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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP# 3G2787 and FAP# 3H5379. Iprodione on grapes and raisins. Evaluation of analytical methods and residue data.

FROM: Nancy Dodd, Chemist
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

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

TO: Henry Jacoby, P.M. No. 21
Fungicide-Herbicide Branch
Registration Division (TS-767)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

Rhone-Poulenc Inc. proposes a temporary tolerance for combined residues of the fungicide 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 at 60 ppm and in or on raisins at 180 ppm (food additive tolerance).

Tolerances have been established on kiwifruit at 10 ppm and on cherries (seet and sour), peaches, and nectarines at 20 ppm. Temporary tolerances on apricots and plums (fresh prunes) at 20 ppm and on almonds at 0.05 ppm have been established. Proposed tolerances of 10 ppm on apricots, plums, and prunes are in reject status and an additional petition on those crops is under review. A petition for a temporary tolerance on lettuce is currently under review. Tolerances of 0.8 ppm on meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep and 0.15 ppm on milk are pending.

Under the proposed EUP, a total of 9720 lbs. Rovral (4860 lbs. a.i.) will be shipped for use on a total of 355 acres in CA, NY, OR, PA, and MI, from April 1983 to December 1984. The majority of the tests are to be conducted in CA.

Conclusions

1a. The metabolism of iprodione in plants is adequately understood. The residues of concern are parent, its isomer (RP 30228), and the des-isopropyl metabolite (RP 32490).

1b. The metabolism of iprodione in animals has been adequately defined for purposes of the proposed temporary tolerance. Metabolism in animals involves hydrolysis, oxidation, and N-dealkylation reactions. Major extractable residues in animal tissues are the des-isopropyl metabolite RP 32490 and parent. Major residues in milk are the hydroxylated metabolite RP 36114, RP 32490, and parent.

2. Adequate analytical methods are available for enforcement of the proposed temporary tolerances on grapes and raisins.

3a. Residues in grapes resulting from the proposed use will not exceed the proposed temporary tolerance of 60 ppm.

3b. Residues in raisins may exceed the proposed temporary food additive tolerance of 180 ppm. A temporary tolerance of 300 ppm would be adequate.

3c. There are no residue data for raisin waste. However, since a major portion of raisin waste is comprised of cull raisins, we conclude for the purpose of this temporary tolerance that residues on raisin waste would not exceed 300 ppm. A temporary food additive tolerance of 300 ppm is needed for raisin waste.

3d. Although the process used to obtain grape juice does not appear to be reflective of commercial equipment, we can assume for purposes of this temporary tolerance that residues in grape juice will not exceed the proposed temporary tolerance of 60 ppm on grapes.

3e. We conclude, using the concentration factor of 2X in going from grapes to wet pomace and a dry-down factor of 5 in going from wet to dry pomace, that a 600 ppm temporary food additive tolerance for dried grape pomace is needed.

4a. Because of the lack of both a poultry feeding study and appropriate storage stability data for the available cattle feeding study, we are unable to make a conclusion concerning secondary residues in meat, milk, poultry, and eggs.

4b. The proposed use on grapes falls in Section 3 of 40 CFR 180.6(a) with respect to residues in meat, milk, poultry, and eggs, provided that use is restricted to grapes to be used for the fresh market only.

Recommendations

We recommend against the proposed use because of the deficiencies cited in Conclusions 3b, 3c, 3e, and 4a. However, we would have no objections to the proposed use if it were limited to grapes to be used for the fresh market only.

For a future permanent tolerance, the following would be needed:

1. Appropriate tolerances for secondary residues in meat, milk, poultry, and eggs.

2. A poultry feeding study.

3. A storage stability study for residues of iprodione in milk and liver when stored for 4 and 8 months, respectively, at 0°F.

4. Completion of method try-outs by this Agency on cattle liver and milk.

5. Residue data for raisin waste reflecting the maximum proposed use.

6. Residue data for grape juice and wet and dried pomace prepared from grapes bearing aged iprodione residues at or near the proposed tolerance level on either pilot scale equipment designed to simulate commercial equipment or actual commercial equipment.

Manufacture

The manufacturing process was reviewed in PP# 8G2087 (A. Rathman, 3/2/79), to which we refer. Technical iprodione is 95% pure with none of the impurities comprising more than [redacted] of the material. None of these impurities is expected to present a residue problem.

Formulation

Rovral is a wettable powder formulation containing 53.16% technical iprodione, [redacted]. All inerts are cleared under Section 180.1001(c).

