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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

OCT 15 1992

MEMORANDUM

SUBJECT: **Iprodione.** Subdivision O, Guideline 171-4(k) Data. Rhone-Poulenc Study "Rovral/Grapes/Chemigation/Magnitude of the Residue, Study No. USA91R22." Reregistration Case No. 2335. Chemical No. 109801 MRID #424371-01. DP Barcode D182097. CBRS #10507.

FROM: Steven A. Knizner, Chemist
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THRU: Andrew Rathman, Section Head
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TO: Kathryn Davis, PM Team 51
Accelerated Reregistration Branch
Special Review and Reregistration Division (H7508W)

In support of reregistration of the List B contact fungicide iprodione, Rhone-Poulenc Ag Company has submitted a field trial study entitled "Rovral/Grapes/Chemigation/Magnitude of the Residue, Study No. USA91R22.", dated July 30, 1992. Rhone-Poulenc Ag Company committed to performing a grape residue study employing chemigation application of iprodione in their 90-Day Response to the Iprodione Phase 4 Review.

Tolerances are established (40 CFR 180.399) for the combined residues of iprodione [3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide)] (RP-26019), its isomer 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide (RP-30228), and its metabolite 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide (RP-32490) in or on numerous raw agricultural commodities, including grapes at 60 ppm.

1/11

Phone-Poulenc has previously submitted a magnitude of the residue study using ground application of iprodione (MRID #410716-01, 1989). This study has not been reviewed by CBRS and may not be adequate. Briefly, in the study, a total of fourteen field trials were conducted in CA(5), NY(2), WA(2), PA(2), OR(2), and OH(1). Iprodione was applied four times (last application on day of harvest) at 1.0 lb ai/A using commercial ground application methods. Four samples (three treated and one untreated control) were collected from each site. Samples were analyzed using the Rhone-Poulenc Analytical Method No. 151. The stated limit of detection for iprodione, its isomer, and metabolite was 0.05 ppm. Results were corrected for recovery (mean recovery for concurrent fortifications was 101.1, 104.4, and 96.6% respectively for iprodione, its isomer, and metabolite). Total residues on treated samples (n=42) ranged from 0.12 to 4.7 ppm, with an average value of 2.31 ppm and standard deviation of 1.24. Only one treated sample had quantifiable levels ($\geq$ 0.05 ppm) of either the isomer or metabolite (sample CA-88-236 had 0.06 ppm of the isomer).

Conclusions

1. **Geographic Representation** - CBRS concludes that until the registrant provides additional information about the numbers of growers contacted in NY concerning chemigation application of fungicides, and documentation from sources knowledgeable about grape cultivation in NY (e.g., NY Department of Agriculture or NY grape growers trade associations), the geographic representation of this study is not adequate. Alternatively, the registrant could amend the label to prohibit chemigation application in NY. This deficiency is upgradeable.

2. **Application** - CBRS concludes that the number of applications and the application rate are consistent with the maximum number of and rate of application on the label directions for grapes.

3. **Analytical Method** - CBRS concludes that a complete copy of the analytical method should be submitted.

a. The analytical method was not validated prior to analysis of samples as called for in the study protocol. This was not noted as a deviation from the study protocol. The registrant should explain why the method was not validated prior to sample analysis.

b. Fortified samples were analyzed concurrently with each sample set. Although most recovery values were within an acceptable range (70 to 110%), recovery values of 67% for the isomer and 118.0% for the metabolite were obtained for fortifications at 0.5 ppm (5X the LOQ). These values are outside the range considered acceptable in the study protocol. The protocol stated that should this situation occur, "the results for that bunch of analyses will be rejected and the samples reanalyzed". The registrant needs to explain why the protocol was not followed. This was not noted as

a deviation. The registrant should also explain why concurrent fortifications were made at such high levels (5X or 10X the LOQ).

4. **Results** - Total residue on treated grapes ranged from 0.26 to 1.10 ppm. Only one treated sample had levels of either the isomer or metabolite above the LOQ (sample CA-91-190 had 0.090 ppm of the metabolite).

a. Some of the values reported for the isomer and metabolite are below the limit of detection (0.05 ppm). The registrant must either submit evidence of the suitability of the method for determination of metabolite and isomer in the 0.005 - 0.05 ppm range or assign 0.05 ppm (LOD) to those values <0.05 ppm.

b. Chromatograms and raw data were sparse. For any one site (of the three studied) all sample and standard chromatograms and all raw data (peak heights and retention times) must be submitted. The submissions must be clearly labeled with sample/standard number and date of analysis.

5. **Storage Stability** - Storage stability data are needed. The registrant stated that a storage stability study is presently underway. Samples were stored frozen between 57 and 161 days from harvest until analysis.

Recommendations

Pending resolution of the concerns raised in Conclusions 1, and 3-5, the study is not adequate. The study is upgradeable by supplying the requested information.

