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3-17-87

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

MAR 17 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP 6F3443/FAP 6H5507 - Iprodione on Rice, Rice Straw, and Rice Hulls. Evaluation of Analytical Method and Residue Data. EPA Accession No. 264288. RCB Nos. 1326 and 1327.

FROM: R. W. Cook, Chemist
Residue Chemistry Branch
Hazard Evaluation Division (TS-769C)

TO: Lois A. Rossi, Acting PM 21
Fungicide-Herbicide Branch
Registration Division (TS-767C)

and

Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Charles L. Trichilo, Chief
Residue Chemistry Branch
Hazard Evaluation Division (TS-769C)

The petitioner, Agrochemical Division, Rhone-Poulenc, Inc., proposes the establishment of tolerances for combined residues of the fungicide iprodione [3-(3,5-dichlorophenyl)-N-(methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide], its isomer [3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide], its metabolite [3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide] expressed as iprodione equivalents in or on rice at 10 ppm and rice straw at 20 ppm and food additive tolerances for the combined residues as above on rice hulls at 50 ppm.

Combined residues of iprodione are currently regulated under 40 CFR 180.399(a) on a variety of raw agricultural commodities of plant origin. Agricultural commodities of animal origin are regulated under 40 CFR 180.399(b) where the combined residues (as above) include the additional metabolite [N-(3,5-dichloro-4-hydroxyphenyl)-ureidocarboxamide], all expressed as iprodione equivalents. A Registration Standard for iprodione has not been completed.

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Conclusions:

1. The metabolism of iprodione in plants and animals is adequately understood. In plants the residues of concern, expressed as iprodione equivalents, are iprodione, [3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide] (RP-26019); 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide (RP-30228); and 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide (RP-32490). The residues of concern in animals are iprodione; 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide (RP-30228); 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide (RP-32490); and N-(3,5-dichloro-4-hydroxyphenylureidocarboxamide (RP-36115), all expressed as iprodione.

2. Adequate methods are available for enforcement purposes. Enforcement methods are available in Pesticide Analytical Manual, Vol. II (PAM-II).

3a. The available residue data are not adequate to draw any conclusions regarding the proposed tolerances.

3b. Additional residue data reflecting label instructions for aerial application are needed. Major rice production areas must be represented: Arkansas, Louisiana, Mississippi, Texas, and California.

3c. Additional information on the manner and method of sampling should be provided. We question whether representative samples of rice grain and straw can be gathered from combine or hopper after combining plots as small as 4 x 20 ft. Further, we do not believe a single sample analysis is adequate representation for each location. Replicate samples should be obtained and duplicate analysis conducted.

3d. The label prohibition against use on California rice is not practical. Additional residue data reflecting use (aerial application) on California rice are needed. Alternately, a persuasive argument that the label prohibition is practical may be submitted.

3e. The petitioner should clarify whether study TX-434825-105 reflects two or three applications.

3f. The use directions instruct application at the interval between joint movement and booting and a second application 2 weeks after the first application, but no later than heading. The submitted residue data do not report crop stage of growth at each application. The petitioner should advise us of the crop stages at each application, especially for the stage "heading." Our information indicates various intervals of 25 to 37 days between head initiation and full head, and intervals of 23 to 32 days between full head and harvested. This information should help in determining whether the submitted data reflect the proposed use.

4. In the absence of adequate residue data for rice grain, we are unable to draw any conclusions regarding the proposed food additive tolerance of 50 ppm in rice hulls. Based upon a submitted rice processing study, it appears that a concentration factor of 5X is appropriate for rice hulls. However, in light of the ^{14}C rice-metabolism study showing less than 1X in certain processed fractions, we await petitioner's comments of the differing results demonstrated by TX-434285-113 and the ^{14}C study in regards to residue concentration factors for rice processing fractions.

5. Absent adequate residue data for rice grain, we are unable to draw any conclusions regarding residues in meat, milk poultry, and eggs.

6. We believe a feed additive tolerance for rice bran is needed. The petitioner should so propose.

7. A Codex sheet is attached. A pathway for resolving differences between the Codex expression, 3 ppm iprodione <u>per se</u> on rice (husked, unpolished) and the U.S. tolerance (combined iprodione and its isomer and its metabolite) at 10 ppm cannot be ascertained. There are no Canadian or Mexican tolerances for iprodione on rice.