Proposed Use

Apply 1.5-2 lbs. Rovral/A (0.75-1.0 lb. a.i./A) as a foliar spray in 50-200 gals. water/A to thoroughly cover the bunches. Four applications should be made as follows: one at early to mid-bloom, one prior to bunch closing, and two within one month prior to harvest. There is a 0-day preharvest interval.

Nature of the Residue

Plants

No new metabolism data are submitted with this petition. Previous reviews on the metabolism of iprodione in strawberries and wheat (PP# 8G2087, A. Rathman, 3/2/79) and in peaches (PP# 2F2596, R. Perfetti, 5/13/82) are summarized below.

Studies on strawberries and wheat indicated that iprodione which is applied to soil is taken up by roots and translocated to aerial portions of the plant. After foliar treatment, most of the radioactivity remains at the site of application.

Residues in strawberries, wheat, and peaches were parent, the isomer 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide (RP 30228), and a lesser amount of a des-isopropylated metabolite (RP 32490).

We conclude that the metabolism of iprodione in plants is adequately understood. The residues of concern are parent, its isomer (RP 30228), and the des-isopropyl metabolite (RP 32490).

Animal Metabolism

No new animal metabolism studies are submitted with this petition. The petitioner refers to ^{14}C metabolism studies which were previously reviewed (M. Kovacs, PP# 2F2728, 10/25/82).

Metabolism of iprodione in the cow and goat involved hydrolysis, oxidation, and N-dealkylation reactions. The major extractable residues in goat liver tissue were the des-isopropyl metabolite (see chemical names below) RP 32490 (19.6% of the total extractable ^{14}C residue), parent (13.4% of the total extractable ^{14}C residue), two unidentified metabolites comprising 8.9% and 5.7% of the total extractable ^{14}C, and nine other identified metabolites, each comprising no more than 3% of the total extractable ^{14}C. The major extractable residues in goat kidney tissue as a percentage of the extractable ^{14}C residues were RP 32490 (11.8%), RP 36115 (7.5%), and an unknown (22.7%). Nine other metabolites were identified, each comprising no more than 3.6% of the total extractable residue. In goat muscle, RP 32490 comprised 36% of the total extractable ^{14}C residue. In goat fat, RP 32490, RP 26019, and RP 30228 accounted for 68%, 7.6%, and 3.2%, respectively, of the total extractable ^{14}C residue. Residues in cow liver were not characterized because of the bound nature of the ^{14}C residue. Residues in cow muscle and fat were not characterized because of the low levels of the ^{14}C activity. The major extractable residues in milk were RP 36114, RP 32490, and parent.

A summarized study of the rat indicated that the main products excreted by the rat were parent, RP 32490, and RP 36114.

We conclude that the metabolism of iprodione in animals has been adequately defined for purposes of the proposed temporary tolerance. Metabolism in animals involves hydrolysis, oxidation, and N-dealkylation reactions. Major extractable residues in animal tissues are the des-isopropyl metabolite RP 32490 and parent. Major residues in milk are the hydroxylated metabolite RP 36114, RP 32490, and parent.

RP 26019 - iprodione

RP 30228 - isomer of iprodione: 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide

RP 32490 - des-isopropyl metabolite

RP 36114 - hydroxylated metabolite: 1-(3,5-dichloro-4-hydroxyphenyl)-biuret

RP 36115 - N-(3,5-dichloro-4-hydroxyphenyl)-ureido carboxamide

Analytical Methods

Grapes and Raisins

Rhone - Poulenc Analytical Method No. 151, as revised in 1981, was used to determine residues in grapes. The sample of grapes is macerated with 10% water in actone and filtered. The filtrate is evaporated. A 1% sodium sulfate solution is added to the residue before extraction with 10% ethyl acetate/methylene chloride. The ethyl acetate/methylene chloride solution is dried over sodium sulfate, evaporated, and redissolved in 3:1 ethyl acetate/toluene. The sample is cleaned up on a gel permeation column and then on a Florisil column. Two fractions are eluted from the Florisil column. One fraction contains parent and isomer RP 30228. The other fraction contains the des-isopropyl metabolite RP 32490. These fractions in benzene were analyzed by GLC using a ^{63}Ni electron capture detector. The limit of detection on grapes, pomace, juice, and raisins is 0.05 ppm.

The method was modified for pomace, juice, and raisins. The modification for pomace is an initial 30-minute soaking in water before grinding. For juice analysis, dilute juice with 0.5% HCl in acetone, filter, evaporate, and proceed with the liquid-liquid partition step. For raisins, soak and smash in water for 2 hours before grinding.

