CYPRODINIL (207)

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EXPLANATION

Cyprodinil is a fungicide belonging to the anilinopyridine group. It is a systemic foliar and seed dressing fungicide that acts as an inhibitor of methionine biosynthesis. Cyprodinil has been registered in many countries to control a range of fungal diseases in cereals, grapes, pome fruit, stone fruit, strawberries, vegetables, field crops and ornamentals, and as a seed dressing for barley.

Cyprodinil was firstly evaluated by JMPR in 2003, when an ADI of 0–0.03 mg/kg bw/day was established. An ARfD was deemed to be unnecessary. A residue definition of cyprodinil was recommended for plant and animal commodities, for both compliance with MRLs and estimation of dietary intake. The residue is fat soluble.

At the Forty-sixth session of the CCPR (2014), cyprodinil was scheduled for evaluation of additional use patterns by the 2015 JMPR.

The Meeting received residue data for oilseed rape and potato, and the proposal to extrapolate from carrot to ginseng.

METHODS OF RESIDUE ANALYSIS

Plant matrices

Method REM 141.01

Method REM 141.01(Dieterle, 1989) was evaluated by the 2003 JMPR. Homogenized samples were extracted with aqueous methanol. The extract was cleaned-up on a cation exchange cartridge. HPLC (single-column or two column-switching systems) with UV detection (λ max 270) was used for the final measurement. The LOQ for plant material was 0.02-0.05 mg/kg. The validation data included a wide range of high-water content crops as well as cereal grains (starchy). As the method was used for the determination of cyprodinil residues in potatoes, no further validation was conducted.

Method number AG-631B

Method AG-631B (Williams, R.K. 1998), with minor modifications was evaluated by the 2013 JMPR. Additional validation on rape seed matrices (seed and meal) are included in the supervised trials. Rape seed and meal samples were extracted by shaking with a methanol/water mixture at room temperature. After centrifugation, a 20 mL aliquot was taken and 2 mL of 1 M HCl was added. The extract was eluted through a SPE column with a methanol/ammonia mixture. The eluent was evaporated to near dryness and reconstituted with methanol. The extract was brought to 10 mL with methanol and bottled water and then diluted to 100 mL final volume and analysed by LC/MS/MS (quantification transition: 226.1 → 93.1). The method was verified at an LOQ of 0.02 mg/kg and an LOD of 0.006 mg/kg for canola seed and meal.

The following modifications were made to the reference method:

1. The extracts were centrifuged at 5000 rpm instead of being filtered.

2. Diethylene glycol diethyl ether was not added.

3. Extracts were brought to 10 mL final volume instead of 2 mL final volume.

These modifications were made to improve the method’s ruggedness and make it suitable for LC/MS/MS analysis.

Table 1 Recovery of cyprodinil from rape seed and rape seed meal using method AG-631B

Commodity	Fortification level (mg/kg)	No. of analyses (n)	Recovery (%)	Mean recovery (%)	% RSD	Reference (Author, Year)
Rape seed	0.02	4	73, 85, 82, 88	83	7.7	Williams, R.K. 1998
	0.1	2	79, 92			
	0.2	2	86, 76			
Rape seed meal	0.02	4	97, 88, 80, 86	97	12	Williams, R.K. 1998
	0.1	2	102, 113			
	0.2	2	104, 109			

Method AG-597B

The principle of method AG-579B (Campbell, D, D, 1996) for the determination of cyprodinil in oil is as follows: 10 g sample of rape seed oil samples were shaken with acetonitrile saturated with hexane. The partition was repeated four more times and the acetonitrile layers combined. The extract was evaporated to less than 5 mL and brought to 10 mL in acetonitrile. The extract was diluted to a suitable final volume and analysed by LC/MS/MS (226.0-108.2). The method was verified at an LOQ of 0.01 mg/kg and an LOD of 0.0033 mg/kg for refined oil.

Table 2 Recovery of cyprodinil from rape seed oil using method A-597B

Commodity	Fortification level (mg/kg)	No. of analyses (n)	Recovery (%)	Mean recovery (%)	% RSD	Reference (Author, Year)
Refined rape seed oil	0.01	4	107, 104, 92, 84	97	8.8	Campbell, D.D. 1996
	0.05	2	107, 89			
	0.1	2	96, 99			

Stability of pesticide residues in stored analytical samples

The stability of cyprodinil residues was investigated concurrently with sample storage as part of the analytical phase of the residue trials at intervals of 0, 3, 6 and 9 months frozen storage in rape seed, meal and oil. Cyprodinil residues are stable in rape seed, meal and oil stored frozen for at least 9 months.

