CHLOROTHALONIL (081)

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EXPLANATION

Chlorothalonil, a benzene substituted with chlorines and dinitriles, is a non-systemic fungicide first evaluated by the JMPR in 1974 and a number of times subsequently. It was reviewed for toxicology by the 2009 and 2010 JMPR within the periodic review program of the CCPR. For the parent substance, chlorothalonil, an ADI of 0–0.02 mg/kg bw and an ARfD of 0.6 mg/kg bw were established. In addition, for the metabolite SDS-3701 (2,5,6-trichloro-4-hydroxyisophthalonitrile), an ADI of 0–0.008 mg/kg bw and an ARfD of 0.03 mg/kg bw were established.

The 2010 JMPR recommended the following residue definitions for chlorothalonil:

Definition of the residue for compliance with the MRL for plant commodities: chlorothalonil.

Definition of the residue for dietary risk assessment for plant commodities: chlorothalonil and SDS-3701, all considered separately.

Definition of the residue for compliance with the MRL and dietary risk assessment for animal commodities: SDS-3701.

At the Fiftieth Session of the CCPR (2018), chlorothalonil was scheduled for evaluation of an additional use on cranberry by the 2019 Extra JMPR. The current Meeting received new information on use patterns, additional analytical methods and supervised field trials on cranberry.

RESIDUE ANALYSIS

Analytical methods

For chlorothalonil and its metabolite SDS-3701, an additional method was provided for cranberry.

Method GRM005.03A (Huebner M.R., 2010)

Approximately 10 grams of homogenized cranberry sample are extracted with acetone- sulfuric acid (10 mol/L) solution (95:5, v/v, 100 mL). After the sample is centrifuged or allowed to settle, a 2-mL aliquot is diluted to 10 mL with water.

The extracts are cleaned up using solid phase extraction (SPE) on a C_{18} phase. Chlorothalonil and SDS-3701 are analysed by liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS). Heated nebulizer APCI negative polarity multiple reaction monitoring (MRM) at m/z=245 → 245 for chlorothalonil and MRM at m/z=245 → 182 for SDS-3701. The procedural recoveries ranged from 65-108% for chlorothalonil and 75–100% for SDS-3701. The RSD values were ≦9.5% for chlorothalonil and ≦7.6% for SDS-3701. The LOQs for both analytes were 0.01 mg/kg. The recovery data are shown in Table 1.

Table 4 Recovery data for method GRM005.03A measuring chlorothalonil and SDS-3701

Matrix	analyte	Fortification level (mg/kg)	n	Recovery range (%)	Recovery, mean (%)	RSD (%)
Cranberry	Chlorothalonil	0.01	3	91-108	100	8.3
		0.5	3	87-94	89	4.4
		10	3	65-78	72	9.5
Cranberry	SDS-3701	0.01	3	85-95	90	5.9
		0.5	3	75-87	82	7.4
		10	3	86-100	92	7.6

USE PATTERN

The Meeting received GAP information for cranberry in the USA as shown in Table 2.

Table 2 Use pattern of chlorothalonil

Crop	Country	Conc. g ai/L or kg Formulation	Application					
			Type	kg ai/ha	Growth stage	No	PHI (days)	Note
Cranberry	USA	Bravo 720 719 g ai/L SC	Foliar	5.5	Not specified	3 (interval: 10 days or more)	50	

RESULTS OF SUPERVISED RESIDUE TRIALS ON CROPS

Residue levels were reported as measured. Application rates were always reported as chlorothalonil equivalents. When residues were not detected they are shown as below the LOQ, e.g., < 0.01 mg/kg. Application rates, concentrations and mean residue results have been rounded to two significant figures. Residue values from the trials conducted according to the maximum GAP were used for the estimation of maximum residue levels, STMR and HR. These results are underlined.

Laboratory reports included method validation including batch recoveries with spiking at residue levels similar to those occurring in samples from the supervised trials. Dates of analyses or duration of residue sample storage were also provided. Field reports provided data on the sprayers used and their calibration, plot size, residue sample size and sampling date.