Percentage recoveries for RP 26019, RP 30228, and RP 32490 ranged from 60.7-124.2% for fresh grapes spiked at levels of 0.5-25.0 ppm, 67.6-120.5% for pomace at spiking levels of 0.5-40.0 ppm, 66.9-119.8% for raisins at spiking levels of 1.0-150.0 ppm, and 71.3-121.8% for juice at spiking levels of 0.5-15.0 ppm.

A confirmatory TLC procedure is available.

A GLC interference study on 11 other pesticides was submitted. No interferences were observed.

This analytical method No. 151 is similar to that on kiwifruit. The method on kiwifruit has undergone a successful method trial.

We conclude that adequate analytical methods are available for enforcement of the proposed temporary tolerances on grapes and raisins.

Meat and Milk

The analytical methods for analysis of bovine tissues (muscle, kidney, liver, and fat) and milk are discussed in PP# 2F2728 (M. Kovacs, 10/25/82). The analytical method for bovine tissues is ADC #623-B. The methods for milk are ADC #623-A and the Rhone-Poulenc Method #159. Both methods are gas chromatographic methods using electron capture detectors. In the review of 10/25/82, method try-outs for residues of iprodione and its non-hydroxylated metabolites in cattle liver and iprodione and its non-hydroxylated and hydroxylated metabolites in milk were requested.

We conclude that the proposed EUP can be restricted so that residues will not result in meat and milk. For a future permanent tolerance, which would involve feed items, successful completion of the requested method trials on cattle liver and milk would be needed.

Residue Data

Grapes

Eleven studies on grapes were conducted in CA (7), NY (2), OH (1), and PA (1). Rovral (50% WP) was applied at the rate of 1.0 lb. a.i./A. Four applications were made except in one study in CA in which 5 applications were made. Residues in NY and CA at a 0-day PHI after 4 applications at the rate of 1.0 lb. a.i./A ranged from 3.14-44.23 ppm RP 26019, 0.00-0.18 ppm RP 30228, and 0.00-0.85 ppm RP 32490. Residues in CA at a 1-day PHI after 4 applications at 1.0 lb. a.i./A are 36.44 ppm RP 26019, 0.13 ppm RP 30228, and 1.10 ppm RP 32490. Corresponding residues in CA, NY, and PA at a 7-8 day PHI are 1.02-49.27 ppm RP 26019, 0.00-0.47 ppm RP 30228, and 0.00-1.89 ppm RP 32490. Corresponding residues in NY and OH at PHI's of 13-25 days ranged from 2.45-35.18 ppm RP 26019, 0.00-0.14 ppm RP 30228, and 0.00-1.90 ppm RP 32490.

We conclude that residues in grapes resulting from the proposed use will not exceed the proposed temporary tolerance of 60 ppm.

Raisins

Residues were determined on raisins in 6 studies in Ca. Four applications of Rovral (50% WP) were made at the rate of 1.0 lb. a.i./A except in one study in CA in which 5 applications were made.

Fresh grapes (7-day PHI) containing residues of 16.37-24.52 ppm RP 26019, RP 30228, and RP 32490 were sun cured for 19 days (site not specified) to produce raisins containing residues of 43.65-59.5 ppm (2.4-2.7X those on fresh grapes).

Fresh grapes (7-day PHI) containing residues of 25.06 ppm were sun cured for 28 days (site not specified) to produce raisins containing residues of 78.42 ppm (3.1X those on fresh grapes).

Fresh grapes (24-day PHI) containing residues of 1.02 ppm were sun cured for 28 days (site not specified) to produce raisins containing residues of 5.34 ppm (5.2X those on fresh grapes).

Fresh grapes (7-8 day PHI) containing residues of 1.68-49.98 ppm were sun cured (time and place not specified) to produce raisins containing residues of 11.38-134.18 ppm (2.7-6.8X those on fresh grapes).

These data indicate that the concentration factor in going from fresh grapes to raisins ranged from 2.4-6.8X and averaged 3.8X, close to the theoretical dry-down factor of 4.5X

We conclude that residues in grapes will concentrate 2.4-6.8X in raisins so residues may exceed the proposed food additive tolerance of 180 ppm on raisins. A level of 300 ppm would be adequate for a temporary tolerance.

Raisin Waste

There are no residue data for raisin waste. However, since a major portion of raisin waste is comprised of cull raisins, we conclude for the purpose of this temporary tolerance that residues on raisin waste would not exceed 300 ppm. We would need residue data for raisin waste for a permanent tolerance.

