6-24-93 R7

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

JUN 24 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#2F04111 (CBTS #9977; Barcode #D178753). Iprodione [3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide] on Cottonseed. Evaluation of Residue Data and Analytical Methods (MRID #423123-00).

FROM: Nancy Dodd, Chemist
Tolerance Petition Section II
Chemistry Branch I- Tolerance Support
Health Effects Division (H7509C)

THROUGH: Debra Edwards, Ph.D., Chief
Chemistry Branch I- Tolerance Support
Health Effects Division (H7509C)

TO: Susan Lewis, PM #21
Fungicide/Herbicide Branch
Registration Division (H7505C)

Rhone-Poulenc proposes the establishment of a permanent tolerance for 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-imidazolidine-carboxamide in/on cottonseed at 0.10 ppm.

CBTS has recommended for a temporary tolerance of 0.10 ppm for combined residues of iprodione, its isomer, and its metabolite on cottonseed provided a revised label for Start 15G is submitted (PP#1G3998, M. Peters, 5/10/93).

Permanent tolerances have been established for combined residues of iprodione, its isomer and its metabolite on various raw agricultural commodities at levels ranging from 0.1 to 150.0 ppm (40 CFR 180.399). Food additive tolerances have been established for iprodione, its isomer and its metabolite on dried ginseng (4.0 ppm) and raisins (300 ppm) (40 CFR 185.3750). Feed additive tolerances have been established for iprodione, its isomer, and its metabolite on dried grape pomace (225 ppm), raisin waste (300 ppm), rice bran (30.0 ppm), rice hulls (50.0 ppm), and soapstock (10.0 ppm) (40 CFR 186.3750).

1/21

Permanent tolerances for animal commodities have also been established for iprodione, its isomer, its metabolite, and an additional metabolite N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide at levels ranging from 0.5 to 5.0 ppm (40 CFR 180.399).

Refer to Attachment 1 for the structures and code numbers of the chemicals which are named in 40 CFR 180.399 as residues of concern.

Iprodione is a List B chemical. A Phase IV review of iprodione has been completed (C. Olinger, 3/15/91).

Referenced data which are discussed in this review were obtained in studies conducted by Rhone-Poulenc or contract labs (Ricerca, Inc.; Analytical Development Corporation; and Gulf South Research Institute).

Conclusions

1. Product Chemistry data gaps are 62-2, 62-3, and 63-11 as discussed in the R. B. Perfetti memo dated 9/9/92 (CBRS #9943; Barcode #D165907). These data gaps should be resolved.

2. The impurities in the technical are not expected to cause a residue problem.

3. CBTS defers to Registration Division concerning whether the inerts in Start 15G are cleared under 40 CFR 180.1001.

4. Chinese mustard is listed in the Section B/label as a crop with crop rotation restrictions but is not included in either the list of crops which may be rotated after harvest or the crops which may by rotated 1 month after the last application of iprodione. This is an omission which should be corrected on a revised Section B/label.

5. The appropriateness of the proposed crop rotation restrictions will be evaluated when the package of crop rotation studies is submitted for CBTS review.

6. The nature of the residue in cotton is adequately defined. The residues of concern are iprodione per se, 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-imidazolidine-carboxamide.

7. The nature of the residue in animals is adequately understood for the proposed use on cotton since the dietary contribution for animals from cottonseed as a result of the proposed use will be small ($\leq$0.025 ppm) and secondary residues in animal commodities (ruminant and poultry) would be expected to be nondetectable (ie. <0.01 ppm in milk and <0.05 ppm in other animal commodities). The

residues of concern in animals are those listed in 40 CFR 180.399(b): parent, its isomer 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide, and its metabolites 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide and N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide.

8. For other uses involving higher proposed tolerances/higher secondary residues in animal commodities, the petitioner should address the animal metabolism issues raised in the Phase IV review and reassess the appropriateness of the existing tolerance expression for animal commodities.

9. An adequate analytical method is available for enforcement of the proposed tolerance on cotton. The method, Rhone-Poulenc Method 151, has been sent to FDA for inclusion in PAM II. Until it is published in PAM II, the method is available from Public Response and Program Resources Branch, Field Operations Division (H7506C).

10. For any new crop field trial studies, toluene should be substituted for benzene when the regulatory method is used for the determination of iprodione and its degradates in the samples. The concurrent fortification data from these studies should be submitted as validation of the substitution of toluene for benzene in the regulatory method.

11. Adequate analytical methods are available for animal commodities resulting from the proposed use on cotton since secondary residues in animal commodities resulting from the proposed use on cotton are expected to be nondetectable (ie. <0.01 ppm in milk and <0.05 ppm in other animal commodities).

12. For other uses involving higher proposed tolerances/higher secondary residues in animal commodities, the petitioner should address the issues raised in the List B Inventory and the Phase 4 review (see page 12 of this review).

13. For other uses involving higher proposed tolerances/higher secondary residues in animal commodities, an independent laboratory validation and an EPA laboratory validation of a method for analysis of the residues of concern on eggs would be needed.