Cranberries

Five residue trials were conducted on cranberries in the USA in 2016 (IR-4 PR No. 11846). Chlorothalonil was applied as a suspension concentrate (SC). Three foliar applications were made to the treated plot at each trial site at a target application rate of 5.5 kg ai/ha. The following adjuvants were mixed with chlorothalonil: Induce NIS in the trial conducted in Wareham; Attach NIS in Chatsworth, R-11 NIS in Warrenton, and Activator 90 NIS in Wisconsin Rapids and Warren. Fruit was sampled 48-51 days after the third (last) application. The residues of chlorothalonil were analysed using an LC/MS/MS method (Method GRM005.03A) with a LOQ of 0.01 mg/kg. Analyses were completed within 23 days of harvest. The residues of chlorothalonil (expressed as chlorothalonil) and SDS-3701 (expressed as SDS-3701) in the trials are shown in Table 3.

Table 3 Residues of chlorothalonil and SDS-3701 in cranberries (GRM005.03A, Storage interval: ≦22 days)

Cranberry Location, year (Variety)	Application						Residue (mg/kg)		Report no.
	Form	No	Intervals (days)	kg ai/ha	Sample	DALT (days)	Chloro-thalonil	SDS-3701 (as SDS-3701)	
Wareham, MA 2016 (Stevens)	SC	3	 10 10	5.5 5.6 5.6	berries	51	0.35, 0.47 (<u>0.41</u>)	<0.01, <0.01 (<u><0.01</u>)	IR-4 11846.16-MA185
Chatsworth, NJ 2016 (Stevens)	SC	3	 10 11	5.6 5.6 5.7	Berries	48	4.2, 1.8 (<u>3.0</u>)	<0.01, <0.01 (<u><0.01</u>)	IR-4 11846.16-NJ256
Warrenton, OR 2016 (Pilgrim)	SC	3	 10 11	5.7 5.7 5.8	Berries	50	7.7, 6.5 (<u>7.1</u>)	<0.01, <0.01 (<u><0.01</u>)	IR-4 11846.16-OR325
Wisconsin Rapids, WI 2016 (Stevens)	SC	3	 10 10	6.1 5.6 5.4	Berries	49	1.7, 2.0 (<u>1.8</u>)	0.019, 0.019 (<u>0.019</u>)	IR-4 11846.16-WI415
Warren, WI 2016 (Stevens)	SC	3	 10 10	6.1 6.1 6.1	Berries	49	4.3, 4.5 (<u>4.4</u>)	<0.01, <0.01 (<u><0.01</u>)	IR-4 11846.16-WI416

FATE OF RESIDUES DURING PROCESSING

No processing study was available for cranberry.

APPRAISAL

Chlorothalonil was reviewed for toxicology by the 2009 and 2010 JMPR within the periodic review program of the CCPR. For the parent substance an ADI of 0–0.02 mg/kg bw and an ARfD of 0.6 mg/kg bw were established. In addition to the parent substance, an ADI of 0–0.008 mg/kg bw and an ARfD of 0.03 mg/kg bw were established for the metabolite SDS-3701 (2,5,6-trichloro-4-hydroxyisophthalonitrile).

The 2010 JMPR recommended the following residue definitions for chlorothalonil:

Definition of the residue for compliance with the MRL for plant commodities: *chlorothalonil;*

Definition of the residue for dietary risk assessment for plant commodities: *chlorothalonil and SDS-3701, all considered separately*;

Definition of the residue for compliance with the MRL and dietary risk assessment for animal commodities: *SDS-3701*.

At the Fiftieth Session of the CCPR (2018), chlorothalonil was scheduled for evaluation of an additional use on cranberry by the 2019 Extra JMPR. The current Meeting received new information on use patterns for chlorothalonil on cranberry and additional analytical methods and supervised field trials.

Methods of analysis

The Meeting received an analytical method for chlorothalonil not previously evaluated by the Meeting. The method was used in the new supervised field trials.

Method GRM005.03A is applicable to cranberries and involved homogenisation with acetone and 10 mol/L sulfuric acid solution (95:5, v/v, 100 mL). Following solid phase extraction (SPE) clean-up, chlorothalonil and SDS-3701 were analysed by liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS). The method was validated for both analytes in cranberries with a LOQ of 0.01 mg/kg.

Stability of pesticides in stored analytical samples

The 2015 JMPR concluded that chlorothalonil and SDS-3701 might degrade in cranberries and no acceptable storage interval above one month could be identified. In the supervised trials received by the current Meeting, the samples were analysed within 22 days of sampling and kept frozen during the storage interval. The Meeting concluded that the residue trial data could be used for evaluation.