TOX concerns permitting, based upon results obtained in this study and those obtained in MRID #410716-01, the registrant should submit a revised petition for a tolerance of 10 ppm for the combined residues of iprodione [3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide)], its isomer 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide, and its metabolite 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide, in or on grapes The CODEX MRL for iprodione (parent only) in or on grapes is 10 ppm.

Detailed Considerations

Field Trials

Three field trials were conducted in CA. The Phase 4 review called for field trials in both CA and NY. In a cover letter attached to the study, Rhone-Poulenc stated that they could not find any growers in NY that applied fungicides via chemigation. The number of growers contacted by Rhone-Poulenc was not given.

CBRS concludes that until the registrant provides additional information concerning the numbers of growers contacted in NY concerning chemigation application of fungicides, and documentation from sources knowledgeable about grape cultivation in NY (e.g., NY Department of Agriculture or NY grape growers trade associations), the geographic representation of this study is not adequate. Alternatively, the registrant could amend the label to restrict chemigation application in NY. This deficiency is upgradeable.

Application

Iprodione (EPA Reg No. 264-482, Rovral 4F, flowable s.c., 4 lbs ai/ gal product, lot no. X06238007, 41.89% by analysis) was applied to grape vines via chemigation at a rate of 1.0 lb ai/A in each of four applications. The first application took place when approximately 15-20% of the plants were in bloom, additional applications were made at pre-bunch closure (approximately 4-5 weeks after first application), verasion (approximately 9-13 weeks after first application), and at harvest (approximately 14-18 weeks after first application). There was a 0-day PHI in all cases. Applications were made using irrigation sprinklers, and spray volumes varied from 0.10 to 0.33 inches/acre. A control (untreated) plot was located at the same site.

CBRS concludes that the number of applications and the application rate are consistent with the maximum number of and rate of application on the label directions for grapes.

Sampling

A single untreated sample and triplicate treated samples of grape fruit were taken the day of the last application of iprodione. A sample consisted of harvesting four bunches of mature grapes from each of four consecutive individual vines by hand. Samples from each vine were selected at random from high, mid, and low levels in both sheltered and exposed areas and from both sides of the vine. Samples were placed in coolers with dry ice until they were transported to the storage facility where they were frozen and stored below -10°C until shipment to Rhone Poulenc Ag Co. (RPAC), in NC. Samples were transported to RPAC by freezer truck in a frozen state. A deviation in sample storage temperature at one site occurred because of a freezer malfunction. The malfunction was of short duration, and no evidence of thawing was observed in samples from this trial.

Analytical Method

Storage time from sampling until analysis of grapes ranged from 57 to 161 days. Grapes were analyzed using the Rhone Poulenc Ag Company analytical method SOP 90277 "Rovral, Determination of RP-26019 and its Metabolites in/on Dry, Succulent, Oily and Non-Oily Crops by Gas-Liquid Chromatography and Thin Layer Chromatography." This method was

previously submitted in PP#6F3443, and is identical to that used for the study involving ground application of iprodione on grapes (MRID #41071601).

A summary of the analytical method was provided, however, a copy of the complete analytical method was not included. Samples were extracted with acetone, interfering substances were removed by liquid-liquid partitioning and Florisil column cleanup. Concentrations of the three analytes were determined using GC with ECD. The Phase 4 Review of the plant residue analytical method indicated a data gap, stating that toluene should be substituted for benzene in the clean-up. Since a copy of the method was not provided, CBRS cannot determine if this substitution was made.

The stated analytical method limit of detection is 0.05 ppm, and limit of quantitation is 0.1 ppm, for iprodione, its isomer, and its metabolite. External standard calibration was used. Linearity was demonstrated for each analyte from 0.1 to 0.5 ug/ml.

The analytical method was not validated prior to analysis of samples as called for in the study protocol. This was not noted as a deviation from the study protocol. The protocol called for method validation by analyzing two sets of untreated control samples fortified at the LOQ, 0.5 and 1.0 ppm iprodione respectively, an untreated control, and a reagent blank. Acceptable recoveries would be 60 to 120% for the LOQ fortification and 70 to 110% for the others. The untreated control and reagent blanks should have no significant apparent iprodione residues.

Representative chromatograms of standards, untreated control grapes, fortified grapes, and treated field samples were provided, along with a typical analytical raw data sheet. The chromatograms were not properly labeled with attenuation or chart speed. No chromatograms for iprodione, its isomer, or metabolite were provided for grapes fortified at the LOQ. No data depicting mixed standards (iprodione, its isomer, and its metabolite in the same sample) were provided.

Fortified samples were analyzed concurrently with each sample set. Iprodione was fortified at 1.0 ppm, and its isomer and metabolite were each fortified at 0.5 ppm. An explanation as to why grapes were fortified at 10X the LOQ for iprodione and 5X the LOQ for the isomer and metabolite is needed.