14a. Analytical reference standards and Material Safety Data Sheets are available for iprodione, its isomer RP30228, and its metabolite RP32490 from the USEPA Chemical Standards Repository, RTP, NC.

14b. An analytical reference standard and Material Safety Data Sheet for the animal metabolite N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide (RP36114) are not available at the repository and should be provided by the petitioner.

15. The metabolites 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide (RP32490) and N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide (RP36114) must be tested through the appropriate multiresidue protocols.

16. Adequate storage stability data are available for iprodione, its isomer RP30228, and its metabolite RP32490 on cottonseed. Residues of RP30228 and RP32490 were stable during 3 months of frozen storage. Iprodione per se decreased by 35% during 3 months frozen storage.

17. Iprodione and the non-hydroxylated metabolites appear to be stable for 22 months in milk and 13 months in liver. The hydroxylated metabolite appears to be stable in milk for 13 months.

18. For other uses involving higher proposed tolerances/higher secondary residues in animal commodities, storage stability data for the hydroxylated metabolite in liver and for all the residues of concern in muscle (cattle or poultry) and eggs would be needed. Storage conditions must reflect the storage conditions of the treated samples with respect to temperature, length of storage, containers, lighting, etc. As stated in "Pesticide Reregistration Rejection Rate Analysis Residue Chemistry, Follow-up Guidance for Generating Storage Stability Data" (EPA 737-R-93-001, February 1993), "the samples used in the storage stability study could either be from crops (or animals) that have been treated with pesticides in the field or from the spiking of control (untreated) samples with known amounts of each analyte".

19. Additional residue data are needed from the major cotton producing state of CA, based on cotton production areas listed in Agricultural Statistics, 1990. At least one study should be conducted in CA. This study could be a bridging study required in Conclusion 20 below. (Toluene should be substituted for benzene in the analytical method as discussed in Conclusion #10 above.)

20. Bridging data from the flowable formulation to the granular formulation are needed. "Bridging data" refers to residue data from applications of the flowable formulation and granular formulation on side-by-side plots, using the same pre-harvest interval and rate of application. (Toluene should be substituted for benzene in the analytical method as discussed in Conclusion #10 above.)

21. An adequate processing study for iprodione on cottonseed has been submitted. Residues of iprodione, RP30228, and RP32490 do not concentrate in processing fractions.

22. The available rotational crop data are not adequate. The petitioner should submit all relevant rotational crop studies as a package for CBTS review when the on-going confined study is completed. Based on data summaries, CBTS has indicated that

rotational crop tolerances will probably be required for the permanent tolerance.

23. The established tolerances for iprodione in meat, milk, poultry, and eggs [40 CFR 180.399(b)] are adequate to cover secondary residues in animal commodities resulting from the proposed use on cotton.

24. For other uses involving higher dietary contributions in the animal diet, the issues regarding the animal feeding studies which were raised in the Phase IV review (C. Olinger, 3/15/91) and subsequently discussed in the List B File memo (L. Cheng, 5/29/92, CBRS #9664 and 9665) would have to be addressed.

25. An International Residue Limit (IRL) Status sheet was attached to the 3/17/93 review of PP#1G3998 (M. Peters). There are no Codex, Canadian, or Mexican tolerances for iprodione on cottonseed. Therefore, no compatibility questions exist for cottonseed with respect to Codex.

26. No "CBTS Action Study Acceptability" form is attached to this review since no data were submitted with this petition.

27. The Section F which proposes a permanent tolerance contains differences in nomenclature for the parent and metabolites compared to 40 CFR 180.399. This review uses the nomenclature in 40 CFR 180.399. The petitioner should revise the Section F to be consistent with the 40 CFR 180.399.

Recommendations

CBTS recommends against the proposed use of iprodione on cotton for reasons given in Conclusions #1, 3, 4, 5, 10, 14b, 15, 19, 20, 22, and 27 above.

For other uses involving higher proposed tolerances/higher secondary residues in animal commodities, the petitioner should be aware of Conclusions #8, 12, 13, 18, and 24.

DETAILED CONSIDERATIONS

PRODUCT CHEMISTRY

Product Chemistry data deficiencies were identified in the Phase IV review (C. Olinger, 3/15/91). Subsequent Product Chemistry reviews were dated 1/10/92 (K. Dockter), 2/4/92 (S. Funk), 6/9/92 (S. Funk), and 9/9/92 (R.B. Perfetti).

Conclusion

Product Chemistry data gaps are 62-2, 62-3, and 63-11 as discussed in the R. B. Perfetti memo dated 9/9/92 (CBRS #9943; Barcode #D165907). These data gaps should be resolved.

RESIDUE CHEMISTRY

Manufacture

The manufacturing process has been previously discussed. The impurities in the technical are not expected to cause a residue problem (PP#8G2087, A. Rathman, 3/2/79).

Conclusion

The impurities in the technical are not expected to cause a residue problem.