Grape Pomace and Juice

To obtain pomace and juice, grapes were crushed and the mixture was passed through a colander. This laboratory process produces wet pomace. We note that this process does not appear to be reflective of commercial equipment. Grapes (7-8 day PHI) containing residues of 1.02-49.98 ppm yielded wet pomace containing residues of 0.74-42.79 ppm (0.2-1.2X those on fresh grapes). Grapes (13-day PHI) containing residues of 2.45 ppm yielded wet pomace containing residues of 4.89 ppm (2.0X those on fresh grapes). Grapes (18-25 day PHI) containing residues of 17.95-27.69 ppm yielded wet pomace containing residues of 36.19-45.7 ppm (1.5-2.5X those on fresh grapes). Based on the available data, we conclude that residues on wet pomace may be 2X those on grapes.

Pomace for stock food is dried to less than 10% moisture to prevent spoilage. We use the theoretical residue concentration factor in going from wet pomace to dry pomace of 5 since 500 lbs. wet pomace forms 100 lbs. dry pomace.

Residues in grape juice were determined in the same 9 studies in which grape pomace was analyzed. Residues of RP 26019, RP 30228, and RP 32490 in grape juice ranged from 0.46-19.51 ppm. Residues in grapes were 1.02-49.98 ppm. Residues in grapes were greater than those in juice in 7 of the 9 studies. The exceptions were 2 studies in California in which residues of 2.48 and 2.32 ppm in juice corresponded with residues in grapes of 1.02 and 1.68 ppm. Residues in juice will not exceed the 60 ppm proposed temporary tolerance on grapes.

Although the process used to obtain grape juice and pomace does not appear to be reflective of commercial equipment, we can conclude for purposes of this temporary tolerance that residues in grape juice will not exceed the proposed temporary tolerance of 60 ppm on grapes. From a 60 ppm residue level on grapes, a concentration factor of 2X, and a dry-down factor of 5, we conclude that a 600 ppm temporary food additive tolerance for dried grape pomace is needed.

For a future permanent tolerance, we will require data for grape juice and wet and dried pomace prepared from grapes bearing aged iprodione residues at or near the proposed tolerance level on either pilot scale equipment designed to simulate commercial equipment or actual commercial equipment.

Meat, Milk, Poultry, and Eggs

No new animal feeding studies are submitted with this petition. We refer to a cattle feeding study which was previously reviewed in connection with PP# 2F2728 (M. Kovacs, 10/25/82). Feeding levels were 5, 15, 50, and 200 ppm for 29 days. In meat, iprodione and its non-hydroxylated metabolites were determined. Iprodione it nonhydroxylated metabolites, and its hydroxylated metabolites were determined in milk. Residues in milk at the 28th day of treatment for levels of 5, 15, 50, and 200 ppm were <0.01, 0.383, 0.389, and 0.329 ppm. Maximum residues in kidney at 5, 15, 50, and 200 ppm feeding levels were <0.05, 0.16, 0.80, and 2.87 ppm, respectively. Maximum residues in muscle at 5, 15, 50, and 200 ppm feeding levels were <0.05, <0.05, 0.07, and 0.13 ppm, respectively. Maximum residues in fat at 5, 15, 50, and 200 ppm feeding levels were <0.05, <0.05, 0.21, and 0.52 ppm, respectively. Maximum residues in liver at 5, 15, 50, and 200 ppm feeding levels were <0.05, 0.13, 0.66, and 1.95 ppm, respectively.

However, the validity of these data was questioned because of the lack of appropriate storage stability data. A request was made in connection with PP# 2F2728 (M. Kovacs, 10/25/82) for a storage stability study showing residues of iprodione in milk and liver when stored for 4 and 8 months, respectively, at 0°F.

No poultry feeding study has been submitted.

Dried grape pomace can comprise up to 20% of the diet of dairy cattle, 30% of the diet of beef cattle and up to 5% of the diet of poultry. Raisin waste may also comprise up to 10% of the cattle diet.

Because of the lack of residue data for raisin waste and dried pomace, the lack of a poultry feeding study, and questions concerning the validity of the available cattle feeding study, we are unable to make a conclusion concerning secondary residues in meat, milk, poultry, and eggs.

We conclude that the proposed use on grapes would fall in Section 3 of 40 CFR 180.6(a) with respect to residues in meat, milk, poultry, and eggs, provided that use is restricted to grapes to be used on the fresh market only.

For a future permanent tolerance, the following would be needed:

1. A poultry feeding study should be submitted.

2. A storage stability study is needed for residues of iprodione in milk and liver when stored for 4 and 8 months, respectively, at 0°F.

3. Appropriate tolerances for secondary residues in meat, milk, poultry and eggs are needed.

RCB:N.Dodd:mch:CM#2:RM810:X77324:3/16/83
cc: Circu., R.F., N. Dodd, Thompson, FDA, TOX, EEB, EFB, PP# 3G2787
RDI: R. Hummel, 3/15/83; R. Schmitt, 3/16/83