8. The statement on page 4, Book 2, Section D, says that the petition is confidential and trade secret

except for the method. The method is inserted in the petition over 100 pages later and bears the claim "Confidential." The method submission is not adequate. For publication in PAM, we require a "clean" copy without any claim of confidentiality; the ambiguous statement mentioned above will not substitute.

9. The petitioner should be advised to add the following:

> Do not apply in areas where catfish and crawfish are commercially cultivated.

Recommendations:

We recommend against the proposed establishment of tolerances for combined residues of iprodione on rice grain, rice straw, and rice hulls, for the reasons cited in Conclusions 3a, 3b, 3c, 3d, 3e, 3f, 4, 5, 6, 8, and 9. For a favorable recommendation, the petitioner should be advised of the following:

1. Additional residue data reflecting label instructions for aerial application are needed. Major rice production areas must be represented: Arkansas, Louisiana, Mississippi, Texas, and California.

2. The label prohibition against use on California rice is not practical. Additional residue data reflecting aerial application on California rice are needed. Alternately, a persuasive argument that the label prohibition is practical may be submitted.

3. The petitioner should advise us of the crop stage at each application, since label directions indicate application at joint movement-booting and again, no later than heading. The submitted residue data are reported at intervals after planting. This information should help in determining whether the residue data reflect the proposed use.

4. Additional information on the manner and method of sampling should be provided. We question whether representative samples of rice grain and straw can be gathered from combine or hopper after combining plots as small as 4 x 20 feet. Further, we do not believe a single sample analysis is adequate repre-

sentation for each location. Replicate samples should be obtained and duplicate analysis conducted.

5. The petitioner should clarify whether study TX-434285-105 reflects two or three applications.

6. The petitioner should comment upon the differing results of study TX-434285-113 and the ^{14}C study. In the first case, the data indicate a concentration factor of 5X is appropriate for rice hulls, while the ^{14}C study shows less than 1X in certain processed fractions. The petitioner should resolve this conflict.

7. The petitioner should propose an appropriate feed additive tolerance for rice bran.

8. The petitioner should be advised to add the following:

> Do not apply in areas where catfish and crawfish are commercially cultivated.

9. We note the statement on page 4, Book 2, Section D, that the petition is confidential and trade secret, except for the method. The analytical method is inserted about 100 pages later and bears the claim "Confidential." The method submission is not adequate. For publication in PAM, we require a "clean" copy without any claim of confidentiality; the ambiguous statement mentioned above will not substitute.

10. The petitioner should be further advised that, pending receipt of residue data or information, additional data or information requests may be necessary.

Detailed Considerations

Formulation

The formulation proposed for use is Rovral® Fungicide, EPA Registration No. 359-685, a wettable powder formulation containing 50% iprodione. Formulation inerts are cleared under 40 CFR 180.1001. We have previously concluded residue problems are not anticipated from either inert ingredients or manufacturing impurities.

Directions for Use

Rice (in all areas except California): Sheath blight: Use 1.0 lb Rovral per acre (0.5 lb ai/A). Apply twice per year. The first application should be made between joint movement and booting. The second application should be applied 2 weeks after the first application but no later than heading. Apply Rovral as a broadcast spray using aerial equipment. Rovral should be used with a minimum of 10 gallons of water per acre.

The petitioner should be advised to add the following:

> Do not apply in areas where catfish and crayfish are commercially cultivated.

Nature of the Residue

Plants:

Plant metabolism studies have been reported on strawberries and wheat (A. Rathman, March 2, 1979), peaches (R. Perfetti, May 13, 1984, PP#2F2596), lettuce (N. Dodd, April 11, 1983, PP#3G2801), and peanuts (N. Dodd, May 31, 1984, PP#4G3037). In ^{14}C-iprodione plant metabolism studies in strawberries, wheat, peaches, and peanuts, the primary residue from foliar application was the parent compound iprodione and smaller amounts of its isomer RP-30228. Soil applications resulted in these two compounds plus small amounts of the metabolite RP-32490.

An additional plant metabolism study is submitted. The study is entitled "Metabolism of ^{14}C Iprodione in Rice and the Determination of ^{14}C Residues in Irrigated Crops" and dated January 1983. Rice plants treated with phenyl-^{14}C-iprodione were harvested at immature and mature stages. Mature plants were divided into two fractions, straw and head/stalks. One-half of the head/stalk sample was shelled into hulls ("chaff") and brown rice. The other half of the head/stalk sample was milled into "mill feed," "bran and polish," and polished rice. Thus, two fractionation studies used the same ^{14}C-treated rice as starting material. Although the results of the two studies are reported together, the two studies must be evaluated separately.

