THIABENDAZOLE (065)

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EXPLANATION

Thiabendazole was evaluated several times by JMPR in the period 1970-1981. The 1997 JMPR reviewed it under the CCPR Periodic Review Programme and proposed withdrawal of the existing CXL for citrus fruit of 10 mg/kg. The residue definition agreed for compliance with MRLs and estimation of dietary intake for plant commodities is thiabendazole; that for compliance with MRLs for animal commodities is the sum of thiabendazole and 5-hydroxythiabendazole. For estimation of dietary intake for animal commodities the definition is the sum of thiabendazole, 5-hydroxythiabendazole and its sulfate conjugate.

The 2000 JMPR received new data from trials on oranges and mandarins carried out in Spain in 1998, on the basis of which an MRL of 3 mg/kg was proposed. At the 35th CCPR meeting, the delegation from Morocco indicated that the proposed MRL for thiabendazole on citrus of 3 mg/kg would need to be increased to support that country's use pattern. At that meeting the delegation of Morocco was invited to submit data to JMPR. At the 36th CCPR meeting the proposed Codex MRL for citrus was returned to Step 6 pending receival of the Moroccan data. Residue trials data to support the use of thiabendazole as a post-harvest treatment on citrus fruits (oranges and mandarins) in Morocco, generated by Morocco Institutions in 2003 and 2004, were submitted in early 2006 for evaluation.

RESIDUE ANALYSIS

Two methods from the open literature were used to analyse the samples from the supervised trials conducted in Morocco. The first was a spectroscopic method with UV detection (Gneagi *et al*., 1974). Under this method the sample was homogenised using ethyl acetate, anhydrous sodium sulfate and aqueous sodium hydroxide. Then, the homogenate was filtered, and an aliquot part was separated from the ethyl acetate extract with a hydrochloric acid solution. The aqueous phase was made alkaline, then extracted with ethyl acetate and the absorbance of the organic layer was measured at 302 nm. The method was validated for thiabendazole recovery only for whole fruits at 0.1, 0.5 and 1 mg/kg fortification levels (one fortified sample at each fortification level) and was found to yield 97–102% recovery in 2003 and 96–99% in 2004. The limit of quantification (LOQ) achieved was 0.1 mg/kg.

The second method, which was used in 2004, was an HPLC method, based on the CEN method EN 14333-3. The extraction and clean up procedure was the same as for the UV method, the difference being that the residue was determined by HPLC reversed phase chromatography with UV (285 nm) and fluorescence detection (emission 385 nm; excitation 315 nm). The recoveries for thiabendazole were tested only for whole fruits at one fortification level (0.1 mg/kg, 3 replicate fortified samples) and were found to be in the range 82–84%, with the latter method providing an improved LOQ (0.01 mg/kg).

USE PATTERN

Table 1 shows the registered use of thiabendazole on citrus in Morocco, as indicated on the official label.

Table 1. Registered post-harvest uses of thiabendazole on citrus in Morocco.

Country	Form	Application			Waiting or withholding period (days)
		Method	Concentration kg ai/hL wax	Number	
Morocco	SC 500 g/L	In mixture with wax	0.375	1	Not stated

RESIDUES RESULTING FROM SUPERVISED TRIALS ON CITRUS

The Meeting received information on supervised residue trials of thiabendazole carried out in Morocco with post-harvest application to:

Oranges (Table 2)
Clementine mandarins (Table 3)

The trials were conducted in 2003 and 2004. Thiabendazole, formulated as a 500 SC, was applied post-harvest on oranges or clementine mandarins as a spray application mixed with wax at the rate of 0.375 kg ai/hL, i.e., according to Moroccan GAP.

In 2003 trials were carried out with several varieties of oranges. Treated fruit was stored at 4–6 ^{o}C and samples were taken < 2 days, 3, 4, 5, 11 or 15 days after application. Whole orange fruits were analysed immediately after sampling. The UV spectroscopic analytical method, reported previously was used.

In 2004 the product was applied to oranges and mandarins. Fruits were stored at 4-6^{0}C and samples were collected < 2, 7 and 15 days after application. Peel and pulp were analysed separately and the residues in whole fruits were calculated on the basis of results for peel and pulp and relative weights. Some of the samples were analysed using the spectroscopic method, while others were analysed using the HPLC method.

One or more samples were analysed at each time interval. Since they were replicate samples, the mean values are reported. No correction for recovery was applied to the analytical results. Control samples were also analysed and have shown no interference or contamination. Residues used for MRL derivation are double-underlined in Tables 2 and 3.