Recovery values for current fortifications are shown in Table 1.

Table 1. Percent recovery for concurrent fortification samples.

Percent Recovery		
Iprodione (fortified at 1.0 ppm)	Isomer (fortified at 0.5 ppm)	Metabolite (fortified at 0.5 ppm)
74.0	67.0	72.0
94.5	88.0	105.0
99.0	72.9	118.0

Two of these recovery values (67% for the isomer and 118.0% for the metabolite) are outside the range considered acceptable in the study protocol. The protocol stated that should this situation occur, "the results for that bunch of analyses will be rejected and the samples reanalyzed". The registrant needs to explain why the protocol was not followed.

CBRS concludes that a complete copy of the analytical method is needed. The analytical method was not validated prior to analysis of samples as called for in the study protocol. This was not noted as a deviation from the study protocol. Some recovery values for concurrent fortifications were outside the range considered acceptable in he protocol. Samples from these batches were not reanalyzed as called for in the protocol. This was not noted as a deviation.

Results

Results of this study are presented in Table 2. Total residues are the sum of iprodione, its isomer, and metabolite. The largest total residue level obtained was 1.10 ppm. Only one treated sample had levels of either the isomer or metabolite above the LOQ (sample CA-91-190 had 0.090 ppm of the metabolite).

Table 2. Results for grapes treated with iprodione from three sites in CA.

Trial No.	Treatment	Residues Found (ppm)			
		Iprodione	Isomer	Metabolite	Total Residue
91-166	0	N.D.	0.015	N.D.	<0.05
	4 X 1.0 lb ai/A	0.085	0.030	N.D.	0.88
		0.083	0.030	N.D.	0.86
		0.045	0.040	N.D.	0.49

Trial No.	Treatment	Residues Found (ppm)			
		Iprodione	Isomer	Metabolite	Total Residue
91-190	0	0.015	N.D.	0.035	0.05
	4 X 1.0 lb ai/A	0.360	0.005	0.090	0.46
		0.220	0.010	0.050	0.28
		0.210	0.010	0.035	0.26
91-191	0	0.020	0.005	N.D.	<0.05
	4 X 1.0 lb ai/A	0.800	0.020	N.D.	0.82
		1.070	0.030	N.D.	1.10
		0.800	0.020	0.020	0.84

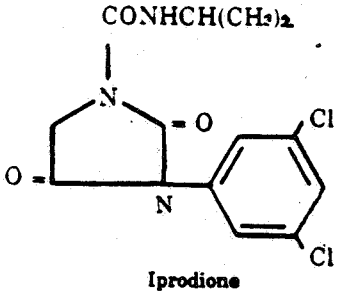
N.D. = none detected

The registrant stated that values below the method LOQ (and sometimes the LOD) were used to determine the totals when available. The registrant must either submit evidence of the suitability of the method for determination of metabolite and isomer in the 0.005 - 0.05 ppm range or assign 0.05 ppm (LOD) to those values <0.05 ppm.

Storage Stability

The registrant stated that a storage stability study is presently underway. Samples were stored frozen between 57 and 161 days from harvest to analysis.

cc: Iprodione S.F., S.F., circ., R.F., List B File, Reg. Stnd. File, S.Knizner
RDI: A.Rathman, 10/15/92 E.Zager, 10/15/92
H7509C:CBRS:SAK:sak:305-6903:Iprod2.rev:CM#2:9/14/92



Iprodione

IPRODIONE (Case 2335/Code 109801)
TENTATIVE RESIDUE CHEMISTRY DATA SUMMARY THROUGH 10/15/92
(FOR AGENCY USE ONLY)[1]

REASSESSMENT OF U.S. TOLERANCES AND POTENTIAL FOR HARMONIZATION WITH CODEX[2]

Guideline Number and Topic[3]	Phase V data requirements satisfied?[4]	MRID(s)[5]
171-3 Directions for use	N[6]	
171-4(a) Plant Metabolism	Y	
171-4(b) Animal Metabolism	N[7]	
171-4(c) Residue Analytical Methods - Plants	N	
171-4(d) Residue Analytical Methods - Animals	N	
171-4(e) Storage Stability	N	
171-4(k) Crop Field Trials		
171-4(k) Root and Tuber Vegetables Group		
Carrots	N[8]	
Potatoes [see 171-4(l)]		
171-4(k) Bulb Vegetables Group		
Garlic	N[9]	
Onions (green and dry bulb)		
171-4(k) Leafy Vegetables (except Brassica)		
Lettuce (leaf)	Y	
Lettuce (head)		
71-4(k) Brassica Leafy Vegetables Group		
Broccoli	Y	
171-4(k) Legume Vegetables (succulent/dried)		
Beans (succulent and dried)	N[10]	
171-4(k) Foliage of Legume Vegetables		
Bean vines and hay	N[10]	
171-4(k) Stone Fruits Group		
Apricots	N[11]	
Cherries		
Nectarines		
Peaches		
Plums (fresh prunes) [see 171-4(l)]		
171-4(k) Small Fruits and Berries Group		