Mature rice head/stalks contained 9.9 ppm of ^{14}C, while mature straw contained 36.1 ppm of ^{14}C-equivalent to iprodione. In the shelling study, rice head/stalks (9.9 ppm) were shelled into hulls (or chaff) with 6.17 ppm and brown rice with 0.78 ppm. When this radioactivity was examined by TLC, the majority of the extractable ^{14}C residue was present as iprodione and its isomer RP-30228. A minor amount of 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazole (RP-25040) was detected, along with trace amounts of N-(3,4-dichlorophenyl)-ureido-(N-(1-methylethyl)carboxamide) (RP-36221) and (RP-36112 + RP-32490). In the milling study, rice head/stalks (9.9 ppm) were milled into "mill feed," with 8.3 ^{14}C-ppm; "bran and polish" with 4.54 ^{14}C-ppm; and polished rice with 0.26 ^{14}C-ppm. The majority of the extractable ^{14}C was present as iprodione and its isomer RP-30228; again, a minor amount of RP-25040 was detected, with traces of RP-36221 and (RP-36112 + RP-32490).

^{14}C-Residues in straw show higher residue levels (than head/stalks) and metabolite distribution shows greater relative amounts of RP-36221, (RP-36112 + RP-32490), and RP-25040. In addition to analysis of rice plants, samples of flood water, hydrosoil, and irrigated crops (Swiss chard, sweet potato) show that ^{14}C from ^{14}C-iprodione treatments will occur in irrigated crops, flood water and hydrosoil. These additional data are of only peripheral interest to the study of iprodione metabolism.

The results of the ^{14}C shelling and milling studies appear to be at variance with the field residue-milling fraction study conducted in No. 434285-113 (TX). In the latter case, residues of iprodione and its isomer and metabolite showed concentration factors up to 5X in rice hulls, and bran. The proposed tolerance levels in rice fractions reflect this expected concentration. However, it appears that these ^{14}C milling and shelling studies do not demonstrate concentration in rice milling fractions. The petitioner should address or explain these various results of the rice processing studies.

We conclude that the residues of concern in rice plants, as well as other plants are iprodione [3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide]; [3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide] [RP-30228]; and [3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide] [RP-32490].

Animals:

The metabolism of iprodione in cows, goats, and rats has been evaluated in our review of PP#2F2728 (M.F. Kovacs, October 25, 1982, almonds). Poultry studies have been reviewed (R. Cook, February 21, 1984, PP#3F2964/FAP#4H5415). We have previously concluded that the residues of concern in animals are iprodione (RP-26019) [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] [RP-30228], and its metabolites [3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide] [RP-32490], and N-(3,5-dichloro-4-hydroxyphenyl ureidocarboxamide) (RP-36115), all expressed as iprodione equivalents. We reiterate that conclusion.

Analytical Method

The analytical method for iprodione, marked "CONFIDENTIAL" is entitled "RHONE-POULENC ANALYTICAL METHOD NO. 162 DETERMINATION OF IPRODIONE AND ITS METABOLITES IN/ON GRAIN AND HAY BY GLC AND TLC. November, 1983. REF NO.: 83/BHL/419/AG." Elsewhere in the submission ("Rovral-Rice Petition for Tolerance Book 2 Section D - Residue Chemistry July 24, 1986") the petitioner states "Rhone-Poulenc considers this Petition to be Confidential and Trade Secret with the Exception of the Enclosed Analytical Method." We conclude that the claim of confidentiality on the cover page of the analytical method precludes publication of the method in PAM-II. Further, the above-quoted statement is not adequate to release the confidential claim, since the statement is not specific to the analytical method. The petitioner should submit a copy of the analytical method without any claim of confidentiality.

The method is claimed to be suitable for the analysis of iprodione and its metabolites in rice, rice straw, and rice hulls. In principle, iprodione residues in ground-up samples of plant tissues are extracted twice with aqueous acetone. After initial extraction, the organic solvent is removed by rotary-evaporation. Next, liquid-liquid partition with 10% ethyl acetate in methylene chloride concentrates residues in the organic fraction. Additional cleanup steps include gel permeation chromatography (mobile phase ethyl acetate/toluene); acetonitrile-hexane cleanup; Florisil column chromatography with 20% ethyl acetate in hexane for fraction 1 (RP-26019 - iprodione and RP-30228 - iprodione isomer) and 30% ethyl acetate in hexane for fraction 2 (RP-32490 - iprodione metabo-

lite). Quantitative determination of residues is by ^{63}Ni electron capture gas chromatography. Rehydration of low moisture samples would likely occur during initial 30-minute soak in 10% aqueous acetone or during 2 hours of mechanical shaking in the same solvent.

