5-13-82

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MAY 13 1982

MEMORANDUM

Subject: PP#2F2596 Iprodione on Stone fruits. Evaluation of analytical methods and residue data and amendment.

From: R.B. Perfetti, Ph.D., Chemist
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Thru: Charles L. Trichilo, Chief
Residue Chemistry Branch
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To: Product Manager No. 21 (H. Jacoby) FHB
Registration Division (TS-767)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

Rhone Ponlenc Chemical Company 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 (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 apricots, cherries (sweet and sour), nectarines, peaches, and plums (fresh prunes) at 10 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 0G2402 respectively.

Conclusions

1) The label should be revised to include a limit on the number of applications of iprodione permitted per year as well as prescribe a minimum interval between applications in the 5 weeks prior to harvest. See the conclusion regarding tolerance levels for peaches and cherries below for a further discussion of these label revisions. The restriction prohibiting feeding treated cover crops to livestock should be modified to read as follows: "Do not feed cover crops grown in treated orchards to livestock". These label modifications should be submitted in a revised Section B.

2) The metabolism of iprodione in stone fruits is adequately understood. The terminal residue of concern will consist of iprodione its isomer and the des-isopropyl metabolite.

3) Adequate analytical methods are available for enforcement purposes .

4a) The 10 ppm proposed tolerance for cherries is not adequate. If the number of treatments of iprodione permitted per year is held to 6, combined residues of this compound in or on cherries would not be expected to exceed 20 ppm. This higher tolerance level along with the label restriction should be proposed and submitted in revised Sections F and B respectively.

4b) The proposed 10 ppm tolerance level for peaches is not adequate. A more appropriate level would be 20 ppm provided the label is revised to allow a maximum of 5 applications of iprodione to peaches per year. This tolerance level would also be acceptable for nectarines again provided a maximum of 5 applications are allowed per year to this crop. This label restriction along with new tolerance proposals for these commodities should be submitted in revised Sections B and F respectively.

4c) Additional residue data for apricots, plums and prunes will be needed before a determination of appropriate tolerance levels for these commodities can be made. Since California is the major growing area for these fruits residue data from this state only will be required. When the residue data is obtained for prunes, residue bearing samples of this commodity's should be dried in order to determine whether residues of iprodione and metabolites concentrate upon processing. If concentration of residues occurs in this fruit, an approppriate food-additive tolerance proposal based on the maximum concentration factors observed should also be submitted in a revised Section F.

4d) The samples of apricots, nectarines, plums and prunes obtained in the additional residue studies required above should not be held in frozen storage for long period of time before analysis or a complete 2 year storage stability study may be required.

5) Since the label contains restrictions prohibiting the grazing of treated orchards or feeding cover crops grown in treated orchards (See conclusion 1 above) to livestock there will be no problems with secondary residues in meat, milk, poultry or eggs under this present use.

6) The International Tolerance Sheet is attached. There are Codex tolerances of 10 ppm on peaches and plums. These tolerances regulate the parent iprodione only. No pathway for making the present recommended 20 ppm tolerance for combined residues of iprodione, its isomer and the des-isopropyl metabolite in or on peaches compatible with the Codex tolerance as expressed can be envisioned.

Recommendation

We recommend that the proposed tolerances not be established for the reasons given in conclusions 1, 4a, 4b and 4c. The requirements for resolution of these deficiencies is also discussed in the apppropriate conclusion above. The petitioner shold also be informed of our possible additional requirement discussed in conclusion 4d.

Note to PAM Editor: Please see our recommendation regarding methodology discussed in the Analytical Methods Section.

Detailed Considerations

Formulation

The formulation proposed for use is Rhone-Ponlenc's Rovral fungicide. Rovral is formulated as a wettable powder containig 53.16% technical iprodione. All inerts in the formulation are cleared under Section 180.1001.