Table 3 Recovery of cyprodinil in stored samples of rape seed and processed rape seed products

Matrix	Fortification lever(ppm)	Storage interval (months)				Reference
		0	3	6	9	
Rape seed	0.2	74	89	80	101	Sagan, K., 2009
Rape seed meal	0.2	99	107	97	78	
Rape seed oil	0.1	102	100	106	105	

Further storage stability data was evaluated by JMPR for the 2003 evaluation of cyprodinil. A study by Kissling (1995) evaluated the stability (at -18 °C) of incurred cyprodinil residues in grapes, apples, wheat ears, and wheat stalks, and of fortified residues in strawberries, potatoes, and wine. Acceptable stability was observed in all of these matrices over 24 months.

Additional storage stability data were also evaluated by the 2013 JMPR. Storage stability data for Avocado, Beans (dry), Blueberry, Broccoli, Cabbage, Mustard greens, Raspberry, Cantaloupe, Cucumber, Squash, Peppers, Tomato (fruit, puree, paste), Basil (fresh), Chives (fresh), Kiwifruit, Lettuce, Spinach, Lemon(dried pulp, juice, oil), Lychee, Parsley (fresh, dried), Carrot, Radish(top, roots), Strawberry, Watercress, Apple and Pear were determined concurrently with sample storage as part of the analytical phase of the residue trials. Cyprodinil was shown to be stable for periods up to 601 days in a wide range of frozen plant matrices.

USE PATTERN

Cyprodinil is registered in the Brazil for use on potatoes, Canada for use on oilseed rape and the USA for use on ginseng, and are summarized in Table 4.

Table 4 Registered uses of cyprodinil in Brazil, Canada and the USA

Crop	Country	Formulation		Application				PHI (days)
		g ai/kg	type	Method	(g ai/ha)	Water L/ha	No	
Potato	Brazil	750	WG	Foliar spray	250	500	4	7
Oilseed rape (canola)	Canada	375	WG	Foliar spray	365.6	>200	1	35
Ginseng	USA	375	WG	Foliar Spray	365.6	>140	4	7

RESULTS OF SUPERVISED RESIDUE TRIALS ON CROPS

The Meeting received information on cyprodinil supervised field residue trials for potatoes and oilseed rape.

Root and tuber vegetables

Potatoes

Three supervised trials with cyprodinil on potatoes were conducted in Brazil (two trials in 1997) and South Africa (one trial in 1992).

In trials conducted in South Africa, 5 foliar applications of cyprodinil (500 WP formulation) were applied at a rate of 175 or 300 g ai/ha. Samples of tubers were collected at PHIs of 0–63 days following the final application.

In Brazil, 5 or 6 applications of cyprodinil (750 WG formulation) were applied at rate of 250–500 g ai/ha). Samples of tubers were collected at PHIs of 0–63 days following the final application in each trial.

Samples were immediately frozen and maintained in frozen storage for periods of 82 to 329 days prior to extraction, and were analysed with the modified method REM 141.01

Table 5 Results of residue trials conducted with cyprodinil in potatoes in Brazil (750 g/kg WG formulation) and South Africa (500WP formulation)

Location, Trial no., Year (Variety)	Application					PHI (days)	Crop Part	Residue (mg/kg)	Reference
	Formulation	Growth Stage	Rate (g ai/ha)	Volume (L/ha)	No.				
Fazenda Vista Alegre, Monte Mor, Brazil , FR 049 and 50/96, 1997, (Achat)	750 WG	BBCH 19	250		6	0	Tuber	< 0.02	FR 049-50/96,
		BBCH 24	250			3	Tuber	< 0.02	
		BBCH 31	250			7	Tuber	< 0.02	
		BBCH 43	250			10	Tuber	< 0.02	
		BBCH 45	250			15	Tuber	< 0.02	
		BBCH 47	250						
	750WG	BBCH 19	500		6	0	Tuber	< 0.02	
		BBCH 24	500			3	Tuber	< 0.02	
		BBCH 31	500			7	Tuber	< 0.02	
		BBCH 43	500			10	Tuber	< 0.02	
		BBCH 45	500			15	Tuber	< 0.02	
		BBCH 47	500						
Sitia Quilombo, Divinolandia, SP, Brazil, FR 051-52/96, 1997, (Monalisa)	750WG	BBCH 19	250		6				FR 051-52/96,
		BBCH 24	250			3	Tuber	< 0.02	
		BBCH 31	250			7	Tuber	< 0.02	
		BBCH 43	250			10	Tuber	< 0.02	
		BBCH 45	250			15	Tuber	< 0.02	
		BBCH 47	250						
	750WG	BBCH 19	500		6	0	Tuber	< 0.02	