IPRODIONE (Case 2335/Code 109801)
TENTATIVE RESIDUE CHEMISTRY DATA SUMMARY THROUGH 10/15/92
(FOR AGENCY USE ONLY)[1]

REASSESSMENT OF U.S. TOLERANCES AND POTENTIAL FOR HARMONIZATION WITH CODEX[2]

Guideline Number and Topic[3]	Phase V data requirements satisfied?[4]	MRID(s)[5]
Blueberries	N[12]	
Boysenberries		
Canberries		
Currants		
Grapes [see 171-4(l)]	N[13]	424371-01
Raspberries		
Strawberries		
171-4(k) Tree Nuts Group		
Almonds	N[14]	
171-4(k) Cereal Grains Group		
Rice [see 171-4(l)]	Y	
171-4(k) Forage, Fodder, and Straw of Cereal Grains		
Rice straw	Y	
171-4(k) Miscellaneous Commodities		
	N[15]	42132801
Kiwi		
Peanuts		
171-4(l) Processed Food/Feed		
Beans (succulent/dried)	Y	
Grapes		
Peanuts		
Potato		
Rice		
171-4(j) Meat/Milk/Poultry/Eggs	N	
171-4(f) Potable Water	N	
171-4(g) Fish	N/A	
171-4(h) Irrigated Crops	N/A	
171-4(i) Food Handling Establishments	N/A	
171-5 Reduction of Residues	N/A	

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[1] Phase IV review completed 03/15/91. This summary is tentative and is subject to correction and change.

[2] Codex has established MRL's for iprodione, as the residue iprodione (# 111), for the following commodities: apple (10 mg/kg); beans (dry) (0.2); cucumber (5); currants, black, red, white (5); garlic (0.1); grapes (10); kiwifruit (5); lettuce, head (10); onion, bulb (0.1); peach (10); pear (10); peppers, sweet (5); plums (including prunes)(10); raspberries, red, black (5); rice, husked (3); strawberry (10); tomato (5); witloof chicory (sprouts)(1).

Canada has established MRL's for iprodione, expressed as the residue of iprodione and the two metabolites regulated in the US, for grapes (10 ppm); cherries, peaches, strawberries (5.0); cucumbers, kiwi fruit (edible portion), tomatoes (0.5); and beans (0.3).

[3] N/A = Guideline requirement not applicable.

[4] Applies to List B only; List A chemicals were not subject to Phase IV of FIFRA '88.

[5] MRIDs that were reviewed in the current submission are designated in shaded type.

[6] Labels are required for kiwifruit (import).

[7] Ruminant study required in Phase IV.

[8] Carrot studies acceptable. Potato tolerance established in 1990; data not reviewed for reregistration.

[9] Aerial studies required in Phase IV for onions.

[10] Aerial and chemigation trials required. Additional geographical representation required for dry beans. Label changes needed.

[11] Product label required for post-harvest uses.

[12] Summary of strawberry field trial data required. Labels with use information for strawberries required. Field trial data required for blueberries, raspberries, grapes. See Phase IV Review.

[13]10/14/92 CBRS. No. 10507. Three field trials were conducted in CA. Iprodione was applied to grapes using chemigation at 1.0 lb ai/A in each of four applications. 0 day PHI. Total residue (parent, isomer, and metabolite) ranged from 0.26 to 1.10 ppm. Only one treated sample had quantifiable levels of either isomer or metabolite (0.090 ppm of metabolite). Study was inadequate because: 1) insufficient geographical representation - data from NY is needed, or more documentation that iprodione is not applied using chemigation in NY, and/or labeling prohibiting application of iprodione using chemigation in NY; 2) Analytical method was not validated prior to analysis of samples, copy of method was not provided; 3) Results reported were below the LOD, not enough raw data were submitted; and 4) Storage stability data are needed - samples were stored frozen up to 161 days from harvest to analysis. Recommended that, based upon results of this study and data in MRID #410716-01, Registrant should propose tolerance of 10 ppm for iprodione, isomer, and metabolite in/on grapes.

[14] Additional data for chemigation and aerial applications required.

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[15] Kiwi field trials (import tolerance) were inadequate: use label(s) required to evaluate application rate, etc.; data must be recalculated without correction; data must not be reported below method lod. Peanut acceptable, but the feed additive tolerance in 40 CFR 186.3750 must be amended to soapstock, peanut.

cc: Iprodione List B File; J. Ellenberger, SRRD.

(1)