The manufacturing process and identities and percentages of impurities was submitted and reviewed in conjunction with PP# 8G 2084 (Review of 3/2/79, A. Rathman) which see. 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

To control fungus on cherries and peaches apply 0.5 to 1 lb active ingredient/acre (0.125 to 0.25 lb active ingredient/100 gallons of spray) as foliar treatment in 20-400 gallons of water per acre using ground equipment or in 15-20 gallons/acre if application is made by air. Applications can be made at early bloom at full bloom, at petal fall or when conditions favor disease infection in the 5 weeks perior to harvest up to and including the day of harvest. Restrictions prohibiting grazing of treated orchards or feeding treated cover crops to livestock are prescribed. No limit on the maximum number of applications which can be made is stated nor is a minimum spacing of applications prescribed. A maximum number of applications permitted per year should be included on the label as well as a minimum interval between applications in the 5 weeks prior to harvest should be given. Also, the restriction against feeding treated cover crops to livestock should be modified to read as follows: "Do not feed cover crops grown in treated orchards to livestock.

These label restrictions should be submitted in a revised Section B. The petitioner should be so informed.

Nature of the Residue

A metabolism study on peaches has been submitted in conjuction with this petition and is discussed below. Previous metabolism studies for iprodione on strawberries and wheat indicated that there is little migration after foliar treatment, but that uptake via the roots system after ground application does occur with subsequent translocation to aerial plant parts. the major identified portion of the residue after foliar treatment consisted of parent, 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2, 4-dioxo-1-imidazolidinecarboxamide (RP30228) and to a lesser extent a des-isopropylated metabolite (RP32490). Plants analyzed after soil treatment showed that the majority of the radioactivity was in a bound form and this was not identified. The portion of the residue which was extractable was found to be parent, RP30228 and RP32409.

The peach metabolism study reflected treating two peach trees with an equivalent of 1 lb active ingredient/acre of ^{14}C-ring labeled iprodione. Three applications were made, one at pink bud stage, one at petal fall and one 8 days prior to harvest. Immature fruit was sampled just prior to and immediately after the third treatment. In addition, leaves were sampled immediatly after the petal fall treatment. All samples of leaves and fruit were counted and leaves contained 82.9 to 91.9 ppm of radioactive residues. Immature fruit picked just before the third spray contained 0.022 to 0.04 ppm of radioactivity and showed 2.01 to 5.63 ppm of radioactive residues immediately after the third spray.

At harvest fruit either picked from the trees or taken from the ground showed 1.55 to 2.31 ppm of radioactivity eight days after the last treatment.

The harvest fruit samples were extracted with acetone, filtered and the acetone was stripped from the filtrate. This solution was partitioned with ethyl acetate and the ethyl acetate solution was evaporated to dryness and then partitioned between hexane and acetonitrile. The hexane layer was saved and the acetonitrile solution was taken to dryness, redissolved in ethyl acetate and further cleaned-up on a Florisil column. The original filter cake was soxhlet extracted twice with methanol. Radioactive residues were then characterized via TLC.

In all, >90% of the radioactive residue in harvested fruit was identified as iprodione with approxiamethy another 5% of the radioactivity characterized as an isomer of iprodione and the desisopropyl metabolite.

The fruit sampled just prior to the third spray (64 days after the last treatment) was worked-up for metabolite identification essentially as described above for harvest fruit. Radioactivity observed in these immature fruit was found to be ca. 66% iprodione.

The metabolism of iprodione in stone fruits is similar to that observed in strawberries and wheat. The terminal residue of concern will consist of iprodione, its isomer and the des-isopropyl metabolite.

Analytical Method

The method used to collect residue data involved blending the sample with acetone (Note: In some analyses one ml of concentrated HCl was added to the acetone before blending), filtration and evaporation of the solvent. To the remaining aqueous solution was added sodium sulfate solution and the solution was extracted with 10% ethyl acetate/methylene chloride. The ethyl/acetate/methylene chloride solution was dried over sodium sulfate, evaporated to dryness and redissolved in 3:1 ethyl acetate/toluene. The sample was further cleaned-up on both a gel permeation column and a Florisil column. The samples were eluted from the Florsil column as two fractions, one containing parent and RP 30228 and the second containing the des-isopropyl metabolite RP 32490. These fractions were taken to dryness, redissolved in benzene and analyzed via glc using a ^{16}Ni electron capture detector. An optional hexane/acetonitrile partitioning is available for very dirty samples of fraction 1.