Table 2. Thiabendazole residues in oranges following post-harvest treatment in Morocco.

Country Location/ Variety	Year	Application			Days after Treatment	Residues in whole fruit (mg/kg)	Author Year (Trial No.)
		Product	kg ai/hL	Type/ Number of treatments			
Morocco Casablanca/ Navel	2004	500SC	0.375	Spray with wax/1	< 2 7 15	5.2 3.2 1.6	Benzine and Tarhy 2004 (0951)
Morocco Casablanca/ Navel	2004	500SC	0.375	Spray with wax/1	< 2 7 15	3.8 2.1 2.7	Benzine and Tarhy 2004 (0951)
Morocco Agadir/ Salustianas	2003	500SC	0.375	Spray with wax/1	6	4.2	Benzine and Tarhy 2003 (0952)

Country Location/ Variety	Year	Application			Days after Treatment	Residues in whole fruit (mg/kg)	Author Year (Trial No.)
		Product	kg ai/hL	Type/ Number of treatments			
Morocco Agadir/ Salustianas	2003	500SC	0.375	Spray with wax/1	< 2	3.3[1]	Benzine and Tarhy 2003 (0952)
Morocco Agadir/ Ortanique	2003	500SC	0.375	Spray with wax/1	3	2.5[2]	Benzine and Tarhy 2003 (0952)
Morocco Agadir/ Orantique Sanguine	2003	500SC	0.375	Spray with wax/1	3	1.6[2]	Benzine and Tarhy 2003 (0952)
Morocco Casablanca/ Sanguine	2003	500SC	0.375	Spray with wax/1	7	3.4[3]	Benzine and Tarhy 2003 (0952)
Morocco Agadir/ Salustianas	2003	500SC	0.375	Spray with wax/1	3-4	2.2 [3]	Benzine and Tarhy Morocco 2003 (0952)
Morocco Agadir/ Salustianas	2003	500SC	0.375	Spray with wax/1	5	1.6	Benzine and Tarhy Morocco 2003 (0952)
Morocco Casablanca/ Sanguine	2003	500SC	0.375	Spray with wax/1	11-13	3.4 [2]	Benzine and Tarhy Morocco 2003 (0952)
Morocco Casablanca/ Sanguine	2003	500SC	0.375	Spray with wax/1	11-13	4[4]	Benzine and Tarhy Morocco 2003 (0952)
Morocco Agadir/ Salustianas	2003	500SC	0.375	Spray with wax/1	3	1.8[3]	Benzine and Tarhy Morocco 2003 (0952)
Morocco Agadir/ Salustianas	2003	500SC	0.375	Spray with wax/1	4	1.8	Benzine and Tarhy Morocco 2003 (0952)
Morocco Casablanca/ Sanguine	2003	500SC	0.375	Spray with wax/1	< 2	2.1 [3]	Benzine and Tarhy Morocco 2003 (0952)
Morocco Casablanca/ M. Late	2003	500SC	0.375	Spray with wax/1	3	3.3[5]	Benzine and Tarhy Morocco 2003 (0952)

[1]: mean of 3 replicate samples
[2]: mean of 2 replicate samples
[3]: mean of 4 replicate samples
[4]: mean of 6 replicate samples
[5]: mean of 8 replicate samples

Table 3. Thiabendazole residues in mandarins following post-harvest treatment in Morocco.

Country Location/ Variety	Year	Application			Days after Treatment	Residues in whole fruit [mg/kg]	Author Year Trial No.
		Product	kg ai/hL	Type/Number of treatments			
Morocco Casablanca/ Clementine	2004	500SC	0.375	Spray with wax/1	< 2 7 15	3.5[1] 1.8[1] 1[1]	Benzine and Tarhy 2004 (0951)
Morocco Agadir/ Clementine	2004	500SC	0.375	Spray/1	< 2 7 15	2.7 2.6 1.3	Benzine and Tarhy 2004 (0951)
Morocco Berkane/ Clementine	2004	500SC	0.375	Spray/1	< 2 7 15	2.7[2] 2.3[2] 1.4[2]	Benzine and Tarhy 2004 (0951)
Morocco Casablanca/ Clementine	2004	500SC	0.375	Spray/1	7 15	2.9 3.5	Benzine and Tarhy 2004 (0951)
Morocco Berkane/ Clementine	2004	500SC	0.375	Spray/1	< 2 7 15	2.7[2] 2.3[2] 2.[2]	Benzine and Tarhy 2004 (0951)
Morocco Casablanca/ Clementine	2004-	500SC	0.375	Spray/1	< 2 7 15	1.3[3] 1.3[3] 1[3]	Benzine and Tarhy 2004 (0951)
Morocco Berkane/ Clementine	2004	500SC	0.375	Spray/1	< 2 7 15	2.8[1] 2.7[1] 2.1[1]	Benzine and Tarhy 2004 (0951)
Morocco Agadir/ Clementine	2004	500SC	0.375	Spray/1	< 2	2.4[3]	Benzine and Tarhy 2004 (0951)