Formulation

Start® 15G is a granular formulation containing 5.0% w/w iprodione, 10% w/w fosetyl-Al, and 85.0% inerts. Registration Division determines whether the inerts in Start 15G are cleared under 40 CFR 180.1001.

Conclusion

CBTS defers to Registration Division concerning whether the inerts in Start 15G are cleared under 40 CFR 180.1001.

Proposed Use

Apply Start 15G in-furrow at planting using a tractor or planter mounted granular applicator which delivers granules to the open seed furrow directly behind the seed drop tube and before the furrow closure devices. Apply at the rate of 2.0-4.0 lbs Start 15G per acre (0.1-0.2 lb iprodione ai/A and 0.2-0.4 lb fosetyl-Al ai/A), based on a 40" row spacing or 13,000 row feet/A. This is equivalent to 2.5-5.0 ounces Start 15G per 1000 feet of row (0.125-0.25 ounces iprodione ai per 1000 ft of row).

Crop rotation restrictions:

The following crops may be rotated after harvest: garlic, dry bulb onions, broccoli, lettuce, peanuts, carrots, beans, and potatoes.

The following crops may be rotated 1 month following the last iprodione application: root crops and tomatoes.

Grazing restriction:

Do not allow grazing or feeding of cotton forage to livestock.

In connection with the review of the EUP, CBTS (PP#1G3998, M. Peters, 3/17/93 and 5/10/93) indicated that the label should specify a 4" band width application. However, in a memo dated 6/9/93 (PP#1G3997, M. Peters), CBTS indicated that this is not necessary for an in-furrow application.

CBTS also indicated in the 3/17/93 memo that, for a permanent tolerance, a preharvest interval must be specified. However, for an in-furrow application, the normal growing period for the crop can be understood to be the preharvest interval.

Conclusions

Chinese mustard is listed in the Section B/label as a crop with crop rotation restrictions but is not included in either the list of crops which may be rotated after harvest or the crops which may by rotated 1 month after the last application of iprodione. This is an omission which should be corrected on a revised Section B/label.

The appropriateness of the proposed crop rotation restrictions will be evaluated when the package of crop rotation studies is submitted for CBTS review. (See the "Rotational Crops" section below.)

Nature of the Residue

Cotton

No additional plant metabolism studies have been submitted with this petition. Plant metabolism studies have previously been reviewed in connection with petitions for tolerances on strawberries and wheat (PP#8G2087), peaches (PP#2F2596), lettuce (PP#3G2801), peanuts (PP#4G3037), and rice (PP#6F3443/FAP#6H5507). CBTS concluded that the residues of concern in plants were the parent, 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-imidazolidine-carboxamide. The Phase IV Review (C. Olinger, 3/15/91) also concluded that additional plant metabolism studies are not needed.

Conclusion

The nature of the residue in cotton is adequately defined. The residues of concern are iprodione per se, 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-imidazolidine-carboxamide.

Animals

No additional animal metabolism studies were submitted with this petition. Ruminant metabolism studies (cows and goats) were previously reviewed in PP#2F2728 (M. Kovacs, 10/25/82) and PP#3F2964 (R.W. Cook, 2/21/84). A poultry metabolism study was previously reviewed in PP#3F2964 (R.W. Cook, 2/21/84).

Additional animal metabolism studies were required after review of summaries of the goat and poultry metabolism studies in the Phase IV Review (C. Olinger, 3/15/91) as follows:

> "The registrant has submitted summaries of poultry and ruminant metabolism studies. A lactating goat was fed radiolabelled iprodione for five days at a level of 188 ppm, and sacrificed within four hours of the final dose. The tissues, milk, and urine were radioassayed by liquid scintillation counting. Characterization of the metabolites was done by co-chromatography using TLC. Residues in milk were not characterized; 25-62% of the TRR was not identified in the remaining tissues."
>
> "Fifteen laying hens were treated with radiolabelled iprodione for 15 days at a level of 10 ppm. Sacrifice occurred 2 hours, 3 days, or 7 days after the final dose. The tissues and urine were radioassayed by liquid scintillation counting. Characterization of the metabolites was done by co-chromatography using TLC. The TRR unidentified ranged from 3% for fat to 47% for liver."
>
> "Although a significant amount of the TRR remained unidentified, these studies are adequate for determination of the metabolites of interest. The registrant has not demonstrated the analytical methods are capable of extracting the residues of concern. Therefore CBRS is requiring another ruminant metabolism study so the registrant may prove the data collection and regulatory methods are valid. [Refer to section 171-4(d), Analytical Method- animal.] Labelling in both the phenyl and imidazole rings is preferred to permit adequate identification of all potential metabolites."

"Data Gap: "The registrant must provide a ruminant metabolism study. Iprodione labelled in the phenyl and imidazole rings should be fed to the livestock for a minimum of three days. Orally treated test animals must be sacrificed within 24 hours of the final dose. The dose administered and the specific activity should be high enough to allow for adequate identification of the metabolites/degradates. The tissues from the metabolism

study must be tested using the data collection method(s) and enforcement analytical method(s)."