Validation data submitted involved fortification of sweet or sour cherries, plums and peaches with iprodione, its isomer (RP 30228) or the des-isopropyl metabolite (RP 32490) at levels of 0.05 to 20 ppm. Recoveries ranged from 73.3 to 149% for parent, from 75.3 to 139.5% for RP 30228 and from 72.3 to 100% for RP 32490. Blank crop values ranged from non-detectable to 1.31 ppm for iprodione with the highest values being found in sour cherries. control values for RP 30228 and RP 32490 were non-detectable to 0.19 ppm and non-detectable to 0.05 ppm respectively in all substrates. Sample chromatograms were submitted.

A conformatory TLC procedure was submitted as well as a limited interference study. No interferences were observed using the glc parameters for iprodione and metabolites.

The petitioner has also submitted an analytical method validation using peaches treated with ^{14}C-labeled iprodione. The study involved analysis of the radioactive samples, control samples and samples fortified with 0.5 ppm of iprodione, and 0.1 ppm each of RP 30228 and RP 32490 using the analytical procedure described above. Comparison of radioactive residues vs glc values indicated that the subject analytical procedure accurately extracts and determines the terminal residue of concern in stone fruits.

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 conclude that adequate analytical methods are available for enforcement purposes (Note to PAM editor: We recommend that the analytical method No. 151, this petition, tab D-4 labeled Report No. 81/008 be included as method B in the PAM. This domument also contains the TLC confirmatory procedure as well as the interference study discussed above).

Residue data

Residue data on cherries submitted in this petition reflected thirteen studies on sweet (5) and sour (8) varieties grown in California (1), Michigan (5), Wisconsin (1), Oregon (3) and New York (3). Plot sizes ranged from three to 5 acres treated. The experiments involved 4 to 7 foliar applications of 1.6 lb active ingredient/acre as the 50% WP formulation using ground equipment or aircraft (1 study). Zero day residue values for iprodione ranged from <0.05 to 3.87 ppm in sweet cherries and from <0.05 to 5.7 ppm in sour cherries. Residues of the isomer of iprodione (RP 30228) in sweet and sour cherries ranged from <0.05 to 0.21 ppm and from <0.05 to 0.38 ppm respectively. All residue values for the des-isopropyl were given as non-detectable. No significant difference between the air vs ground application to cherries was observed.

Residue data submitted in conjuction with PP# 8G2087 showed 0 day residues of iprodione and its metabolites RP 30228 and RP 32490 could range up to 17.28, 0.06 and <0.05 ppm respectively at the 1.0 lb active ingredient/acre (1X) rate when up to 6 applications were made.

Based on the information above it is our judgement that the proposed 10 ppm tolerance for cherries is not adequate. Provided the petitioner limits the number of appliations permitted per year to sweet or sour cherries to 6, a more appropriate tolerance level for combined residues of iprodione and its metabolites would be 20 ppm. The petitioner should be informed that we will require submission of revised sections B and F proposing both the limitation on the number of treatment permitted per year and the higher tolerance level.

Residue data for peaches submitted in this petition involved 23 studies carried out in the states of California (6) Pennsylvania (1), North Carolina (2), South Carolina (2), Ohio (2), New Jersey (1), Texas (3), New York (1), Kentucky (1), Michigan (1), Oregon (1), Alabama (1), and Georgia (1). Plot sizes ranged from 1 tree to 3 acres. The studies involve 2 to 7 foliar applications of 1.0 lb active ingredient/acre as the 50% WP formulation using ground equipment or aircraft (4 experiments) and zero day residues of iprodione and its isomer RP 30228 ranged from 0.08 to 23.25 ppm and from <0.05 to 0.44 ppm respectively. Residues of parent and RP 30228 were 3.7 to 16.06 ppm and 0.11 to 0.3 ppm respectively after a one day PHI and 1.01 and 1.15 and <0.05 and 0.06 ppm after 3 and 7 day PHI's respectively. All analyses for the des-isopropyl metabolite RP 32490 were given as non-detectable.

Zero day residues observed for aerial applications apppeared to be some what lower than those for ground application but given the overall variation in residue levels observed we have no additinal concern with regards to the method of applicaiton of iprodione to peaches. Residue data submitted in conjuction with PP# 8G2087 indicated that after 7 applications of iprodione residues of this compound and its metabolites RP 30228 and RP 32490 could range up to 16.6 ppm, 0.74 and <0.05 ppm respectively after zero days and at the 1X application rate.