[1]: mean of 2 replicate samples
[2]: mean of 3 replicate samples
[3]: mean of 4 replicate samples

FATE OF RESIDUES IN STORAGE AND PROCESSING

In commercial cold storage

Treated fruit were taken and analysed immediately after application (0 days) and after periods of 7 or 15 days in cold storage (4-6 °C), as per common commercial practice. This data shows that there is no significant decrease in residues within the first 7 days of storage, while some degradation occurred after 15 days of storage (Tables 3 and 4). However, given the variability in results and the fact that the reproducibility of the analytical methods was not assessed, no reliable conclusion about storage stability can be drawn. Data evaluated by the 2000 JMPR (Spanish trials) showed that the residues in oranges and mandarins remained stable or decreased slightly during storage up to 15 days.

In processing

The 2000 JMPR estimated processing factors from whole fruit to pasteurised juice. The best estimate from two studies, two replicate samples for each study, was 0.14. It also estimated a processing factor of 5.7 from whole fruits to dry citrus pomace (dried citrus pulp).

RESIDUES IN THE EDIBLE PORTION

Table 4 provides information on the distribution of residues between edible (pulp) and non-edible parts (peel). Values used for the estimation of the distribution factor are underlined.

Table 4. Distribution of residues between peel and pulp of citrus treated at 0.375 kg ai/hL.

Citrus Fruits –Trial No 0951/T04	Residue (mg/kg)				Distribution Factor (pulp)[4]
	DAT[1]	Whole fruit[2]	Peel	Pulp[3]	
Orange	< 2 7 15	5. 2 3.2 1.6	18 11 9.4	< 0.1 < 0.1 < 0.1	
Orange	< 2 7 15	3.8 2.1 2.7	10.3 7.6 4.9	0.84 0.34 0.49	0.21 0.15 0.17
Mandarin-	< 2 7 15	1.5 0.50 0.40	4.5 3.4 2.4	< 0.1 < 0.1 < 0.1	
Mandarin-	< 2 7 15	5.5 3.2 1.7	17 13 11	< 0.1 < 0.1 < 0.1	
Mandarin-	< 2 7 15	2.7 2.6 1.3	18 16 5.7	< 0.1 < 0.1 < 0.1	
Mandarin-	< 2 7 15	2.7 2.6 1.3	13 11 7.4	< 0.1 < 0.1 < 0.1	
Mandarin-	< 2 7 15	2.7 2.6 1.5	16 12 6.8	< 0.1 < 0.1 < 0.1	
Mandarin-	< 2 7 15	2.6 1.5 1.5	11 7 7	< 0.1 < 0.1 < 0.1	
Mandarin-	7 15	2.9 3.5	8.4 7.5	0.22 0.37	0.07 0.10
Mandarin-	< 2 7 15	2.2 2.2 2.2	12 11 8	< 0.1 < 0.1 < 0.1	
Mandarin-	< 2 7 15	2.5 1.7 1.6	13 8 8	< 0.1 < 0.1 < 0.1	
Mandarin-	< 2 7 15	3.4 3 2.4	18 15 11	< 0.1 < 0.1 < 0.1	
Mandarin-	< 2 7 15	0.24 0.11 0.16	0.86 0.4 0.5	< 0.01 < 0.01 0.03	
Mandarin-	< 2 7 15	0.46 0.30 0.33	2.05 0.94 1.2	0.04 < 0.01 < 0.01	0.08
Mandarin-	< 2 7 15	0.35 0.24 0.10	1.3 0.50 0.65	0.09 0.04 < 0.01	0.25 0.16
Mandarin-	< 2 7 15	4.2 4.5 3.4	15 8.8 8.3	0.05 0.07 0.12	0.01 0.01 0.03

Citrus Fruits –Trial No 0951/T04	Residue (mg/kg)				Distribution Factor (pulp)[4]
	DAT[1]	Whole fruit[2]	Peel	Pulp[3]	
Mandarin-	< 2 7 15	3.2 3.2 2.7	17 16 12	< 0.1 < 0.1 < 0.1	
Mandarin-	< 2 7 15	2.4 3.1 1.5	12 9.3 7	< 0.1 < 0.1 < 0.1	
Median Distribution Factor					0.1

[1] Days after treatment

[2] Results calculated from residues in pulp and peel

[3] Values <LOQ are not considered for estimation of the median DF.