The method determines iprodione, its isomer, and its metabolite RP-32490 individually. Recovery values for iprodione on rice grain ranged from 92 percent to 142 percent at fortification levels of 0.05 to 10 ppm; recovery of the isomer RP-30228 ranged from 85 percent to 117 percent at 0.1 to 0.5 ppm fortification levels; and recovery of the metabolite RP-32490 ranged from 81 percent to 116 percent. Recovery values for iprodione in rice straw, rice bran, and rice hulls ranged from 88 percent to 131 percent; recovery values for RP-30228 and RP-32490 in these fractions were 81 percent to 121 percent. The method is claimed to be sensitive to 0.05 ppm. We conclude that sensitivity levels for straw, bran, and hulls are probably higher than 0.05 ppm but that method sensitivity for these fractions is adequate at the proposed tolerance levels.

The thin-layer chromatography confirmation procedure utilizes ethyl acetate in benzene or methylene chloride on silica gel plates with Bratton-Marshall reagent for visualization of the reddish-pink spots.

We conclude that adequate methods are available for enforcement purposes. Enforcement methods are available in PAM-II.

Residue Data

Field trials were conducted in four States: Arkansas (3), Louisiana (3), Mississippi (3), and Texas (2). No field trials were conducted in California and label use directions restrict (prohibit) use in California. In the absence of a rationale or compelling reason excluding California, residue data are required for rice grown in California.

A total of eleven trials were conducted at application rates of 0.5 lb ai/A, maximum of two applications. One trial (TX-434285-113) employed both 0.5 and 1.0 lb ai/A application rates, the higher rate for studies of residues in rice processing fractions. Only four trials followed label instructions to apply as broadcast spray using aerial equipment; the remaining seven trials used either CO_2 backpack sprayer with boom or a

backpack solo mistblower. The aerial applications were made to 1-3 acre plots, while backpack applications were made to small plots ranging from 4 x 20 ft to 18 x 36 ft. In one trial (TX-434285-105) three applications of 0.5 lb ai/A were made. The petitioner should clarify this trial, whether the residue data reflect two or three applications.

The use directions instruct application at the interval between joint movement and booting and a second application 2 weeks after the first application, but no later than heading. The submitted residue data do not report crop stage of growth at each application. The petitioner should advise us of the crop stages at each application, especially the term "heading." Our information indicates various intervals of 25 to 37 days between head initiation and full head, and intervals of 23 to 32 days between full head and harvest. This information should help in determining whether the submitted data reflect the proposed use.

Grain and straw samples were collected form each plot. The reports state "Straw was collected from behind the combine and grain taken from the hopper." Samples were approximately 2 to 3 pounds. Without more information on the method and manner of sampling we question whether representative samples of rice grain and straw can be gathered from combine or hopper after combining plots as small as 4 x 20 ft. In addition, we question whether a single sample is adequate for each location. The range of residue values is large in the backpack trials (residues of iprodione per se ranging from 0.02 ppm to 2.5 ppm in grain receiving very comparable treatments). Also, one ground application at normal rate resulted in residues approximately twice as high as other treatments, including the 2X aerial application.

The petitioner should submit additional residue data, reflecting label instructions for aerial application. Major rice production areas must be represented. An adequate number of samples should be obtained at each location to ensure that the reported residue levels are representative. Such residue trials should include CA rice or alternately, a persuasive argument that the label prohibition against use in CA rice is practical. We believe the label prohibition is not practical and therefore CA residue data are necessary before we can draw any conclusions regarding the proposed tolerances.

Processed Fractions:

Rice is processed into rice hulls, rice bran, and polished rice. Rice hulls and rice bran are animal feed items. Polished rice is used for human food in a variety of ways, as polished or uncoated rice, as coated rice (covered with talc and glucose), or further milled into rice flour.

In field trial 434285-113, TX, iprodione was applied at 0.5 lb ai/A and 1.0 lb ai/A twice by aerial application to a 1 acre plot. Grain and straw samples were collected. The grain samples were fractionated into hulls, bran, and polished rice; however, the relative fractionation or material balance of residues is not reported.

Residues of iprodione and its metabolite and isomer (combined residues) were highest in the first processing fraction, rice hulls, lower in the bran, and lowest in the final milled product, polished rice. These data are tabulated below.