CBTS notes that some of the residues in milk were identified in the cow metabolism study, which was not discussed in the 3/15/91 memo.

CBTS also notes that extractability of radioactive residues in milk using methods #623-A and No. 159 and in liver using method #623-B was determined in PP#2F2728 (Accession #071424, ASD #83/009, dated 2/23/83). (Refer to the discussion below in the section on animal methods).

For the purpose of the EUP on cotton, CBTS concluded that the nature of the residue in animals was adequately understood considering the low residues and limited acreage proposed in the EUP.

As discussed in the "Meat, Milk, Poultry, and Egg" section below, the dietary contribution for animals from cottonseed would be $\leq$0.025 ppm in the feed resulting from the proposed use and permanent tolerance on cotton. Secondary residues in animal commodities (ruminant and poultry) would be expected to be nondetectable (ie. <0.01 ppm in milk and <0.05 ppm in other animal commodities) as a result of the proposed use on cotton.

Conclusion

The nature of the residue in animals is adequately understood for the proposed use on cotton since the dietary contribution for animals from cottonseed as a result of the proposed use will be small ($\leq$0.025 ppm) and secondary residues in animal commodities (ruminant and poultry) would be expected to be nondetectable (ie. <0.01 ppm in milk and <0.05 ppm in other animal commodities). The residues of concern in animals are those listed in 40 CFR 180.399(b): parent, its isomer 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide, and its metabolites 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide and N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide.

For other uses involving higher proposed tolerances/higher secondary residues in animal commodities, the petitioner should address the animal metabolism issues raised in the Phase IV review and reassess the appropriateness of the existing tolerance expression for animal commodities.

Analytical Methods

Cotton

Residue data on cotton commodities were obtained using Rhone-Poulenc SOP 90277: "Determination of RP-26019 and its Metabolites in/on Dry, Succulent, Oily, and Non-Oily Crops by Gas Liquid Chromatography and Thin-Layer Chromatography". The method SOP 90277 is essentially the same as Rhone Poulenc Method 151, which was submitted for inclusion in PAM II (PP#1G3998, J. Garbus, 6/8/92 and 12/15/92; PP#3F2810, R.B. Perfetti , 3/21/83). Both methods (Method 151 and SOP 90277) determine parent (RP26019), its isomer (RP30228), and its metabolite (RP32490). Both methods use thin layer chromatography as a confirmatory method.

As stated in the Phase IV Review (C. Olinger, 3/15/91), "toluene should be substituted for benzene when the regulatory method is used for the determination of iprodione and its degradates in samples from new crop field trial studies. The concurrent fortification data from these studies should be submitted as validation of the substitution of toluene for benzene in the regulatory method".

Radiovalidation data for Rhone-Poulenc Method No. 151 on peaches were submitted in PP#2F2596 (Accession #070442, Tab D-3, dated 10/29/81). The peaches were obtained from a metabolism study which used ^{14}C-phenyl ring labelled iprodione. Total radioactivity was determined by combustion/liquid scintillation counting to be 1.80 ppm. Recoveries through Method No. 151 on peaches were determined by liquid scintillation counting at each step of the method and reported as follows:

procedural step	ppm	% total radioactivity recovered
acetone extracts	1.81	100.7
ethyl acetate in methylene chloride	1.72	95.5
GPC column eluate	1.77	98.4
Florisil column:		
Fraction I (RP26019 & RP30228)	1.67	93.0

procedural step	ppm	% total radioactivity recovered
Fraction II (RP32490)	0.03	1.6

Radiovalidation data for the analytical method for plants were not required in the Phase IV Review, based on the idea that the parent and regulated metabolites are not likely to be bound or conjugated in plants (C. Olinger, 3/15/91).

An interference study was conducted with eleven pesticides. The eleven pesticides were phosalone, malathion, Sevin, parathion, kelthane, methyoxychlor, Guthion, Benlate, captan, dichlone, and dicloran (DCNA). The study indicated that these eleven pesticides did not interfere with the method SOP 90277 (PP#1G3998, MRID #419058-01).

Analytical reference standards and Material Safety Data Sheets are available for iprodione, its isomer RP30228, and its metabolite RP32490 from the USEPA Chemical Standards Repository, RTP, NC as verified by a telephone conversation with P. Beyer on 4/21/93 (Section 18, CBTS #11726, D. Davis, 4/26/93).

Conclusion

An adequate analytical method is available for enforcement of the proposed tolerance on cotton. The method, Rhone-Poulenc Method 151, has been sent to FDA for inclusion in PAM II. Until it is published in PAM II, the method is available from Public Response and Program Resources Branch, Field Operations Division (H7506C).

For any new crop field trial studies, toluene should be substituted for benzene when the regulatory method is used for the determination of iprodione and its degradates in the samples. The concurrent fortification data from these studies should be submitted as validation of the substitution of toluene for benzene in the regulatory method.