[4] Calculated by dividing the residues measured in the pulp by the residues measured in whole fruit

RESIDUES IN ANIMAL COMMODITIES

The dietary burden of thiabendazole residues in farm animals was estimated by the 2000 JMPR on the basis of the data then evaluated (lower GAP compared with that of Morocco). New estimates were made using the highest residue found in whole citrus fruits from the Moroccan trials. These have shown that the additional intake resulting from the Moroccan GAP was 2% for beef cattle and 4 % for dairy cattle; and 2% and 3% respectively when using the median residue from whole fruits. This shows that the additional intake is very low compared with the intake from wet potato pomace, which is the main driver for estimation of animal burden.

APPRAISAL

Thiabendazole is authorised as a post-harvest fungicide on citrus in many countries. It was evaluated several times by JMPR in the period 1970-1981. The 1997 JMPR reviewed it under the CCPR Periodic Review Programme and proposed withdrawal of the existing CXL for citrus fruits of 10 mg/kg. The residue definition, agreed for compliance with MRLs and estimation of dietary intake for plant commodities, is thiabendazole; that for compliance with MRLs for animal commodities is the sum of thiabendazole and 5-hydroxythiabendazole. For estimation of dietary intake for animal commodities it is the sum of thiabendazole, 5-hydroxythiabendazole and its sulfate conjugate. The JMPR 2000 received new data from Spain on the basis of which an MRL of 3 mg/kg was proposed. At the CCPR meeting in 2003, the delegation from Morocco had commented that the proposed MRL for thiabendazole on citrus fruits of 3 mg/kg would need to be increased to support the country's use pattern. At that meeting the delegation of Morocco was invited to submit data to JMPR. During the CCPR meeting in April 2004 the MRL for citrus fruits was returned to Step 6 pending receival of the data.

The current Meeting received data from residue trials to support the uses of thiabendazole as a post-harvest treatment on citrus fruits in Morocco.

Methods of analysis

For the analysis of the samples from supervised trials conducted in Morocco two methods from the open literature were used. The first one is an old spectroscopic method with UV detection developed in France in 1974. Limited validation was carried out (on whole fruits at 0.1, 0.5 and 1 mg/kg fortification levels, one fortified sample at each fortification level). The recoveries yielded were 96–102%, with an LOQ of 0.1 mg/kg.

The second method was a reversed phase HPLC method (standard CEN method). The recoveries for thiabendazole were tested only for whole fruits at one fortification level (0.1 mg/kg, 3 replicate fortified samples) and were found to be in the range of 82–84%. The LOQ was estimated to be 0.01 mg/kg.

Results of supervised trials on crops

Citrus fruits

The Meeting received, for evaluation, post-harvest application data from trials conducted in Morocco during 2003 and 2004. Thiabendazole, formulated as 500 SC, was applied to oranges (15 trials) and clementine mandarins (eight trials) according to the nationally authorised use pattern (GAP). This consisted of a spray application, mixed with wax, at a rate of 0.375 kg ai/hL. Treated fruit samples were stored at 4–6°C from harvest to analysis. Samples were taken for analysis < 2 days, 3, 4, 5, 11 or 15 days after application. Whole orange samples were analysed in 2003, while in 2004 peel and pulp were analysed separately.

The residue levels in whole oranges treated according to Moroccan GAP, in ranked order, were: 1.6 (2), 1.8 (2), 2.1, 2.2, 2.5, 3.3 (2), 3.4 (2), 3.8, 4, 4.2 and 5.2 mg/kg.

Those in orange pulp were: < 0.1 and 0.84 mg/kg.

The residue levels in whole mandarins treated according to Moroccan GAP, in ranked order, were: 1.3, 2.4, 2.7 (3), 2.8, and 3.5 (2) mg/kg.

