10-25-82

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

OCT 25 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP# 2F2728. Iprodione on Almonds, Meat and Meat Byproducts and Milk.
Evaluation of analytical methods and residue data.

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THRU: Charles L. Trichilo, Chief
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TO: Henry Jacoby, Product Manager (21)
FHB Registration Division (TS-767)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

Rhone-Poulenc Chemical Company, Agrochemical Division, requests the establishment of tolerances for combined residues of the fungicide Iprodione [3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide], its isomer RP 30228 [3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide] and its metabolite RP 32490 [3-(3,5-dichloro-phenyl)-2,4-dioxo-1-imidazolidinecarboxamide] in or on almond nutmeat at 0.05 ppm and almond hulls at 0.25 ppm; for combined residues of iprodione and its non-hydroxylated metabolites, typically RP 32490 in meat and meat byproducts (meat, kidney, fat, liver) of cattle, goats, hogs, horses and sheep at 0.80 ppm and for combined residues of iprodione, its nonhydroxylated metabolite RP 32490 and its hydroxylated metabolite N-(3,5-dichloro-4-hydroxyphenyl)-ureido carboxamide in milk at 0.15 ppm.

A tolerance for residues of iprodione on kiwi fruit has been established at 10 ppm. Temporary tolerances on various stone fruits at 20 ppm and on almonds at 0.05 ppm have been established previously in conjunction with PP#'s 8G2087 and OG2402, respectively.

A tolerance proposal for residues of iprodione on cherries, peaches and nectarines at 20 ppm is also pending (PP# 2F2596).

Conclusions

1a. The nature of the residue in plants is adequately delineated. The primary residues will consist of the parent compound and its isomer RP 30228.

1b. Both lactating dairy cow and goat C^{14} metabolism studies were submitted in this petition. The metabolic pathway of iprodione metabolism in both the lactating cow and goat were similar in nature and involved hydrolysis, oxidation and N-dealkylation reactions. The primary residues of concern will consist of the parent compound, iprodione and its principal nonhydroxylated (des-isopropyl) metabolite RP 32490 in animal tissues, and in bovine milk, Iprodione, RP 32490 and its principal hydroxylated metabolite RP 36114. A summarized non-ruminant (rat) C^{14} metabolism study indicated the parent compound itself, the des-isopropyl metabolite RP 32490 and the hydroxylated metabolite RP 36114 to be the major residues of concern.

2a. An adequate analytical method is available for enforcement of the proposed tolerances for almond hulls and nutmeat.

2b. Pending successful completion of the initiated method trial, adequate analytical methodology is available for enforcement of the proposed meat and meat byproducts and milk tolerances. (Note to PM: No tolerances for iprodione can be established for meat, fat, meat byproducts and milk until the method trial is successfully completed.)

3. The submitted residue studies for almond nutmeats and hulls do not reflect the proposed use that permits aerial application of Rovral® to almond trees. We cannot render a favorable judgment regarding the adequacy of the proposed tolerances for almond hulls and nutmeats until the petitioner either (1) submits additional residue data reflecting aerial application of Rovral® at the recommended label rates or (2) modifies Section B to delete aerial application from the Rovral® label.

4a. In regard to the dairy cattle feeding study, milk and liver samples were stored prior to analysis. We cannot reach a final conclusion regarding appropriate meat and milk tolerances until the petitioner submits storage stability data at 0°F for residues of iprodione in milk and liver for a period of 4 and 8 months, respectively and until the results of the requested method tryout are available.

4b. Provided the deficiencies in 4a have been resolved, we feel that a more appropriate tolerance proposal for milk and meat and meat byproducts would be 0.02 ppm for milk and 0.1 ppm for meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep. These tolerances are adequate to cover secondary residues expected from the proposed use on almonds; future upward revisions of the tolerances can be proposed as petitions involving additional feed items are submitted. The proposed use falls into Sec. 180.6(a)(2) for meat, fat and meat byproducts of cattle, goats, hogs, horses, sheep and for milk.

4c. Because no poultry feed items are involved here, there will be no problem of secondary residues in poultry tissues and eggs.

5. An International Residue Limit Status sheet is attached. There are no foreign tolerances for residues of iprodione on almonds (nutmeats and hulls).

Recommendations

We recommend that the proposed tolerances not be established for the reasons given in conclusions 2b, 3, 4a, and 4b. The requirements for resolution of these deficiencies are also discussed in the appropriate conclusion above.

If and when meat tolerances are established, they should be for the "meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep."