Definition of the residue

Based on new information, the present Meeting reassessed the toxicity of the metabolites R611965 and R417888 and their relevance in dietary exposure.

The metabolite R611965 is covered by the ADI and ARfD of parent chlorothalonil, but it was noted that it is at least 10 times less potent. R611965 is the predominant residue in all rotational crops, representing 29–63% of the TRR in confined studies. Additionally, various field rotational crop studies were submitted to the 2010 JMPR, indicating potential residues of R611965 in succeeding crops:

Commodity group	Max. Residues of R611965 per trial [a] (mg/kg)	Field rotational crop median residue (mg/kg)	Field rotational crop highest residue (mg/kg)
Leafy and Brassica crops	<0.03, <0.05, <0.05, 0.18, 0.24, 1.1, 2.2	0.18	2.2
Legume vegetables	0.03, 0.14, 0.74, 1.0	0.44	1.0
Root tops	0.03, 0.04, 0.07, 0.1, 0.43, 0.49, 0.65, 0.91	0.265	0.91
Root and tuberous vegetables, bulb vegetables	0.02, 0.02, <0.03, 0.03, 0.08, 0.15, 0.2, 0.56, 0.59, 0.89	0.115	0.89
Cereal grains	<0.03, 0.04, 0.05, 0.06, 0.44, 0.56, 0.58	0.06	Not necessary
Oilseed and pulse crops	<0.03, <0.03, 0.04, 0.13	0.035	Not necessary
Fruiting vegetables	<0.03, <0.03, 0.14, 1.5	0.085	1.5

[a] up scaled (unless <LOQ) to the highest annual rate reported by the 2010 JMPR (20 kg ai/ha eq.)

Taking into account the 10 times lower potency of R611965, the Meeting concluded that its contribution to the overall dietary risk arising from its presence in commodities obtained from rotational crops is insignificant compared to parent chlorothalonil. The IESTI based on the median or highest residues found in field rotational crop studies represents a very small proportion of the ARfD (up to 5%).

Based on the chemical structure of R611965, conversion into SDS-3701 does not occur. SDS-3701 is the only chlorothalonil related residue found in commodities of animal origin. Therefore, the Meeting concluded that R611965 is irrelevant for the consideration of chlorothalonil residues in animal commodities.

The Meeting concluded that the inclusion of R611965 in the residue definition of chlorothalonil for dietary exposure purposes is unnecessary at this time. The relevance of this metabolite should be revisited in the next periodic review.

The metabolite R417888 is covered by the ADI and ARfD of chlorothalonil. Since the compound was not found in food or feed commodities, the Meeting concluded that its inclusion in the residue definition of chlorothalonil for dietary exposure purposes is unnecessary.

The Meeting confirmed its previous residue definition recommendations for chlorothalonil.

Results of supervised residue trials on crops

The Meeting received supervised trial data for applications of chlorothalonil on cranberries conducted in the USA.

Cranberry

The 2010 JMPR concluded that the overall information received was insufficient and recommended withdrawal of its previous recommendation for chlorothalonil in cranberries of 5 mg/kg.

The current Meeting received five new supervised field trials conducted in the USA and matching the GAP in the USA for cranberries at a rate of 3 × 5.5 kg ai/ha with a PHI of 50 days. In cranberries following treatment with chlorothalonil according to the US GAP, residues of chlorothalonil were (n=5): 0.41, 1.8, 3.0, 4.4 and 7.1 (highest individual value of 7.7) mg/kg.

In the same trials, the residues of SDS-3701 expressed as SDS-3701 were (n=5): < 0.01 (4), 0.019 mg/kg.

The Meeting estimated maximum residue level, STMR and HR values of 15, 3.0, and 7.7 mg/kg for chlorothalonil in cranberries, respectively. The Meeting also estimated STMR and HR values of 0.01 and 0.019 mg/kg, respectively, for SDS-3701.

RECOMMENDATIONS

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed below are suitable for establishing maximum residue limits and for IEDI and IESTI assessment.