Those in mandarin pulp were: 0.03, 0.04, 0.09, < 0.1 (11), 0.12, and 0.37 mg/kg.

The Meeting agreed to combine the data for whole oranges and mandarins to provide a data set for whole citrus fruit. The combined citrus fruit data set (23 values), in ranked order were: 1.3, 1.6 (2), 1.8 (2) 2.1, 2.2, 2.4, 2.5, 2.7 (3), 2.8, 2.9, 3.3 (2), 3.4, (2), 3.5, 3.8, 4, 4.2, and 5.2 mg/kg. Residue levels in citrus pulp, in ranked order were: 0.03, 0.04, 0.09, < 0.1 (12), 0.12, 0.37 and 0.84 mg/kg.

On the basis of the trials carried out according to the Moroccan GAP the Meeting estimated a maximum residue level of 5 mg/kg for thiabendazole in citrus, replacing the previous recommendation of 3 mg/kg. The Meeting also estimated a median and a highest residue for whole fruits of 2.7 and 5.2 mg/kg respectively, for use in the calculation of the farm animal dietary burden. The Meeting recommended an STMR of 0.1 mg/kg and a HR of 0.84 mg/kg for citrus fruits.

Fate of residues in edible portion

The results from the 2004 trials provide information about distribution of residues between peel and pulp. These show that the majority of the residue remains on the peel. In only a few cases detectable residues of 0.03–0.84 mg/kg were found in the pulp. However, it should be noted that the sensitivity of the analytical method used on the majority of the samples was unsatisfactory (LOQ = 0.1 mg/kg). The distribution factors (DF) for residues into pulp ranged between 0.01 and 0.25, with a median DF of 0.1.

Farm animal dietary burden

The Meeting noted that the additional animal dietary burden, from residues in citrus treated according to the Morocco GAP, would be insignificant when compared to the contribution from wet potato peel as calculated by the 2000 JMPR. Thiabendazole accounted for 2% of the total dietary burden for beef cattle and 4% for dairy cattle when using the highest residue, and 2% and 3% respectively, when using the median from whole fruits.

RECOMMENDATIONS

On the basis of the data from supervised trials with post-harvest application of thiabendazole on citrus fruits (oranges and clementine mandarins) in Morocco carried out according to the GAP, the Meeting concluded that a residue concentration below is suitable for establishing a Codex Maximum Residue Limit and for assessing dietary intake.

Definition of the residue (for compliance with MRLs and for estimation of dietary intake): for plant commodities: *Thiabendazole.*

For compliance with MRLs for animal commodities: *Sum of thiabendazole and 5-hydroxythiabendazole.*

For estimation of dietary intake for animal commodities: *Sum of thiabendazole, 5-hydroxythiabendazole and its sulfate conjugate.*

Summary of recommendations for MRLs, STMRs and HRs for imidacloprid

CCN	Name	MRL, mg/kg		STMR mg/kg	HR mg/kg
		New	Previous		
FC0001	Citrus fruits	5 Po	3 Po	0.1	0.84

DIETARY RISK ASSESSMENT

Long-term intake

The IEDI of thiabendazole was estimated for the 13 cluster diets using the STMRs estimated by a previous JMPR for avocado, cattle kidney, cattle liver, cattle meat, cattle milk, mango, melon, papaya, pome fruit, potato and strawberry and the STMR for citrus fruits estimated by the current JMPR. The maximum ADI established in 1997 is 0.1 mg/kg bw and the calculated IEDIs were 2–20% of this ADI (See Annex 3 of the 2006 Report). The Meeting concluded that the intake of residues of thiabendazole resulting from the uses considered by a previous JMPR and by the current JMPR was unlikely to present a public health concern.

Short-term intake

The IESTIs of thiabendazole by general population and by children was calculated for commodities for which STMRs or HRs was estimated by the 2000 Meeting and the current Meeting (Annex 4 of 2006 Report). The current JMPR estimated two ARfDs for thiabendazole: one for general population; and the other for women of child-bearing age. The ARfD for general population is 1 mg/kg bw and the calculated IESTIs for children up to 6 years range from 0 to 60% and those for general population from 0 to 20% of this ARfD. The ARfD for women of child-bearing age is 0.3 mg/kg bw and the calculated IESTIs for women of child-bearing age range from 0 to 70% of this ARfD. The Meeting concluded that the short-term intake of residues of thiabendazole resulting from the use considered by the current JMPR is unlikely to present a public health concern.

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