Location, Trial no., Year (Variety)	Application					PHI (days)	Crop Part	Residue (mg/kg)	Reference
	Formulation	Growth Stage	Rate (g ai/ha)	Volume (L/ha)	No.				
		BBCH 24	500			3	Tuber	< 0.02	
		BBCH 31	500			7	Tuber	< 0.02	
		BBCH 43	500			10	Tuber	< 0.02	
		BBCH 45	500			15	Tuber	< 0.02	
		BBCH 47	500						
Bultfontein, South Africa, 2168-91, 1992, (BP 1)	500 WP	Begin flower drop to End Flower drop	175	480	5	0	Tuber	< 0.02	2169-91
			175	480		7	Tuber	< 0.02	
			175	480		13	Tuber	< 0.02	
			175	480		28	Tuber	< 0.02	
			175	480		63	Tuber	< 0.02	
Bultfontein, South Africa, 2169-91, 1992, (BP 1)	500 WP	Begin flower drop - End Flower drop	300	480	5	0	Tuber	< 0.02	2169-91
			300	480		7	Tuber	< 0.02	
			300	480		13	Tuber	< 0.02	
			300	480		28	Tuber	< 0.02	
			300	480		63	Tuber	< 0.02	

Oilseeds

Rape seed

Sixteen supervised trials with cyprodinil on canola (oilseed rape) were conducted in Canada in 2009. Fourteen of the trials were conducted in region 14 but at only nine field sites. Thus, there were only nine independent trials. One application of cyprodinil (WG formulation) was made at the rate of 365.6 g ai/ha with a PHI of 35 days, with adjuvant added. Samples of rape seed were collected at normal commercial harvest, 35 to 53 days after application.

Samples were immediately frozen and maintained in frozen storage for periods of up to 200 days prior to extraction. Residues of cyprodinil in seed and meal were determined using method AG-631B and residues of cyprodinil in oil were determined using method AG-597B.

Table 6 Summary of residue data from Canada supporting the Canada GAP for use of cyprodinil on oilseed rape

Location, Trial no., Year (Variety)	Application					PHI (days)	Crop Part	Residue (mg/kg)	Reference
	Formulation	Growth Stage	Rate (g ai/ha)	Volume (L/ha.)	No.				
Elm Creek, MB, Canada, CER04169/07, 2009, (5030)	WG	BBCH 57 - 62	345.9			48	Seed	< 0.02	CER04169/07
Delisle, SK, Canada, CER04169/07, 2009, (5108)	WG	BBCH 62 - 63	362.7			35	Seed	< 0.02	
Minto, MB, Canada, CER04169/07, 2009, (Liberty Link Invigor 5020)	WG	BBCH 55 - 62	367.1			44	Seed	< 0.02	
						48	Seed	< 0.02	
						53	Seed	< 0.02	
						57	Seed	< 0.02	
Minto, MB, Canada, CER04169/07, 2009 , (Invigor 5108)	WG	BBCH 62 - 63	368.4			37	Seed	< 0.02	
Boissevain, MB, Canada, CER04169/07, 2009 , (Liberty 5030)	WG	BBCH 55 - 63	369.3			52	Seed	< 0.02	
		BBCH 55 - 63	1119.7			52	Seed	< 0.02	
							Meal	< 0.02	
							Oil	< 0.01	