Based on the information discussed above, we conclude that provided a maximum of 5 applications of iprodione per year are made to peaches an appropriate tolerance level for combined residues of this material and its metabolites on this commodity would be 20 ppm. The petitioner should be informed that submission of revised Sections B and F proposing a 5 application/year limit for treatment of peaches and the higher tolerance level of 20 ppm are neeeded before a favorble recommendation for a tolerance on this crop could be made by RCB.

No additional residue data for apricots, nectarines, plums or prunes was submitted in this petition. Earlier data submitted in conjunction with PP# 862087 involved 1 study each on apricots and nectarines using only 1 tree and 2 experiments on prunes again employing only 1 tree each. We do not find these data adequate for determination of appropriate tolerance levels in these crops with the exception of nectarines. Based on the data for peaches a tolerance of 20 ppm on this crop would be acceptable for nectarines provided the 5 application per year limit is also imposed for this crop.

The petitioner should be informed that we will need some additional residue data for apricots , plums and prunes before any conclusion as to appropriate tolerance levels for residues of iprodione on these commodities could be made. Since California is the major growing area for these fruits residue data from this state only will be required. When the data for prunes is obtained residue bearing samples of this commodity should be dried in order to determine whether residues of iprodione and metabolites concentrate upon processing. If concentration of residues occurs in the prunes an appropriate Food-Additive tolerance proposal based on the maximum concentration factor observed should also be submitted in a revised Section F.

Finally, the samples of treated peaches and cherries were stored frozen from 107 to as long as 712 days before analysis. Since the petitioner has submitted a pseudo storage stability study in conjuction with PP# 8G2087 indicating that iprodione residues were stable in frozen storage for ca. 1 year and since ca. 60% of the peach and cherry samples were stored less than 1 year we are not raising any questions with respect to the accuracy of the residue data for peaches and cherries at this time. Also, more weight was given to samples which had been stored for <1 year. The petitioner should be informed however that the samples of apricots, plums and prunes obtained in the additional residue studies required above should not be stored for a long period of time before analysis or a bona fide 2 year storage stability study maybe needed.

Meat, Milk, Poultry and Eggs

Since the label contains restrictions prohibiting the grazing of treated orchards or feeding cover crops grown in treated orchards to livestock there will be no problems with secondary residues occuring in meat, milk, poultry or eggs under this present use (Note: The cover crop restriction must be revised as discussed in the Proposed Use Section above).

Other Considerations

The International Tolerance Sheet is attached. There are tolerances of 10 ppm on peaches and plums. The tolerances regulate the parent iprodione only. We can see no pathway for making the present recomended 20 ppm tolerance for combined residues of iprodione, its isomer and the des-isopropyl metabolite in or on peaches compatible with the Codex tolerance.

TS-769:RCB:RPerfetti:vg:CM#2:Rm810:X77324:5/7/82
cc:RF, Circ, Perfetti, Thompson, FDA, TOX, EEB, EFB, PP#2F2596
RDI: Quick, 5/5/82; Schmitt, 5/5/82

PERFETTI

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL 3-(3,5-Dichlorophenyl)-N-(1-methyl ethyl)2,4-Dioxo-1-imidazolidinecarboxamide PETITION NO 2F2596

CCPR NO. (iprodione)

Codex Status

☐ No Codex Proposal Step 6 or above

Residue (if Step 9): _____

IPRODIONE (metabolites are excluded)

Crop(s)	Limit (mg/kg)
peaches	10
plums	10

CANADIAN LIMIT

Residue: _____

Crop	Limit (ppm)
none	

Proposed U. S. Tolerances

iprodione, 3-(1-methyl ethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide and 3-(3,5-dichlorophenyl)-2,4-dioxo-1-

Residue: imidazolidine carboxamide

Crop(s)	Tol. (ppm)
apricots	10 ppm
sweetcherries	
sour cherries	
nectarines	
peaches	
plums	
fresh prunes	

MEXICAN TOLERANCIA

Residue: _____

Crop	Tolerancia (ppm)
none	

Notes: