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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Reregistration of Iprodione. Product Chemistry: Stability (63-13). Residue Chemistry: Kiwi Field Trials (171-4(k)). DP Barcode D172676. MRID Nos. 41958501 and 42132801. CBRS No. 9165.

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In support of the reregistration of the List B contact fungicide iprodione, or 3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide, Rhone-Poulenc has submitted a product chemistry stability study entitled "Iprodione, Technical - Determination of Stability; Document Number: 4053-91-0060-AS-001," dated 05/24/91 and a kiwi field trial study entitled "Residues of Iprodione in/on Kiwi Fruit Resulting From Foliar Applications of Rovral Flo 250g/l," dated 10/10/91. The performing laboratory for the stability study was Ricerca, Inc. The performing laboratory for the field trials conducted in New Zealand was Rhone-Poulenc Ag Co., Research Triangle Park.

Tolerances have been established for the combined residues of iprodione, 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-

imidazolidinecarboxamide, and 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide in/on numerous rac's, including an import tolerance of 10.0 ppm for kiwi fruit (40 CFR 180.399).

Conclusions

63-13:

1. Iprodione is stable to heat (< 150° C), metal (Fe, Sn, Al), metal ions (Fe⁺³), and light. Iprodione showed no instability for up to 30 days at 55° C. The GLN 63-13 requirement for technical iprodione is fully satisfied.

171-4(k):

2. A flowable soluble iprodione concentrate, 23.8% a.i. by analysis, was applied in 3 applications of 0.668 lb. a.i./acre each to kiwi at 10 sites in New Zealand. Application was by ground spray (knapsack). The appropriateness of the use pattern cannot be determined until requested labels are submitted. Field trials must be conducted with representative formulations at the maximum label rates and minimum PHI. The registrant must indicate which formulation was used, 24% or 42%. The amount of water of dilution added and the total volume applied per acre must be given. Any adjuvant used must be identified. The registrant must confirm the kg a.i./Ha used.

3. Total residue measured on the kiwifruit ranged from 0.6 ppm to 4.9 ppm. However, these results were corrected for method losses. Results not corrected must be presented. Results without correction, the appropriate recovery factor, and the corrected results must be presented.

4. The analytical method limit of detection is 0.05 ppm for iprodione and each of the two metabolites. The registrant reported metabolite concentrations below 0.05 ppm. Accuracy and precision must be demonstrated at 0.01 ppm, or all values reported below 0.05 ppm must be amended to < 0.05 ppm.

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

6. Storage stability data are acceptable, but they must be recalculated without correction for method losses and metabolite values reported below 0.05 ppm must be changed to < 0.05 ppm, unless the registrant supplies accuracy and precision data for the method at 0.01 ppm.

Recommendations

The requirements for data on the stability of technical iprodione (GLN 63-13) have been satisfied. CBRS recommends that no additional action is needed.

The kiwi field trial study (GLN 171-4(k)) is unacceptable for the reasons stated in Conclusion Nos. 2 - 6. However, the study is upgradeable, and the registrant should submit the requested information.

Detailed Consideration

Stability (62-13)

The test material was technical iprodione (96.4%), batch no. 9015501. Hplc analysis of the technical (n = 17) yielded a concentration of 97.57%, s.d. 0.780. The reference substance was iprodione (99.9%), lot no. EA20025D8. Both were supplied by Rhone-Poulenc.

Accelerated storage tests were performed on technical iprodione and mixtures of iprodione and iron powder (about 5% iron w/w) and iprodione and ferric chloride (about 5% ferric chloride w/w). Five 5 - 10 g samples of iprodione and six 5 - 10 gram samples of each of the two mixtures were placed in 5-dram glass vials and sealed. One vial of each sample type was maintained at ambient conditions for 30 days, and one vial of each type was stored in a freezer (-18° C) for 30 days. The remainder were heated at 55° C in a constant temperature cabinet. One of each type of sample was removed at 7, 14, 21, and 30-day intervals and frozen until analyzed.

Two individual weighings of each sample were analyzed by hplc. Each weighing was analyzed twice, for a total of four determinations per sample. The mobile phase (isocratic) consisted of pH 4.5 sodium acetate aqueous buffer, methanol, and acetonitrile, 1.9:1.5:1.0. The flow rate was 1.5 ml/min, and the retention times were about 6.7 minutes for propiophenone internal standard and 20.2 minutes for iprodione. The detector was uv (220 nm), and the column was Alltech Nucleosil C18.

Results of the accelerated storage tests are summarized in Table 1. No decomposition was observed, relative to the controls. Some apparent decomposition of the iron/iprodione mixture is attributed by the registrant to lack of sample homogeneity.

To determine stability to light, technical iprodione was placed on Petri dishes to a depth of 2 mm and exposed to the light of Sylvania 350 black light lamps (290 - 380 nm). Cellulose

triacetate sheets were used to filter out uv radiation. The exposure was continuous for 30 days. Samples were removed and analyzed (hplc) after 7, 14, 21, and 30 days. The control sample iprodione concentration was 96.37%. The mean iprodione concentration for the 4 sampling dates was 96.35%, range 95.76 - 97.09%. Thus, no decomposition occurred. There was no visible change.

Table 1: Accelerated Stability Test (55° C) for Technical Iprodione					
Substrate	7 Days	14 Days	21 Days	30 Days	Mean
Iprodione Control (ambient)					96.37
Iprodione Control (-18° C)					97.38
Iprodione	96.63	96.74	97.23	97.00	96.90
Iprodione/Iron Control (ambient)					92.38
Iprodione/Iron Control (-18° C)					91.34
Iprodione/Iron	94.21	96.08	95.02	92.91	94.55
Iprodione/FeCl ₃ Control (ambient)					92.80
Iprodione/FeCl ₃ Control (-18° C)					92.49
Iprodione/FeCl ₃	92.60	91.73	92.14	93.14	92.40

Thermal stability of iprodione and metal/iprodione mixtures was studied by thermal gravimetric analysis (tga) and by differential scanning calorimetry (dsc). The dsc measurements were made from 25° - 150° C under both air and nitrogen. The only observed activity was a endotherm attributed to melting at about 132° C. Scan rate was 20° C/min., and sample size was 3 - 6 mg. No decomposition (exotherm/endotherm) was observed at or below 150° C. Similar behavior was exhibited by mixtures of iprodione and iron, aluminum, and tin. Example thermograms were included.

The tga analyses were conducted over a temperature range of 50° - 150° C at a heating rate of 10° C per minute under both air and nitrogen atmospheres. No weight changes were observed. Thermograms were included.

Technical iprodione has been shown to be stable to light and heat

(55° C) for up to 30 days. It is also stable to iron and ferric ion for up to 30 days. Decomposition or oxidation of iprodione does not occur under 150° C, and iprodione does not readily react with iron, aluminum, or tin at temperatures below 150° C. An adequate stability study has been conducted.

Kiwi Field Trials (171-4(k))

Iprodione (Registration No. 264-482, Rovral 4F, flowable s.c., 2.08 lbs. a.i./gal, 23.8% a.i. by analysis) was applied to the foliage of kiwi plants at a rate of 0.668 lb. a.i./A (0.75 kg/Ha) in each of three applications. The registrant appears to miscalculate 0.75 kg/hectare as 0.84 lb./acre (p. 87). Total application was 2.0 lbs. a.i./acre (2.25 kg a.i./Ha). Application was made with knapsack sprayers. Most plots were 16.4 ft. X 33 ft, or 0.0124 acres. According to the protocol, the fungicide was diluted so that 214 gallons/acre (1 gallon concentrate to 669 gallons diluent, 0.08 gallon per foot of row) was applied. Information on water of dilution and gallons of spray solution applied per acre are not provided in the actual trial descriptions, however. Application was made at 10 separate sites in New Zealand from November 1990 through May 1991. Control plots (0X) were located at each site. The interval between the first and second application ranged from 29 days to 43 days. The interval between the second and final application ranged from 110 days to 119 days. The PHI was one day in all cases.

CBRS is unable to evaluate the acceptability of the application conditions, because a use label was not supplied. The registrant was directed to supply labels with the study in the List B Phase IV DCI. The formulation should be typical of that used, and the application method(s) should be that/those routinely used. The maximum number of applications at the maximum application rate and minimum PHI should be represented. Registration No. 264-482 is for a 41.6% material, not 24% as given by the registrant. Clarification (label) is needed. An inspection of the most recent label (03/02/92) for Rovral 4 Flowable Fungicide, registration no. 264-482, does not reveal any use on kiwifruit.

Triplicate samples of 16 pieces of fruit each were taken from each treated plot. A 16 piece sample was taken from each of the control plots. Samples were stored frozen and shipped on dry ice to Rhone-Poulenc, RTP, for analysis. Samples were stored frozen ($\leq -18^{\circ}$ C) at RTP. The elapsed time from harvest to analysis ranged from 14 days to 34 days.

Analytical method SOP No. 90277 was used. A weighed sample (10 - 20 g) of whole fruit is blended with acetone (200 ml) and filtered. The blending and filtration is repeated, and the combined acetone fractions are evaporated to dryness. The residue is extracted with 10% ethyl acetate in methylene chloride, and the extract is evaporated to dryness. The residue is dissolved in benzene (15 ml) and chromatographed on activated Florisil. Iprodione and 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide (RP-30228) are eluted in the second fraction, ethyl acetate/benzene (7.5/92.5). The remaining regulated metabolite, 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide (RP-32490), is eluted in the fourth fraction, ethyl acetate/benzene (50/50). The solvents are evaporated and the extracts (dissolved in hexane or benzene) are analyzed by gc/ec on a 3% SP2250 packed column at the following temperatures: 265° C for iprodione; 150° C for RP-30228; 270° C for RP-32490. Retention times are approximately 121 seconds, 66 seconds, and 130 seconds, respectively. Based on spiked sample data for stone fruit and almonds, a summary of which was presented, the limit of detection is estimated to be 0.05 ppm for each analyte. External standard calibration was used. Linearity was demonstrated for each analyte from 0.1 to 0.5 ug/ml.

The analytical method is a variation of that submitted in Phase IV (MRID 92083073).

Results of the analysis of samples from the ten field trials are summarized in Table 1. Example chromatograms and an example raw data sheet for 4 analyses were provided. The remainder of the raw data was not included. The results were corrected for procedure recoveries (fortified control recoveries) determined with each set of samples. Results should be reported without recovery correction. Recovery results are summarized, but it is not possible to discern which recoveries accompany which sample(s). This is a deficiency.

Some of the values reported for the metabolites are below the limit of detection (0.05 ppm). The registrant must either submit evidence of the suitability of the method for determination of metabolites in the 0.01 ppm - 0.05 ppm range or assign 0.05 ppm (lod) to those values < 0.05 ppm.

All control samples yielded a total residue < 0.05 ppm, except the control for site 90-279, where the total residue was 0.07 ppm (0.05 ppm RP32490 + 0.01 ppm each of iprodione and RP30228). The registrant attributes the finding to spray drift. Chromatographic interference seems more likely, given a metabolite as the major contributor. Chromatograms were not supplied for this control sample.

Table 1: Residues of Iprodione and Regulated Metabolites Found in/on Kiwifruit					
Test Site	Iprodione ¹ (ppm)	RP30228 ^{1,2} (ppm)	RP32490 ^{1,3} (ppm)	Total ^{4,5} (ppm)	
				Average ¹	Maximum
90-270	2.56	0.08	0.03	2.67	2.74
90-271	2.42	0.20	0.03	2.65	3.36
90-272	2.62	0.05	0.04	2.72	3.37
90-273	4.29	0.16	0.09	4.54	4.86
90-274	0.41	0.01	0.03	0.45	0.67
90-275	0.49	0.02	0.01	0.52	0.56
90-276	2.74	0.09	0.03	2.87	3.18
90-277	2.23	0.17	0.02	2.42	2.69
90-278	4.20	0.04	0.03	4.27	4.65
90-279	3.26	0.03	0.02	3.31	3.88
Average (ppm)	2.52	0.08	0.03	2.64	3.00
Range (ppm)	0.41 - 4.29	0.01 - 0.20	0.01 - 0.09	0.45 - 4.54	0.56 - 4.86
¹ Average of analysis of 3 samples. ² 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide. ³ 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide. ⁴ Results were corrected for method recovery. Uncorrected results are not available. ⁵ Storage stability tests (see text) indicate up to a 15% loss. Therefore, residues reported could be 15% below actual values at time of harvest.					

Summary data only are presented for the recovery of iprodione and the regulated metabolites from kiwifruit. Example chromatograms are included. Kiwifruit was spiked at 5.0 (n = 1), 4.0 (n = 2), 2.0 (n = 1), 1.0 (n = 4), and 0.5 ppm (n = 2) with iprodione. Kiwifruit (n = 10) was spiked at 0.5 ppm each of the regulated metabolites. The text implies that average recoveries were not used in correcting sample concentrations. Rather, recoveries determined with each sample or group of samples was used. The recovery data are summarized in Table 2. CBRS notes that the registrant reports different average recoveries for the metabolites on page 11 (Results and Conclusions) and on page 15 (Summary of...Recoveries...). CBRS assumed the page 15 values to be correct. The use of 0.5 ppm fortification recovery data for the correction of metabolite values is inappropriate, because most of the metabolite values were < 0.2 ppm. Regardless, uncorrected results should have been reported.

Table 2: Recovery of Iprodione and Metabolites from Kiwifruit

Analyte	Fortification Level (ppm)	Recovery Range (%)	Average Recovery (%)	Standard Deviation (%)
Iprodione	0.5 - 5.0	61 - 114	98.1	15.1
RP30228	0.5	74 - 123	103	16.1
RP32490	0.5	60 - 118	90.3	15.5

Storage Stability

A storage stability study was conducted to determine possible loss of residue during frozen storage of kiwifruit samples prior to preparation and analysis. Three samples of kiwifruit were prepared and analyzed on 05/22/91, five days after receipt from New Zealand. The samples were then stored frozen (-18° C) for 33 days (06/25/91), the maximum storage interval for samples prior to analysis. Summary results were provided; no raw data were included. These results, corrected for method recovery, are given in Table 3. Results should have been reported uncorrected.

Table 3: Storage Stability of Iprodione and Metabolites in/on Kiwifruit (- 18° C)						
Sample No.	Elapsed Time (days)	Iprodione (ppm)	RP30228 (ppm)	RP32490 (ppm)	Total (ppm)	Loss (%)
RK10906	0	3.02	0.32	0.02	3.36	0.0
	33	3.15	0.16	0.05	3.36	
RK10907	0	2.44	0.17	0.04	2.65	7.9
	33	2.24	0.14	0.06	2.44	
RK10908	0	1.81	0.12	0.02	1.95	15
	33	1.52	0.08	0.06	1.66	

cc: RF, Iprodione List B File, circ., S. Funk, C. Furlow (PIB, FOD).

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