Analytical reference standards and Material Safety Data Sheets are available for iprodione, its isomer RP30228, and its metabolite RP32490 from the USEPA Chemical Standards Repository, RTP, NC.

Animals

Satisfactory method validations for analytical methods on ruminant commodities were completed by EPA (PP#2F2728, Mark Law, 4/19/83 and M. Kovacs, 5/24/83). The method validations were conducted on the following three methods:

Rhone-Poulenc Method #159: Determination of Hydroxylated Iprodione Metabolites in Cow Milk by Electron Capture Gas Chromatography

ADC #623-A: Analytical Method for Determination of Iprodione and its Nonhydroxylated Metabolites in Bovine Milk

ADC #623-B: Analytical Method for Determination of Iprodione and its Nonhydroxylated Metabolites in Bovine Tissue.

The petitioner has indicated (PP#2F2728, Accession #070989) that method #159 determines residues containing the dichloroaminophenol moiety in milk. Methods #623A and #623B determine residues containing the dichloroaniline moiety in tissues and milk.

The methods were validated at 0.01 ppm for iprodione, RP32490 [3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide], and RP36114 [N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide] in milk and at 0.05 ppm for iprodione and RP32490 in liver. The methods were forwarded to FDA for inclusion in PAM II (M. Bradley, 2/27/87).

Rhone-Poulenc Analytical Method No. 164 was also submitted in PP#3F2964 (Accession #071951). Method No. 164 is an analytical method for determination of iprodione and its non-hydroxylated metabolites in chicken tissues and eggs by electron capture gas chromatography.

As part of a storage stability study (PP#2F2728, Accession #071424, ASD #83/009, dated 2/23/83), Rhone-Poulenc analyzed radioactive samples of cow milk and goat liver from the animal metabolism studies. Total radioactivity in milk and liver was determined by oxidative combustion. Milk was analyzed by method #623-A for iprodione and non-hydroxylated metabolites and by method No. 159 for hydroxylated metabolites. Liver was analyzed by method #623-B for iprodione and non-hydroxylated metabolites. Results before storage were as follows:

commodity	oxidative combustion	#623-A/B	#159
milk	0.432 ppm	0.11 ppm	0.108 ppm
liver	7.04 ppm	4.25 ppm	-----

CBRS later determined (List B Inventory, R. Perfetti, 8/6/90 review of MRID #00106082 from PP#2F2728, method 159 on milk and method 164 on milk and tissue) that "methods for residue analysis in cow tissue and milk are not suitable for tolerance enforcement for several reasons: use of hazardous materials (benzene, diazomethane), low recoveries (especially RP-36114), much use of internal standards to correct for low recoveries, and the lack of a confirmatory method".

Additional animal analytical data were required in the Phase IV Review (C. Olinger, 3/15/91) as follows:

"The registrant must submit data collection and regulatory analytical method(s) for the determination of iprodione, its

isomer, and its metabolites in/on animal commodities. If new metabolites (which require regulation) are found in the new animal metabolism studies, then analytical method(s) must be developed for them as well. The tissues from the metabolism study must be tested using the data collection method(s) and enforcement analytical method(s), including methods which have been previously used to generate residue data. Any regulatory methods submitted will require an independent method validation as described in PR Notice 88-5 (July 15, 1988). The registrant must provide justification for the use of hazardous reagents such as diazomethane or benzene in any regulatory analytical method."

CBTS notes that the method for eggs has not undergone an EPA method validation. To support other uses involving higher proposed tolerances/higher secondary residues in animal commodities, a method for eggs which determines all the residues of concern should undergo independent laboratory validation and an EPA lab validation.

Analytical reference standards and Material Safety Data Sheets are available for iprodione, its isomer RP30228, and its metabolite RP32490 from the USEPA Chemical Standards Repository, RTP, NC as verified by a telephone conversation with P. Beyer on 4/21/93 (Section 18, CBTS #11726, D. Davis, 4/26/93). An analytical reference standard and Material Safety Data Sheet for the animal metabolite N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide (RP36114) are not available at the repository and should be provided by the petitioner.

Conclusion

Adequate analytical methods are available for animal commodities resulting from the proposed use on cotton since secondary residues in animal commodities resulting from the proposed use on cotton are expected to be nondetectable (ie. <0.01 ppm in milk and <0.05 ppm in other animal commodities).

For other uses involving higher proposed tolerances/higher secondary residues in animal commodities, the petitioner should address the issues raised in the List B Inventory and the Phase 4 review.

For other uses involving higher proposed tolerances/higher secondary residues in animal commodities, an independent laboratory validation and an EPA laboratory validation of a method for analysis of the residues of concern on eggs would be needed.

Analytical reference standards and Material Safety Data Sheets are available for iprodione, its isomer RP30228, and its metabolite RP32490 from the USEPA Chemical Standards Repository, RTP, NC.

An analytical reference standard and Material Safety Data Sheet for the animal metabolite N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide (RP36114) are not available at the repository and should be provided by the petitioner.