Location, Trial no., Year (Variety)	Application					PHI (days)	Crop Part	Residue (mg/kg)	Reference
	Formulation	Growth Stage	Rate (g ai/ha)	Volume (L/ha.)	No.				
Boissevain, MB, Canada, CER04169/07, 2009, (Round-Up Ready 9551)	WG	BBCH 52 - 63 (Majority of plot was BBCH 62-63)	364.1			46	Seed	< 0.02	
Rosthern, SK, Canada, CER04169/07, 2009, (5020)	WG	BBCH 62 - 63	366.3			35	Seed	< 0.02	
						42	Seed	< 0.02	
						49	Seed	< 0.02	
						56	Seed	< 0.02	
Rosthern, SK, Canada, CER04169/07, 2009, (5030)	WG	BBCH 62 - 63	378.2			53	Seed	< 0.02	
Hepburn, SK ,Canada, CER04169/07, 2009, 45H72	WG	BBCH 62 - 63	375.7			38	Seed	< 0.02	
	WG	BBCH 62 - 63	1126.9			38	Seed	< 0.02	
							Meal	< 0.02	
							Oil	< 0.01	
Hepburn, SK, Canada, CER04169/07, 2009, (45H73)	WG	BBCH 62 - 63	366.2			38	Seed	< 0.02	
Innisfail, AB, Canada, CER04169/07, 2009, (5108)	WG	BBCH 62 - 66	390.6			41	Seed	< 0.02	
Innisfail, AB, Canada, CER04169/07, 2009, (9551)	WG	BBCH 62 - 63	382.8			52	Seed	< 0.02	
Penhold, AB, Canada, CER04169/07, 2009, (5020)	WG	BBCH 62 - 63	371.8			41	Seed	Mean = <u>< 0.02</u> (0.021, 0.017)	
Penhold, AB, Canada, CER04169/07, 2009, (9551)	WG	BBCH 62 - 63	374.9			52	Seed	< 0.02	
Sylvan Lake, AB, Canada, CER04169/07, 2009, (5020)	WG	BBCH 62 - 63	367.4			42	Seed	< 0.02	
Sylvan Lake, AB, Canada CER04169/07, 2009, (5020)	WG	BBCH 65 - 67	375.2			42	Seed	Mean = <u>< 0.02</u> (< 0.02, < 0.02)	

LOQ for seed is 0.02mg/kg. LOQ for oil is 0.01mg/kg

FATE OF RESIDUES IN PROCESSING

The determination of cyprodinil residues in processed fractions of oilseed rape was included in the residue study conducted in Canada. The application rate of cyprodinil was 1098 g ai/ha, 3-times the label rate. The process included seed cleaning, seed pro-conditioning and flaking, seed cooking, pressing the flake to mechanically remove a portion of the oil, solvent extraction of the press-cake to remove the remainder of the oil, and desolventizing and toasting of the meal. No residues (<LOQ) were found in seed, meal and oil. Therefore, no processing factors can be established because no measurable residues were found in the seed samples before processing.

APPRAISAL

Cyprodinil was first evaluated for residues and toxicological aspects by the 2003 JMPR. An ADI of 0–0.03 mg/kg bw for cyprodinil was established, and an ARfD was concluded as unnecessary. The residue definition was established as cyprodinil for both compliance with MRLs and dietary risk assessment for both plant and animal commodities. The residue is fat soluble.

Cyprodinil was evaluated by 2013 JMPR for additional crops. A number of Codex Maximum Residue limits for cyprodinil were established. Cyprodinil was scheduled by the Forty-sixth CCPR meeting in 2014 for evaluation of residue data for additional crops by the JMPR.

Methods of analysis

The Meeting received two analytical methods for determination of cyprodinil residues in plant matrices which are relevant to this evaluation. The LOQ for the HPLC-MS/MS (226.01–93.10) methods for rapeseed and meal was 0.02 mg/kg, and for rape seed oil, 0.01 mg/kg.

Stability of residues in stored analytical samples

The Meeting received information on the storage stability of cyprodinil residues in plant matrices from trials conducted in conjunction with the residue studies submitted to the Meeting. These data and stability data from JMPR 2003 and 2013 covers the maximum storage period for samples in the residue studies submitted to this Meeting.

Residues of supervised trials on crops

The Meeting received supervised trial data for application of cyprodinil to oilseed rape, potatoes, and carrots, which was evaluated by 2013 JMPR.

Potato

Cyprodinil is registered in the Brazil for use on potatoes at a GAP of 4× 0.25 kg ai/ha and PHI of 7-days.

The residues of cyprodinil in potatoes from two trials conducted in Brazil and one trial in South Africa matching the Brazilian GAP were all < 0.02 mg/kg (LOQ). The meeting noted that three trials were insufficient to make a recommendation for a maximum residue level for potatoes.

Ginseng

The meeting received the request to extrapolate the maximum residue level from carrots to ginseng. The 2013 Meeting received supervised residue trials of carrots matching the US GAP. The Meeting noted that although the US GAP for ginseng is the same as that for carrots, the growth traits and cultivation practices are significantly different, and agreed not to extrapolate from carrots to ginseng.