Detailed Considerations

Formulation

Iprodione is formulated as Rovral® a wettable powder and contains 53.16% of technical iprodione, [redacted] The inerts are cleared under Sec. 180.1001.

(WEB INGREDIENT INFORMATION IS NOT INCLUDED)

The manufacturing process and identities and percentages of impurities was submitted and reviewed in conjunction with PP# 8G2084 (review of 3/2/79, A. Rathman). Technical iprodione is typically 95% pure with none of the impurities comprising more [redacted] of the material. We would expect no additional residue problems with the low levels of these impurities in the formulation.

Proposed Use

Rovral® is a fungicide for use in the control of Brown Rot Blossom Blight (Monilinia laxa) and suppression of Shothole (Coryreum beijerinckii) on almonds. A foliar spray is to be applied at the rate of 0.125 lbs active/100 gallons in sufficient water to obtain thorough coverage (100-400 gallons per acre by ground application and 20 gallons per acre by aerial application). Application is made at the pink bud stage and if conditions are favorable for disease development, a second application should be made at full bloom. The maximum recommended use rate is 0.5 lb active/A/application.

There is a restriction against grazing treated orchards or feeding treated cover crops to animals.

Nature of the Residue

Plant Metabolism

No data on the fate of iprodione on almonds has been submitted. However, a study on the metabolism of iprodione on strawberries and wheat was reviewed in PP# 8G2087. In this study ^{14}C-Iprodione uniformly labeled in the phenyl ring was applied either as a ground (pre-plant) or foliar treatment.

Autoradiographs of plants given foliar treatments show that most of the activity remains at the site of application. The majority of the activity from plants given foliar treatment was due primarily to the parent compound. The isomer, 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide (RP 30228), was also detected, but was a minor constituent of the residue.

In the case of soil treatments, residues are taken up in the roots and translocated to the aerial portions of the plant. The majority of the activity was in a bound form (especially in the roots) and was not identified. Activity in the leaves and stems also contained a high portion of bound residue with the extractable residue identified as the parent, RP 30228 and RP 32490.

Since the use under consideration here is a foliar application, we consider the fate of iprodione in plants

sufficiently understood. The primary residues will consist of the parent compound and the isomer RP 30228. Both are determined by the proposed method of analysis for almond nutmeat and hulls, Rhodia Analytical Method No. 151.

Animal Metabolism

Dairy Cattle

A study was conducted to determine the metabolic fate of ^{14}C-phenyl ring labeled 3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide [^{14}C-Iprodione, (^{14}C-RP 26019)] in the dairy cow. Two cows were dosed orally with ^{14}C iprodione at a daily rate of approximately 2 mg/kg body weight, which corresponds to approximately 60 ppm based on the daily feed intake. One cow received a single dose; the other cow received multiple doses over a period of 5 days. Excretion was monitored daily and became insignificant 7 days after dosage, at which time the cows were slaughtered. Liver, kidney, muscle, fat, heart and blood were collected from each carcass. Urine, feces and milk were collected throughout the treatment and withdrawal periods. Total ^{14}C and extractable ^{14}C residue levels were determined for urine and milk by direct radioassay (LSC) and for tissues and feces by oxidative combustion folowed by LSC of the resulting CO_2 collected. Samples of milk, tissue, and excreta were exhaustively extracted with various solvents to determine the total extractable and total bound C^{14} residue levels. The identities of major metabolites in the urine, feces and milk extracts were confirmed by one or two dimensional TLC with four (4) different solvent systems following co-chromatography with the added reference standards (iprodione, RP 36114, RP 36115, RP 36119 and RP 32490). Separated spots were first located on each plate using X-ray film then scraped from the Silica Gel plates for quantitative analysis by LSC.

For the single dose cow, 47.0, 27.4, 0.4 and 0.7% of the total administered C^{14} dose was recovered in the urine, feces, milk and tissue. For the multidose cow these same comparable values were 41.6, 45.9, 0.3 and 0.3%. Total residues expressed as iprodione equivalents peaked at 0.17 ppm (single dose) in milk 24 hours postdose and at 0.43 ppm (multidose) 108 hours after initial dose. The depletion of the milk residue level during withdrawal was rapid; the residue decreased to half of the maximum within 36 hours. With the exception of liver, none of the analyzed tissues contained more than 0.05 ppm total C^{14} residues expressed as iprodione equivalents; 0.003 ppm was found in the muscle. The liver contained higher total C^{14} residue levels (0.13 ppm, single dose; 0.45 ppm, multidose) however, most of this residue proved to be unextractable with only 10% extractable by acetone. Additional

refluxing of liver filter cakes with concentrated HCl or NaOH or hydrolysis with proteolytic enzyme released an additional 9 to 73% of total C^{14} activity depending upon the method of treatment. The fractionation results for liver indicate that significant amounts of the ^{14}C-residue were incorporated into naturally-occurring components, suggesting that the ^{14}C-residues in liver may result from metabolic incorporation of ^{14}C-labeled fragments of iprodione.