Multiresidue Methods

Additional multiresidue methods data were required in the Phase IV Review (C. Olinger, 3/15/91) as follows:

> "Multiresidue data are available for iprodione and its isomer. Data are required for the regulated metabolite 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide" (RP32490) through Multiresidue Protocols A, C, D, and E.
> "If method validations of the multiresidue methods are found to be necessary, representative plant matrices must be tested."
>
> "The iprodione metabolite N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide must be tested through multiresidue Protocols B, C, D, and E. If method validations of the multiresidue methods are found to be necessary, representative animal matrices must be tested."

Conclusion

The metabolites 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide (RP32490) and N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide (RP36114) must be tested through the appropriate multiresidue protocols.

Storage Stability

Cottonseed

No storage stability data were submitted with this petition. Previously reviewed storage stability data on cottonseed spiked at a level of 1.0 ppm indicated that residues of the isomer (RP30228) and the metabolite (RP32490) were stable during 3 months of frozen storage but that the parent decreased by 30-35% (PP#1G3998, J. Garbus, 6/8/92).

Conclusion

Adequate storage stability data are available for iprodione, its isomer RP30228, and its metabolite RP32490 on cottonseed. Residues of RP30228 and RP32490 were stable during 3 months of frozen storage. Iprodione per se decreased by 35% during 3 months frozen storage.

Animal Commodities

Storage stability in milk and liver (PP#2F2728, Accession #071424, MRID #00131418) were discussed in the Phase IV Review (C. Olinger, 3/15/91):

> "Milk samples were analyzed for the parent, its isomer and both the hydroxylated and non-hydroxylated metabolites. A determination for the hydroxylated metabolite was not made for the liver samples. Iprodione and the non-hydroxylated metabolites appear to be stable for 22 months in milk and 13 months in liver. The hydroxylated metabolite appears to be stable in milk for 13 months."

The analytical methods used were Rhone-Poulenc Method #159, ADC #623-A and ADC #623-B.

As stated in "Pesticide Reregistration Rejection Rate Analysis Residue Chemistry, Follow-up Guidance for Generating Storage Stability Data" (EPA 737-R-93-001, February 1993), the representative animal commodities to be examined for storage stability are "muscle (cattle or poultry), liver (cattle or poultry), milk, and eggs. If residues are stable in these matrices, analyses of other tissues (fat, kidney) will not be needed."

Conclusion

Iprodione and the non-hydroxylated metabolites appear to be stable for 22 months in milk and 13 months in liver. The hydroxylated metabolite appears to be stable in milk for 13 months.

For other uses involving higher proposed tolerances/higher secondary residues in animal commodities, storage stability data for the hydroxylated metabolite in liver and for all the residues of concern in muscle (cattle or poultry) and eggs would be needed. Storage conditions must reflect the storage conditions of the treated samples with respect to temperature, length of storage, containers, lighting, etc. As stated in "Pesticide Reregistration Rejection Rate Analysis Residue Chemistry, Follow-up Guidance for Generating Storage Stability Data" (EPA 737-R-93-001, February 1993), "the samples used in the storage stability study could either be from crops (or animals) that have been treated with pesticides in the field or from the spiking of control (untreated) samples with known amounts of each analyte".

Residue Data

No additional residue data for iprodione were submitted with this petition. The petitioner has referenced previously reviewed residue data (PP#1G3998, J. Garbus, 6/8/92 and 12/15/92). The residue data reflected application of a flowable formulation at 10

sites in the six states of AR (2), GA (1), LA (1), OK (1), TX (3), and MS (2). The application rate was 1.0 ounce Rovral® 4 Flowable per 1000 row feet (0.42 oz ai/1000 row feet) in 9 of the 10 trials and 1.67 ounce Rovral® 4 Flowable per 1000 row feet (0.70 oz ai per 1000 row feet) in the 10th trial. (The rate of 0.42 oz iprodione ai/1000 row feet is 1.7-3.4X the proposed use rate of Start 15G, which is 2.5-5.0 oz Start 15G/1000 row ft or 0.125-0.25 oz iprodione ai/1000 row ft). Cotton was harvested at PHI's of 129 to 169 days. The samples were frozen immediately after sampling. The time from sampling to analysis ranged from 17 to 85 days. Residues in cottonseed were <0.05 ppm for iprodione, its isomer, and its metabolite except for one value of 0.05 ppm for the parent and one value of 0.06 ppm for the metabolite.

The 6/8/92 memo stated that for a permanent tolerance, "additional crop field trials will be required as well as data for cotton forage unless an appropriate label restriction is imposed against the latter. An appropriate enforcement method also will need to be proposed, possibly with independent laboratory validation."

Concerning the need for residue data on cotton forage unless an appropriate label restriction is imposed, the proposed label includes a label restriction against grazing or feeding of cotton forage to livestock so that no residue data on cotton forage are needed.

Concerning the analytical method, CBTS (PP#1G3998, J. Garbus, 12/15/92) has concluded that Rhone-Poulenc SOP 90277 is essentially the same as RP Method 151. RP Method 151 has been submitted to FDA for inclusion in PAM II. Therefore, additional method validations will not be needed for Rhone-Poulenc SOP 90277.

