crops
		Federal district		National		
		TMDI	Refined intake[b]	TMDI (range)[c]	Refined intake[d]	
EBDC[e]	0.03 (BRA)	70	12	47 (34–70)	31	36
Metam sodium	0.001 (GER)[f]	130	38	115 (73–140)	41	4
Propineb	0.005 (BRA)	61	25	52 (37–61)	34	7
Thiram	0.01 (BRA)	100	2	60 (34–100)	–	9

[a] For parent compound.
[b] Using the mean residues. Levels <LOQ (<0.10 mg/kg) were considered to be at 1/2 LOQ; for citrus, papaya and banana, residues in edible portion.
[c] Average and range of intake in 10 Brazilian capitals and the Federal District.
[d] Data from the National Pesticide Monitoring Program (PARA, 2003). As only ranges of residues are reported, mean residues were estimated: for apple, strawberry and tomato (>50% samples >LOQ), mean = [(highest level + lowest positive level)/2] × %positive samples/100. For banana, orange, papaya and lettuce (<50% samples >LOQ), 1/2 LOQ level was used. LOQ is 0.08 mg/kg CS_2 for all crops with exception of banana (0.01 mg/kg).
[e] The intake of the EBDC mancozeb, maneb and metiram, which have the same ADI, were grouped for the calculation.
[f] From Germany (BgVV, 2001).

The NTMDI intake calculated in this study was refined by substitution of the mean residue values reported by the PARA program (2003). The adjusted %ADI was considerably lower for all compounds, with the exception of thiram (Table 3). As none of the crops registered for thiram use were analyzed within the PARA program, the refinement of the intake for this compound was not possible.

With the exception of metam sodium, dithiocarbamate intake in the Federal District was the highest among the eleven regions where food consumption data was collected (Table 3). The Federal District, which includes the Brazilian capital, has the highest income of the country, and as consumption data was obtained from survey responses pertaining to how much food is purchased, family income has a direct impact on total food consumption. For metam sodium, the Federal District intake placed second, just behind Porto Alegre (data not shown), in the south of the country. In this city, the consumption of potato is the highest in the country (IBGE, 1999), probably due to the strong European influence in the region.

4. Conclusion

Dithiocarbamate is one of the major fungicide groups used in the production of agricultural crops in Brazil, and the most common pesticides found in food monitoring programs in many countries (PARA, 2003; Ripley et al., 2000; Dogheim et al., 1999; EU, 2001). The methodology used in these programs relies on the measurement of CS_2 generated by the acid hydrolysis of these compounds. Although dithiocarbamates are non-systemic fungicides, CS_2 residues, have been found in the pulp of many fruit crops. In addition, CS_2 has been detected in non-treated crops, probably due to its natural presence in the plant or by generation from sulfur compounds during the acid digestion procedure used in the laboratory assay. As a result, dithiocarbamate intake calculations using residue data generated by the CS_2 based methodology might be overestimated.

Methodologies which determine the dithiocarbamate compounds individually are time consuming and considerably more expensive than the CS_2 based method. The need for implementation of such methodologies in a monitoring laboratory should be discussed in light of the potential risks that the dietary dithiocarbamate exposure presents to the health of a given population.

Chronic dietary intake of the dithiocarbamates by the Brazilian population did not exceed the ADI for any registered compound, except metam sodium, when the current national MRL were used as the baseline for residue concentrations. The use of MRL as the residue parameter is very conservative, as it assumes that the pesticide is always present in all registered crops at a set tolerance level and it does not consider any processing which might occur with the food, including peeling. The estimated intake was drastically reduced for all compounds to levels below the ADI when residue data generated in this study and by the PARA program replaced the national MRL. Furthermore, from the data available, it is unlikely that the Brazilian population is at risk for developing health-related problems after long-term consumption of crops treated with dithiocarbamates based on the dietary risk assessment. The current methodology used in the laboratories for enforcement purposes is sufficient to adequately assess the risk to consumers.

Acknowledgments

The authors wish to thank the Brazilian Agency for Research (CNPq) for supporting this project by granting scholarships for Ana Paula Cardoso, Andrea Moscardine, Andreia Nunes O. Jardim, Denise Ricardo de Souza, Mônica Moraes Nunes and Rafaela Maciel Rebelo. We also thank Colleen Y. Warfield for reviewing the English language.

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