No metabolites of iprodione were characterized in liver due to the bound nature of C^{14} residues as described above; in addition, no residue characterization was attempted in fat or muscle tissue due to the low levels of total ^{14}C activity. In urine, the identities of the major metabolites RP 36115 [N-(3,5-dichloro-4-hydroxyphenyl)-ureido carboxamide and RP 32490 [3-(3,5-dichlorophenyl)2,4-dioxo-1-imidazolidine carboxamide] representing ca 32 and 21%, respectively, of the total ^{14}C residue were confirmed by one-dimensional and two-dimensional TLC with added reference standards. For the single dose cow, the identified metabolites represented 70.6% of the total ^{14}C residues; the corresponding value for the multidose cow was 68.2%. None of the remaining six (6) identified metabolites of Iprodione in urine accounted for more than 5% of the total ^{14}C residue. In feces, the identities of the major metabolites iprodione [3(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidine carboxamide] and RP 36114 representing (13-32%) and (21-29%), respectively, of the total extractable ^{14}C residue were confirmed by one-dimensional TLC analysis with added reference standards. For the single dose cow, the identified metabolites represented 57.0% of the total extractable ^{14}C residue; the corresponding value for the multidose cow was 66.0%. With the exception of RP 36115 [N-(3,5-dichlorophenyl)-ureido carboximide (6.6 to 10.1%) none of the remaining three (3) identified metabolites of iprodione in feces accounted for more than 10% of the total extractable ^{14}C residue.

In milk the sample from the single dose cow contained 35.4% of the total ^{14}C-residue as nonhydroxylated metabolites of iprodione and 22.7% as hydroxylated metabolites. The corresponding values for the multidose cow were 22.5% nonhydroxylated metabolites and 36.8% hydroxylated metabolites. In milk the identities of the major metabolites RP 36114 (hydroxylated) and RP 32490 (nonhydroxylated) representing (25-38%) and (10-23%), respectively, of the total extractable ^{14}C residue were confirmed by one-dimensional TLC analysis with added reference standards. After enzyme hydrolysis with Glusulase, additional RP 36114 was extracted; this material probably existed in the milk as glucuronide and/or sulfate conjugates. For the single dose cow, the indentified metabolites represented 64.8% of the total extractable ^{14}C-residue, the corresponding value for the

multidose cow was 62.4%. Iprodione comprised 3 to 4% of the total extractable ^{14}C residue in milk with none of the remaining six (6) identified metabolites generally exceeding 5% of the total extractable ^{14}C-residue.

In summary, the fate of iprodione in the lactating cow was primarily characterized by extensive urinary and fecal excretion. The major metabolites in the urine and milk were RP 36114 and RP 32490. In the feces, iprodione and RP 36114 were the dominant compounds. The formation of RP 36114 shows hydroxylation to be a major pathway in the metabolism of iprodione in the dairy cow; minor amounts (<1% of the total ^{14}C residue) of other hydroxylated metabolites were also found.

Goat

A study was conducted to determine the metabolic fate of ^{14}C-phenyl ring labeled iprodione in the lactating goat. One goat was dosed orally for five days with ^{14}C-Iprodione at a daily rate of approximately 2 mg/kg of body weight which corresponds to approximately 200 ppm based on daily feed intake. Slaughter was 4 hours after the final dose. Liver, kidney, muscle, fat, and blood were collected from the carcass. Urine, feces, and milk were collected throughout the treatment period. Total ^{14}C-residue levels were determined for urine and milk by direct radioassay (LSC) and for tissues and feces by oxidative combustion followed by LSC of the resulting CO_2 collected. Samples of tissue, and excreta were exhaustively extracted with various solvents to determine the total extractable and total bound C^{14} residue levels. The identities of major metabolites in the urine and tissue extracts were confirmed by one or two dimensional TLC with three (3) different solvent systems following cochromatography with the added reference standards iprodione, RP 36114, RP 36115, RP 36119 and RP 32490. Separated spots were first located on each plate using X-ray film then scraped from the Silica Gel plates for quantitative analysis by LSC.