Definition of the residue for compliance with the MRL for plant commodities: *chlorothalonil*

Definition of the residue for dietary risk assessment for plant commodities: *chlorothalonil and SDS-3701 (2,5,6-trichloro-4-hydroxyisophthalonitrile), all considered separately.*

Definition of the residue for compliance with the MRL and dietary risk assessment for animal commodities: *SDS-3701 (2,5,6-trichloro-4-hydroxyisophthalonitrile).*

The residue is not fat-soluble.

CCN	Commodity	Recommended Maximum residue level (mg/kg)		STMR or STMR-P mg/kg	HR or HR-P mg/kg
		New	Previous		
FB0265	Cranberry	15	W	Chlorothalonil: 3.0 SDS-3701: 0.01	Chlorothalonil: 7.7 SDS-3701: 0.019

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The ADI for chlorothalonil and its metabolite SDS-3701 are 0–0.02 and 0–0.008 mg/kg bw, respectively. The International Estimated Daily Intakes (IEDIs) for chlorothalonil and SDS-3701 were estimated for the 17 GEMS/Food Consumption Cluster Diets using the STMR or STMR-P values estimated by the JMPR. The results are shown in Annex 3 of the 2019 Extra JMPR Report.

The IEDIs ranged from 10–50% and 4–10% of the maximum ADI for chlorothalonil and SDS-3701, respectively. The Meeting concluded that long-term dietary exposure to residues of chlorothalonil and its SDS-3701 metabolite from uses considered by the JMPR is unlikely to present a public health concern.

Acute dietary exposure

The ARfD for chlorothalonil and SDS-3701 are 0.6 and 0.03 mg/kg bw, respectively. The International Estimate of Short Term Intakes (IESTIs) for chlorothalonil and SDS-3701 were calculated for the food commodities and their processed commodities for which HRs/HR-Ps or STMRs/STMR-Ps were estimated by the present Meeting and for which consumption data were available. The results are shown in Annex 4 of the 2019 Extra JMPR Report.

For chlorothalonil, the IESTIs varied from 0–9% (children) and 0–3% (general population) of the ARfD. For SDS-3701, the IESTIs were 0% (children) and 0% (general population) of the ARfD. The Meeting concluded that acute dietary exposure to residues of chlorothalonil and SDS-3701 from uses considered by the present Meeting is unlikely to present a public health concern.

Threshold of toxicological concern (TTC) consideration for metabolites

The metabolite R613636 could be assessed using the TTC approach (Cramer Class III threshold of 1.5 µg/kg bw per day). Formation of R613636 was only observed following simulated sterilization (120 °C, 20 min, pH 6) but not after simulated pasteurization or cooking, and represented up to 23% (mean of individual samples) of the recovered residue. R613636 was not found in unprocessed plant or animal commodities.

The Meeting applied a factor of 0.23 to the maximum IEDI of 9.33 µg/kg bw for parent chlorothalonil estimated by the current Meeting to address the formation of R613636 during sterilization resulting in an estimated exposure of 2.37 µg/kg bw per day.

The Meeting noted that the 17 Cluster diets model contains no information allowing refinement for sterilized foods. However, considering the small difference (less than two-fold) between the estimated exposure and the threshold of toxicological concern for a Cramer Class III compound of 1.5 µg/kg bw per day, it seems very unlikely that the daily diet contains a high percentage (>50%) of foods subject to high temperature treatment. Therefore, noting that the current IEDI model does not include details of food processing, the Meeting concluded that exposure to R613636 is likely to be below the TTC for Cramer Class III compounds and that based on the uses evaluated by the JMPR, residues of R613636 are unlikely to present a public health concern.

The metabolites SYN548764 and R611968 could be assessed using the TTC approach (Cramer Class III threshold of 1.5 µg/kg bw per day). Since these metabolites were not identified in food or feed commodities, they are unlikely to present a public health concern.

REFERENCES

Code	Author(s)	Year	Title
GRM005.03A	Heubner M. R.	2010	Analytical Method for the Determination of Total Chlorothalonil Residues in Crop Commodities by LC-MS/MS Syngenta Method GRM005.03A Syngenta File No. R044686_50164 GLP unpublished
IR-4 PR No. 11846	Jolly C.	2017	Chlorothalonil: Magnitude of the Residue on Cranberry Report No. IR-4 PR No. 11846 Syngenta File No. R044686_52414 GLP unpublished