Additional residue data are needed from the major cotton producing state of CA, based on cotton production areas listed in Agricultural Statistics, 1990. At least one study should be conducted in CA. This study could be a bridging study.

Bridging data from the flowable formulation to the granular formulation are needed. "Bridging data" refers to residue data from applications of the flowable formulation and granular formulation on side-by-side plots, using the same pre-harvest interval and rate of application.

For any new crop field trial studies, toluene should be substituted for benzene when the regulatory method is used for the determination of iprodione and its degradates in the samples. The concurrent fortification data from these studies should be submitted as validation of the substitution of toluene for benzene in the regulatory method.

Conclusion

Additional residue data are needed from the major cotton producing state of CA, based on cotton production areas listed in Agricultural Statistics, 1990. At least one study should be conducted in CA. This study could be a bridging study.

Bridging data from the flowable formulation to the granular formulation are needed. "Bridging data" refers to residue data from applications of the flowable formulation and granular formulation on side-by-side plots, using the same pre-harvest interval and rate of application.

For any new crop field trial studies, toluene should be substituted for benzene when the regulatory method is used for the determination of iprodione and its degradates in the samples. The concurrent fortification data from these studies should be submitted as validation of the substitution of toluene for benzene in the regulatory method.

Processing Studies

No additional processing studies have been submitted with this petition. Processing studies were previously reviewed (PP#1G3998, J. Garbus, 6/8/92). Cottonseed was treated at the rate of 5.0 oz Rovral® 4 Flowable per 1000 row ft (2.1 oz iprodione ai per 1000 row ft or 8.4 X the proposed use rate). (The maximum theoretical concentration factor for cottonseed is 6X, as stated in "Pesticide Reregistration Rejection Rate Analysis, Residue Chemistry", EPA 737-R-93-001). Cottonseed was harvested 135 days after treatment and processed into hulls, meal, crude oil, refined oil, and soapstock. Samples were analyzed using Rhone-Poulenc method #SOP 90277, which determines iprodione, RP30228, and RP32490. The cottonseed was processed 8-9 days after sampling. All of the cottonseed fractions were analyzed within 21 days after processing. No residues above the limit of detection of 0.05 ppm were found in/on the cottonseed or processed fractions.

Conclusion

An adequate processing study for iprodione on cottonseed has been submitted. Residues of iprodione, RP30228, and RP32490 do not concentrate in processing fractions.

Rotational Crops

No rotational crop data were submitted with this petition. The Environmental Fate and Ground Water Branch (EFGWB), which previously reviewed some rotational crop studies, rejected the studies primarily due to the absence of analyses for residues in soil.

Rhone-Poulenc indicated in a meeting on March 2, 1993 with RD, CBTS, and CBRS that they will submit a letter which addresses the deficiencies in the previously submitted studies. The petitioner also indicated that one confined study is in progress for submission to EPA in 1994.

CBTS/CBRS gave Rhone-Poulenc a copy of its recent guidance for rotational crop studies in the meeting on March 2, 1993. CBTS suggested that the petitioner submit all relevant rotational crop studies as a package for CBTS review when the on-going confined study is completed. Based on the data summaries, CBTS indicated in the meeting that rotational crop tolerances will probably be required for the permanent tolerance.

Conclusion

The available rotational crop data are not adequate. The petitioner should submit all relevant rotational crop studies as a package for CBTS review when the on-going confined study is completed. Based on data summaries, CBTS has indicated that rotational crop tolerances will probably be required for the permanent tolerance.

Meat, Milk, Poultry, and Eggs

Use on cottonseed involves ruminant and poultry feed items. The seed can be 25% of the beef cattle diet and 20% of the dairy cattle diet. The meal can be 10% of the poultry diet.

A dairy cattle feeding study at 5, 15, 50 and 200 ppm in the diet has previously been reviewed (PP#2F2728, M. Kovacs, 10/25/82). Residues in dairy cattle reflecting a 5 ppm feeding level were <0.05 ppm in muscle, kidney, fat, and liver and <0.01 ppm in milk.

A poultry feeding study at 2, 20, and 100 ppm in the diet was discussed in PP#3F2964 (R.W. Cook, 2/21/84). Residues in poultry reflecting a 2 ppm feeding level were <0.05 ppm in muscle, 0.18 ppm in fat, 0.137 ppm in eggs, 0.61 ppm in liver, and 0.33 ppm in kidney.

The dietary contribution from cottonseed would be $\leq$0.025 ppm, which is negligible compared to the dietary contribution from other animal feeds with established tolerances.

In the Phase IV Review (C. Olinger, 3/15/91), CBRS indicated that the poultry feeding study is not adequate because residues of the hydroxylated metabolite (which is regulated) were not determined in the tissues and eggs, and because the analytical method was not adequately validated. CBRS indicated that the capability of the method to extract all the residues of concern using poultry tissues and eggs from radioactive metabolism samples must be demonstrated. CBRS (L. Cheng, 5/29/92, CBRS #9664 and

#9665, DP Barcode D175846 and D175865) reviewed a submission which was a response to the 3/15/91 memo. Recovery data for iprodione and the metabolite RP32490 in fortified eggs, liver, muscle, and fat were reported. CBRS (L. Cheng, 5/29/92) indicated that no residue or recovery data on RP36114 in poultry and eggs had been provided, and that a new poultry feeding study as discussed in the Data Call In must be submitted.

In the Phase IV Review (C. Olinger, 3/15/91), CBRS also indicated that the ruminant feeding study was not adequate because recovery data were not reported. CBRS (L. Cheng, 5/29/92, CBRS #9664 and #9665, DP Barcode D175846 and D175865) reviewed a submission which was a response to the 3/15/91 memo. Recovery data were submitted for iprodione and its metabolite RP32490 in kidney, muscle, fat, liver, and milk and for RP36114 in milk. Residues found by the analytical methods and by LSC using radioactive goat and milk tissues from the metabolism study were also compared. CBRS (L. Cheng, 5/29/92) indicated that "the registrant has submitted sufficient method validation data for the cow feeding study for our Phase V review. A determination of the adequacy of this study and thus whether a new cow feeding study is required will be made when the review is completed." CBTS notes that recovery data were not reported for the isomer RP30228.

Conclusion

The established tolerances for iprodione in meat, milk, poultry, and eggs [40 CFR 180.399(b)] are adequate to cover secondary residues in animal commodities resulting from the proposed use on cotton.

For other uses involving higher dietary contributions in the animal diet, the issues regarding the animal feeding studies which were raised in the Phase IV review (C. Olinger, 3/15/91) and subsequently discussed in the List B File memo (L. Cheng, 5/29/92, CBRS #9664 and #9665) would have to be addressed.

Other

An International Residue Limit (IRL) Status sheet was attached to the 3/17/93 review of PP#1G3998 (M. Peters). There are no Codex, Canadian, or Mexican tolerances for iprodione on cottonseed. Therefore, no compatibility questions exist for cottonseed with respect to Codex.

No "CBTS Action Study Acceptability" form is attached to this review since no data were submitted with this petition.

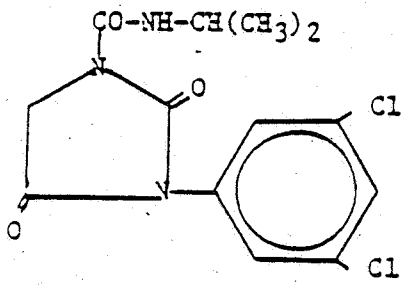
The Section F which proposes a permanent tolerance contains differences in nomenclature for the parent and metabolites compared to 40 CFR 180.399. This review uses the nomenclature in 40 CFR

180.399. The petitioner should revise the Section F to be consistent with the 40 CFR 180.399.

Attachment 1: Structures and code numbers of the chemicals which are named in 40 CFR 180.399 as residues of concern

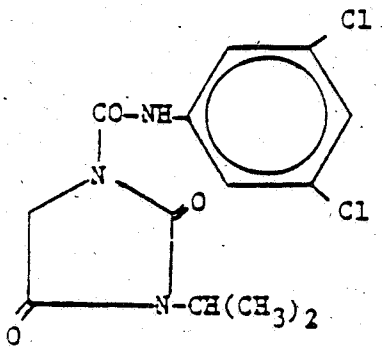
cc with Attachment 1: RF, SF, Circu., N. Dodd (CBTS), E. Haeberer (CBTS), PP#2F4111, PM #21, PM #22, List B File

RDI:E. Haeberer:6/23/93:R. Loranger:6/23/93
H7509C:CM#2:Rm804F:N. Dodd:nd:6/24/93



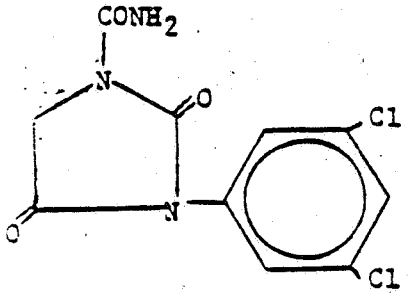
RP 26019

3-(3,5-dichlorophenyl)-N-(1-methyl-ethyl)-2,4-dioxo-1-imidazolidine-carboxamide



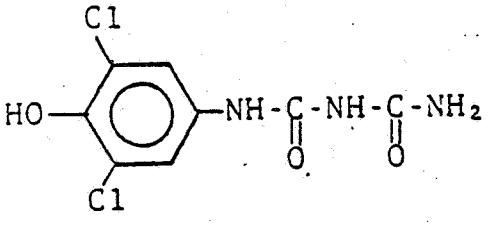
RP 30228

3-(1-methylethyl)-N-(3,5-dichloro-phenyl)-2,4-dioxo-1-imidazolidine-carboxamide



RP 32490

3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide



RP 36114

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