For the goat, a total of 63.8% of the administered dose was recovered in the samples collected: 50.7% in urine, 8.7% in feces, 0.3% in milk and 4.1% estimated in tissue. After 5 days of dosing, the ^{14}C residue level in the milk was 1.54 ppm and had not yet plateaued. Of the 4% of the total dose recovered in the tissues, the liver contained the highest level of ^{14}C residue (7.04 ppm). Approximately 60% of the ^{14}C residue in liver was extractable with acetone and 81% with HCl/Acetone.

Metabolites of iprodione were characterized in urine, liver, kidney, muscle and fat. In urine, the identities of the major metabolites RP 36114, RP 36115 and RP 32490

representing 23.1, 10.7 and 13.5% respectively of the total ^{14}C residue were confirmed by one-dimensional and two-dimensional TLC with added reference standards. The identified metabolites represented 56.3% of the total ^{14}C residue. None of the remaining eight (8) identified metabolites accounted for more than 4% of the total ^{14}C residue, however, two (2) unidentified metabolites comprised 10.5% of the total ^{14}C residue. In liver the identities of iprodione and the major metabolite RP 32490 representing 13.4% and 19.6% respectively of the total ^{14}C residue were confirmed by one-dimensional and two-dimensional TLC with added reference standards. The identified metabolites represented 40% of the extractable residue (38% nonhydroxylated and 2% hydroxylated). None of the remaining nine (9) identified metabolites accounted for more than 3% of the total extractable ^{14}C residue; however, two (2) unidentified metabolites comprised 14.6% of the total extractable ^{14}C residue. In kidney, the identities of the major metabolites RP 32490 and RP 36115 representing 11.8% and 7.5% respectively of the total extractable 14C residue were confirmed by one-dimensional and two-dimensional TLC with added reference standards. The identified metabolites represented 32% of the total extractable residue (27% nonhydroxylated and 5% hydroxylated). None of the remaining nine (9) identified metabolites accounted for more than 3.6% of the total extractable residue. One unknown metabolite, designated "Unknown X" comprised 22.7% of the total extractable residue. In muscle, RP 32490, comprising 36% of the total extractable 14C residue was the only major metabolite. The identified metabolites (6) represented 44% of the total extractable residue (TER) none of which exceeded 3.1% of the (TER). An unknown metabolite, designated "Unknown X" comprised 4.7% of the (TER). In fat, RP 32490, comprising 68% of the (TER) was the only major metabolite. The identified metabolites (5) represented 82% of the (TER) none of which exceeded 3.2% of the (TER). Two unknowns comprised a total of 3.6% of the (TER).

Rat

The petitioner has summarized the results of a non-ruminant (rat) feeding study; however, the details of the study are not presented in the subject petition. In that study four (4) rats were treated with 100 mg/kg each of iprodione, administered in one single dose, orally, in the form of a suspension containing a mixture of unlabeled material and 14C uniformly labeled phenyl ring iprodione. The elimination of radioactivity reached 99% four days after dosing at which time the rats were sacrificed. Two thirds

of the excretion took place in the urine and one-third in the feces. A large number of metabolites were detected and identified, although present at very low levels. The major metabolic products identified in the rat included the parent compound itself, the des-isopropyl metabolite RP 32490 and the hydroxylated metabolite RP 36114.

In conclusion, the metabolic pathway of iprodione metabolism in ruminants (lactating cow and goat) and non-ruminant (rat) appear to be similar in nature. The metabolic pathway in animals has been adequately delineated for the proposed use and involves hydrolysis, oxidation and N-dealkylation reactions. The primary residues of concern will consist of the parent compound iprodione, and its principal nonhydroxylated (des-isopropyl) metabolite RP 32490 in animal tissues and in bovine milk, iprodione, RP 32490 and its principal hydroxylated metabolite RP 36114. The above residues are determined as iprodione equivalents in bovine tissue or milk by either of the proposed methods of analysis for iprodione and its nonhydroxylated metabolites in bovine tissues (ADC # 623-B), iprodione and its nonhydroxylated metabolites in bovine milk (ADC # 623-A) or hydroxylated metabolites of iprodione in bovine milk (Rhone-Poulenc #159).

Analytical Methodology

Almond Hulls and Nutmeat

The analytical method used to generate the almond hull and nutmeat residue data for this petition was Rhodia Analytical Method No. 151. The samples were analyzed for parent compound (RP 26019) and its two metabolites 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 method involves extraction of the residue by blending with acidified acetone. After filtration, the solvent is evaporated. The aqueous phase is extracted with 10% ethyl acetate in methylene chloride and drained through a bed of anhydrous sodium sulfate. The solvent is evaporated and the residue is dissolved in ethyl acetate/toluene; 3:1 (v/v). The sample is then subjected to further clean-up with gel permeation and Florisil column chromatography.