Iprodione Residues in Rice Processing Fractions
Texas Trial No. 434285-113

Rice	Application Rate	RP-26019	RP-3022	RP-32490	Total Iprodione	CF
Grain	0.50	1.99	0.41	0.17	2.57	--
Grain	1.00	3.61	0.45	0.19	4.25	--
Hulls	0.50	8.95	0.87	1.04	10.86	4.23
Hulls	1.00	17.60	1.42	1.22	20.24	4.76
Bran	0.50	5.22	0.84	0.25	6.31	2.46
Bran	1.00	5.75	1.63	0.30	7.68	1.81
Polished	0.50	0.14	0.07	0.00	0.21	0.08
Polished	1.00	0.42	0.16	0.00	0.58	0.14

CF (Concentration Factor) = Processed Residue/Raw Crop Residue.
CF calculated on combined residues.

Based upon these data, the use of 5X as a concentration factor is appropriate for hulls. It would appear that a food/feed additive tolerance is also needed for the bran.

Meat, Milk, Poultry, and Eggs:

The animal feed items of concern herein are rice grains with hulls, rice straw, and rice milling byproducts (which include hulls, bran, and polish). The milling byproduct polish is no longer isolated during processing, but is included in the bran fraction or in rice mill feed. For further information on current practices in rice milling, see L. Propst memorandum dated August 26, 1981.

Rice straw is used to a maximum of 10 percent in the diet of beef cattle, and not used by poultry or swine. Rice grain with hulls and milling byproducts as hulls and bran are used in the diet of both beef and dairy cattle to the extent of 25 percent of the diet, while in poultry these feeds are used to 40 percent in turkey or broilers and to 20 percent of the diet of laying hens.

As noted above under Residue Data, we are unable to determine appropriate residue levels in the raw agricultural commodities rice grain and rice straw, and consequently, we are unable to estimate dietary burdens of residue of iprodione in animals. Since rice feedstuffs are used by animals and since finite residues are found in rice and straw, we would conclude that secondary residues may be present in meat, milk, poultry, and eggs from the proposed use. However, in the absence of adequate residue data on rice, we are unable to draw conclusions on the proposed tolerance level for rice hulls. Further, rice bran is an important animal feed item derived from rice processing. A feed additive tolerance should be proposed for rice bran.

Other Considerations

International Tolerances

The Codex MRL for iprodione *per se* on rice (husked, unpolished) is 3 mg/kg. There are no Canadian or Mexican tolerances for residues of iprodione on rice. The proposed U.S. tolerance of 10 ppm for combined iprodione residues on rice grain differs from the Codex MRL. No pathway is currently available for making the present proposed 10 ppm tolerance for combined residues of iprodione, its isomer and its meta-

bolite in or on rice compatible with the Codex tolerance as expressed. A Codex sheet is attached.

Removal of Residues:

The petitioner remarks that practical methods for removal of residues are not applicable for this petition.

Attachment: International Residue Limit Status Sheet

cc: R.F., Circu, R.W. Cook, PP 6F3443/FAP 6H5507
PMSD(ISB), TB, EAB
RDI:Section Head:RSQuick:Date:2/27/87:RDSchmitt:Date:2/27/87.
TS-769:RCB:Reviewer:R.W. Cook:2/26/87:CM#2:Rm810:557-7324
89713:Cook:C.Disk:KENCO:3/3/87:de:vo:tar

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J. Lewis 1/30/87

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Iprodione

CODEX NO. 111

CODEX STATUS:

☐ No Codex Proposal Step 6 or above

Residue(if Step 8): Iprodione per se.

Crop(s)	Limit (mg/kg)
Rice (husked, unpolished)	3

PROPOSED U.S. TOLERANCES:

Petition No. PP6F3443

RCB Rewiewer Cook

Residue: per 40 CFR 180.399(a)

Crop(s)	Limit (mg/kg)
Rice grain	10
Rice straw	20
Rice hulls	50 FAT

CANADIAN LIMITS:

☑ No Canadian limit (on rice)

Residue: parent + metabolites* on other commodities

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

☑ No Mexican limit (on rice)

Residue: parent only according to reference.

Crop(s)	Limit (mg/kg)

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NOTES: * Metabolites: 3-isopropyl-N-(3,5-dichlorophenyl)-2,4-dioxoimadazolidine-1-carboxamide and 3-(3,5-dichlorophenyl)-2,4-dioxoimadazolidine-1-carboxamide

Form revised 1986