Rape seed

Cyprodinil is registered in Canada for use on rape seed at a GAP of 1× 0.365 kg ai/ha and a 35-day PHI.

Nine independent residue trials were conducted in rapeseed at GAP in Canada. Residues in seed of rape seed at the 35 day PHI were all < 0.02 mg/kg (n=9).

Based on the residues from the Canadian trials, the Meeting estimated a maximum residue level of 0.02 mg/kg for seed of rape seed and an STMR of 0.02 mg/kg.

Processing studies

A processing study for oilseed rape was evaluated by the current Meeting in which the application rate of cyprodinil was 1098 g ai/ha, 3-times the label rate. No residues (< LOQ), were found in seed, meal and oil, and therefore no processing factors could be established.

Residues in animal commodities

Farm animal dietary burden

Dietary burden calculations incorporating all commodities considered by the current, 2003 and 2013 Meetings for beef cattle, dairy cattle, broilers and laying poultry are presented in Annex 6. The calculations are made according to the livestock diets of the USA/Canada, the European Union, Australia and Japan as laid out in the OECD table. The animal dietary burden is the same as the results from 2013 meeting, and the Meeting confirmed the previous recommendation of MRLs in animal products.

	US/CAN		EU		AU		Japan	
	Max.	Mean	Max.	Mean	Max.	Mean	Max.	Mean
Beef cattle	0.91	0.37	13.9	1.8	5.8	1.4	0.46	0.46
Dairy cattle	1.7	0.87	13.5	1.4	23.3	1.8	0.26	0.26
Poultry—broiler	0.49	0.49	0.80	0.54	0.12	0.12	0.066	0.066
Poultry—layer	0.49	0.49	4.1	0.76	0.12	0.12	–	–

RECOMMENDATIONS

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

Definition of the residue for plant and animal commodities for compliance with MRLs and for estimation of dietary intake: *cyprodinil.*

The residue is fat soluble

CCN	Commodity	Recommended Maximum residue level (mg/kg)		STMR or STMR-P mg/kg	HR or HR-P mg/kg
		New	Previous		
SO 0495	Rape seed	0.02		0.02	

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Dietary Intakes (IEDIs) of cyprodinil were calculated for the 17 GEMS/food cluster diets using STMRs/STMR-Ps estimated by the current Meeting and by the 2003 JMPR. The ADI is 0–0.03 mg/kg bw and the calculated IEDIs were 6–70% of the maximum ADI (0.03 mg/kg bw). The Meeting concluded that the long-term intakes of residues of cyprodinil, resulting from the uses considered by the current Meeting and by the 2003 JMPR are unlikely to present a public health concern.

Short-term intake

The 2003 JMPR decided that an ARfD was unnecessary and concluded that the short-term intake of cyprodinil residues is unlikely to present a public health concern.

REFERENCES

Code	Author(s)	Year	Title
Report No. AG-631B	Williams, Robert	1998	Analytical Method AG-631B for the Determination of Residues of CGA219417 in Crops by High Performance Liquid Chromatography with Column Switching. Not published.
Report No. AG-597B	Campbell D.D.	1996	Analytical method for the determination of CGA 173506 in crops by high performance liquid chromatography including validation data. Not published.
Report No. FR 049-96 , FR 050-96	Machado Thais R.	1997	Determination of the residue level of stated potato peels after application of the fungicide Unix 750 WG, with the objective to provide data for the registration team to present to the authorities. Not published.
Report No. FR 051-52-96	Gebara Amir B.	1997	Determination of the concentration of Cyprodinil residues in potato tubers after application of Unix 750 WG fungicide.Not published.
Report No.2168-91	Dieterle R.	1993	CGA219417, WP 50, Potatoes, South Africa. Not published
Report No.2169-91	Dieterle R.	1993a	CGA219417, WP 50, Potatoes, South Africa. Not published
Report No. CER 04169/07	Sagan K.	2009	Amendment_A9219B - Residue Levels on Canola Seed and Processed Fractions, Meal and Refined Oil, from Trials Conducted with SWITCH 62.5 WG in Canada during 2007 (Fludioxonil/Cyprodinil WG). Not published.
Report No. 07090	Chen H.	2002	Cyprodinil and Fludioxonil: Magnitude of the Residue on Carrot. Not published.