One fraction of the eluate from the Florisil column contains iprodione and RP 30228, and a second fraction contains RP 32490. These fractions are taken to dryness, redissolved in

toluene and analyzed via GLC using a 63Ni electron capture detector. The parent compound and its two metabolites are all determined on the same column, a 3% OV17 on Chromosorb whp 80/100, however differing column conditions (flow rate and column operating temperatures) are employed for the quantitative analysis of each compound. We note that in neither this petition nor in the MTO submitted in conjunction with PP# 0E2414 were sample chromatograms submitted showing the resolution of GLC peaks arising from iprodione and its isomer RP 30228 which are both present in the some eluate fraction from the Florisil column. However, we feel no need to pursue the issue any further since the proposed tolerance for almonds is expressed as combined residues of iprodione and its metabolites RP 30228 and RP 32490.

A TLC procedure is available for residue confirmation. In addition, the company tested the method in the presence of a number of pesticides. Results show that, with the exception of methoxychlor, none of the pesticides interfered with the determination of iprodione or its metabolites. The peak for methoxychlor on the iprodione column was close to the retention time for iprodione. A sample spiked with methoxychlor was taken through the entire analytical procedure. Results show that methoxychlor, after going through the analytical procedure, does not interfere with the determination of iprodione.

In almond nutmeats and almond hulls, samples were fortified at levels ranging from 0.05 to 2.0 ppm. In the nutmeat, recoveries of the parent compound ranged from 74.6 to 121.4% with the mean value being 94.5%. Recoveries for the metabolite RP 30228 ranged from 70.3% to 118.7% with the mean value being 90.7%. Recoveries for the metabolite RP 32490 ranged from 65.8% to 121.0% with the mean value being 89.8%. In the almond hulls, recoveries of the parent compound ranged from 72.5% to 123.8% with the mean value being 97.7%. Recoveries for the metabolite RP 30228 ranged from 71.4% to 109.6% with the mean value being 86.6%. Recoveries for the metabolite RP 32490 ranged from 76.8% to 117.0% with the mean value being 94.1%. Control values for iprodione ranged from non-detectable (<0.01) to 0.05 ppm on almond hulls and from non-detectable to 0.03 ppm on almond nutmeats. Control values for RP 30228 ranged from non-detectable (<0.01) to 0.01 ppm on almond hulls and were non-detectable on almond nutmeats. Control values for RP 32490 were non-detectable on almond hulls and ranged from non-detectable to 0.03 ppm on almond nutmeats. The limit of detection for the combined residues of iprodione, RP 30228 and RP 32490 in both almond hulls and almond nutmeat is approximately 0.05 ppm. Sample chromotograms were submitted in the petition.

The method described above is similar to the procedure which has undergone a successful method trial on kiwi fruit at levels of 0.01 and 7 ppm with minor modifications. We consider Rhodia Analytical Method 151 acceptable for enforcement of the proposed tolerances on almond hulls and almond nutmeat.

Bovine tissues (Muscle, Kidney, Liver and Fat)

The analytical procedure utilized for residue determinations of iprodione and its non-hydroxylated metabolites in muscle, kidney, liver and fat (ADC #623-B) consisted of: solvent extraction with acetone, partitioning into hexane and acetonitrile followed by hydrolysis with NaOH, derivatization of the hydrolysate containing the non-hydroxylated metabolites to the N-heptaflurobutyrl derivative of 3,5-dichloroaniline, florisil column cleanup and gas chromatography using a 63Ni electron capture detector. Residues in tissue samples were expressed as ppm iprodione equivalent.

Method ADC #623-B was validated by analyzing control cow tissue fortified with iprodione (RP 26019) and its major non-hydroxylated metabolite (RP 32490) in tissue. Following fortification levels of 0.1 to 0.5 ppm in kidney, muscle, fat and liver; recoveries of iprodione and RP 32490 ranged from (72.5 - 87.6%), (77.0 - 81.2%); (72.1 - 80.6%), (57.0 - 89.9%); (56.5 - 64.7%), (62.2 - 75.4%); (68.3 90.1%), (55.1 - 72.1%), respectively. The sensitivity limit for the analytical procedure (reported as ppm; iprodione equivalents) was 0.05 ppm for all tissues analyzed. Sample chromatograms were submitted by the petitioner.

Milk

The analytical procedure utilized for residue determinations of iprodione and its nonhydroxylated metabolites in bovine milk (ADC # 623-A) consisted of: solvent extraction with acetone, partitioning into hexane and acetonitrile, hydrolysis of the residue with NaOH, distillation, derivatization of the benzene extract containing the non-hydroxylated metabolite to the N-heptafluorobutyrl derivative of 3,5- dichloroaniline, florisil column cleanup and gas chromatography using a ^{63}Ni electron capture detector. Residues in milk samples were expressed as iprodione equivalents.

Method ADC# 623-A was validated by analyzing cow milk fortified with iprodione (RP 26019) and the major non-hydroxylated metabolite in milk RP 32490. Following fortification levels of 0.01 to 0.20 ppm in milk, recoveries of

iprodione and RP 32490 ranged from (79.2 to 101.7%) and (75.4 to 88.7%) respectively. The sensitivity limit for the analytical procedure (reported as iprodione equivalents) was 0.005 ppm. Sample chromatograms were submitted by the petitioner.

The analytical procedure utilized for residue determinations of the hydroxylated metabolite of iprodione in bovine milk (Rhone-Poulenc Method No. 159) consisted of: solvent extraction with acetone, sample cleanup using an aluminum sulfate precipitation and a hexane/acetonitrile partition, mild acid hydrolysis to release conjugated metabolites, followed by a basic hydrolysis to convert hydroxylated metabolites to a common moiety 4-methoxy-3,5-dichloro aniline, derivatization of the aniline to heptafluorobutyrate with HFBA, clean-up by Florisil column chromatography and analysis by gas chromatography using a 63Ni electron capture detector.

The Rhone-Poulenc method No 159 was validated by analyzing cow milk fortified with the major hydroxylated metabolite in bovine milk, RP36114. Following fortification levels of 0.01 to 0.20 ppm, recoveries of RP 36114 in milk ranged from (47.7 - 77.1%) and averaged 61.8%. The limit of sensitivity for residues of RP36114 in milk by this analytical procedure was reported at 0.01 ppm. Sample chromatograms were submitted by the petitioner.

The analytical methodology discussed above which is proposed for enforcement of the requested meat and milk tolerances will also require validation (MTO by EPA chemists) prior to establishment of any of the proposed tolerances. We are presently somewhat concerned over the only marginally adequate recoveries being reported for non-hydroxylated metabolites in bovine liver and hydroxylated metabolites in milk (avg. 64.5 and 61.8%) respectively, and would hope that the MTO will demonstrate both very reproducible as well as adequate recoveries to somewhat alleviate this concern.

We conclude, that pending the successful completion of the requested method trial for residues of iprodione and its non-hydroxylated metabolites in cattle liver and iprodione and its non-hydroxylated and hydroxylated metabolites in milk, that adequate analytical methodology is available to enforce the proposed meat and milk tolerances.

Residue Data

Almond Nutmeats and Hulls

Samples were stored at 0°F prior to analysis for periods ranging from 10 to 13 months. No storage stability data for

iprodione residues on almond nutmeats and hulls have been submitted. However, storage stability data on strawberries, grapes, peaches, and cherries submitted in conjunction with PP# 8G2087 indicated that overall iprodione residues were stable in frozen storage for ca 1 year. Since almond samples were stored for periods approximating 1 year we are not raising any questions with respect to the accuracy of the residue data for almond nutmeats and hulls.

Residue studies with Rovral® (RP26019) were conducted on eleven plots of California almond trees. In all of the studies two ground applications of Rovral 50WP in 400 gallons per acre, via handgun, were made with the first application at the red tip stage and the second application at the full bloom stage. Application rates were 0.5 lb ai/A/Application and 0.75 lb ai/A/Application for a total application rate of 1.0 lb ai/A (1X) and 1.50 lbs ai/A (1.5X). None of the residue studies reflected aerial applications of Rovral® which is permitted on the label submitted in Section B.

Almond samples were collected after they had fallen to the ground. Random nut samples from each study were taken and separated into hulls and nutmeat. These samples were analyzed for parent compound (RP 26019) and its two metabolites (RP 30228 and RP 32490) by Rhodia Analytical Method No. 151 dated December 1978.

Nutmeats

No residues (<0.05 ppm) of RP 26019, RP 30228 and RP 32490 were found in/on the nutmeat from any of the treated almonds, including the exaggerated total rate (1.5X) of 1.50 lbs ai/A. PHI's ranged from 175 to 220 days which is within the normal time period from almond full bloom stage to normal harvest.

Hulls

No residues (<0.05 ppm) of RP 30228 and RP 32490 were found on the hulls from any of the treated almonds, including the exaggerated (1.5X) rate. Residues of RP 26019 at 0.12 ppm were found in hull samples from one study reflecting the 1X application rate. Residues of RP26019 at 0.12 and 0.23 ppm were found in hull samples from two studies both reflecting the 1.5x application rate. The 0.23 ppm hull residue was from the same test site that showed a residue (0.12 ppm) at the use rate.

All residue values for nutmeats and hulls were corrected for apparent residue values for check samples that varied from <0.05 to 0.05 ppm for RP 26019 and were <0.05 ppm for RP 30228 and RP 32490 and for recovery values that averaged 90% for RP 26019 on almond hulls.

As stated above, the submitted residue studies do not reflect the proposed use that permits aerial application of Rovral® to almond trees. We cannot render a favorable judgment regarding the adequacy of the proposed tolerances for almond hulls and nutmeats until the petitioner either (1) submits additional residue data reflecting aerial applications of Rovral® at the recommended label rates or as an alternative (2) modifies Section B to delete aerial application from the Rovral® label.

Meat, Milk, Poultry and Eggs

Dairy Cattle Feeding Study

A dairy cattle feeding study was conducted with iprodione to provide a basis for establishing tolerances, if needed, for iprodione (and its metabolites) residues in meat and meat by-products of cattle, goats, hogs, horses and sheep and in milk.

Technical iprodione was incorporated at four dose levels (5, 15, 50 and 200 ppm) in the daily diet of lactating Holstein and Brown Swiss dairy cows for 29 days. These levels represent 80-3,200 fold of the expected animal exposure level through ingestion of iprodione-treated almonds. There were 3 cows in each treatment group plus one control. The control animal was fed the same diet as treated animals except iprodione was omitted. Actual diet assays showed that the average dosing level was 4.6, 14.4, 50.5 and 192.2 ppm in the daily diet.

The control cow was slaughtered on the morning of the 27th day of dosing. The treated cows were slaughtered approximately 4 hours after the morning dose on the 29th day. Liver, kidney, composite muscle, and composite fat (omental, renal and subcutaneous) tissues were collected at sacrifice for all treated animals including control. During the dosing period milk samples were collected twice daily on treatment days 2, 5, 8, 11, 14, 17, 20, 23, 26, 27, 28 and 29. All milk and tissue samples were frozen immediately after collection.

The analytical methodology employed on the milk and tissue samples collected have been described in detail above under Analytical Methodology. Milk samples collected on treatment days 8, 17 and 28 were analyzed for iprodione, its nonhydroxylated metabolites, and its hydroxylated metabolites. Tissue samples (muscle, kidney, liver and fat) collected at slaughter were analyzed for iprodione and its nonhydroxylated metabolites.

All residue values (expressed as ppm iprodione equivalents) discussed below were corrected for the average recovery of concurrently analyzed fortified controls (75.3, 78.5,

79.3, 81.6 and 90.3%) respectively for milk, muscle, kidney liver and fat, and with the exception of milk, were obtained at the end of the dosing period. Representative chromatograms for each sample type were submitted.

Milk

Total maximum residues at the 15, 50 and 200 ppm feeding level and at 8, 17 and 28 days of treatment were (0.099, 0.027, 0.035); (0.196, 0.169, 0.136); and (0.383, 0.389, 0.329 ppm) respectively. All residues were reported as <0.01 ppm at the 5 ppm feeding level. Control values were reported as <0.010 ppm.

Muscle

Total maximum residues at the 5, 15, 50 and 200 ppm feeding levels were <0.05, <0.05, 0.07 and 0.13 ppm respectively. Control values were reported as <0.05 ppm.

Kidney

Total maximum residues at the 5, 15, 50 and 200 ppm feeding levels were <0.05, 0.16, 0.80 and 2.87 ppm respectively. Control values were reported as <0.05 ppm.

Fat

Total maximum residues at the 5, 15, 50 and 200 ppm feeding levels were <0.05, <0.05, 0.21 and 0.52 ppm respectively. Control values were reported as <0.05 ppm.

Liver

Total maximum residues at the 5, 15, 50 and 200 ppm feeding levels were <0.05, 0.13, 0.66 and 1.95 ppm respectively. Control values were reported as <0.05 ppm.

Overall, the average total residue in milk increased linearly with iprodione feeding level and the average total residue had plateaued by treatment day 7. A linear concentration dependence on feeding level was also evident for liver, kidney and fat, with kidney having the highest overall residue levels and muscle the lowest.

In connection with the dairy cattle feeding study we note that milk, kidney, muscle liver and fat samples were stored at 0°F for 3.5, 7, 7.5, 8 and 8.5 months respectively from time of dairy cattle slaughter to time of analysis. The petitioner has submitted a one year storage stability study at

0°F for residues of iprodione on strawberries, grapes, peaches and cherries in conjunction with PP# 8G2087. Although that study indicated that overall, residues of iprodione were relatively stable during frozen storage, the data were erratic and in addition we feel that the results cannot be translated to residue storage stability in animal substrates. Accordingly, we will require the petitioner, at a minimum, to submit storage storage stability data at 0°F for residues of iprodione in milk and liver for a period of 4 and 8 months respectively.

Almond hulls which are used for livestock feed can comprise up to 25% of the diet of beef and dairy cattle and 50% of the diet of finishing lambs. No established permanent tolerances for iprodione on RAC's from which animal feed items can be derived are in effect. A beef or dairy cow fed a diet of 25% as almond hulls bearing 0.25 ppm iprodione or a finishing lamb on a 50% diet of the same commodity would ingest 0.06 ppm and 0.13 ppm respectively of iprodione. These levels are considerably less than the levels of iprodione (5, 15, 50 and 200 ppm) employed in the dairy cattle feeding study submitted with this petition.

The petitioner on the premise that total residues of iprodione and its metabolites derived from current (almond) and future (apricots, grapes, plums, prunes and peaches) uses could approach 50 ppm in the dairy cattle diet and in consideration of the maximum residues found at the 50 ppm dosing level in the dairy cattle feeding study (0.80 ppm in kidney and 0.136 ppm in milk at 28 days of treatment) has proposed the following tolerances for milk and meat and meat byproducts: 0.15 ppm milk and 0.80 ppm meat and meat byproducts (meat, kidney, fat, liver) of cattle, goats, horses and sheep.

We cannot reach any final conclusion in the present review regarding appropriate meat and milk tolerances until both the results of the requested storage stability study on milk and liver and the requested method tryout on the same substrates have been obtained. However, contingent upon the results of the requested storage stability study and a successful MTO of the proposed meat and milk methodologies we do recommend at this time that a more appropriate tolerance proposal for milk and meat and meat byproducts would be 0.02 ppm for milk and 0.1 ppm for meat and meat byproducts (meat, kidney, fat, liver of cattle, goats, hogs, horses and sheep) (§ 180.6(a(2) applies). These tolerances represent approximately 2X the limit of detection for combined residues of iprodione and its metabolites in milk (0.01 ppm) and in meat and meat byproducts (0.05 ppm). Our tolerance suggestions which consider only the feed item involved in this petition (almond hulls which can contribute approximately 0.06 ppm

iprodione to the total diet of dairy cattle) are adequate to cover residues expected from the proposed use on almonds. The petitioner at a later date can propose upward revisions of these tolerances as future petitions involving additional feed items are submitted.

No residues are expected in poultry or eggs because almond hulls are not a poultry feed item.

Other Considerations

The International Tolerance Sheet is attached. There are no foreign tolerances for residues of iprodione on almonds (nutmeat and hulls).

RCB-5:EPA:DCR-34854:efs:Warton Kovas:x-77324
REVISED:RCB-5:EPA:DCR-34856:bje:10/20/82:Warton Kovas:x-77324

REVIEWER: MARTY KOVACS

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL IPRODIONE PETITION NO 2F2728

CCPR NO. 111

Codex Status

[ ] No Codex Proposal Step 6 or above

Residue (if Step 9): _____

Crop(s)	Limit (mg/kg)
None (on specified commodities)	

CANADIAN LIMIT

Residue: _____

Crop	Limit (ppm)
none (on specified commodities)	

Proposed U. S. Tolerances

Residue: 3-(3,5-DICHLOROPHENYL)-N-~~(1-METHYLETHYL)~~-2,4-DIOXO-1-IMIDAZOLIDINECARBOXIMIDE, ITS ISOMER AND HYDROXYLATED + NON-HYDROXYLATED METABOLITES

Crop(s)	Tol. (ppm)	
ALMOND NUTMEAT	0.05	PARENT + ISOMER + HYDROXYLATED AND NON-HYDROXYLATED MET.
ALMOND HULLS	0.25	
MEAT + MEAT BYPRODUCTS (MEAT, KIDNEY, FAT, LIVER) OF CATTLE, GOATS, HOGS, HORSES + SHEEP	0.80	PARENT + NON-HYDROXYLATED MET.
MILK	0.15	PARENT + HYDROXYLATE AND NON-HYDROXYLATED METABOLITES

MEXICAN TOLERANCIA

Residue: _____

Crop	Tolerancia (ppm)
none	

Notes: