12-31-91 RF

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

DEC 31 1991

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Memorandum:

Subject: Addendum to 92-NC-0003, Iprodione on Apples

From: Francis B. Suhre, Section Head
Special Review Section II
Chemistry Branch II Reregistration Support
Health Effects Division (H7509C)

Thru: Edward Zager, Chief
Chemistry Branch II Reregistration Support
Health Effects Division (H7509C)

To: Susan Stanton, PM-41
Emergency Response and Minor Use Section
Registration Support Branch
Registration Division (H7505C)

Registration Division (RD) has requested clarification of conclusion #3 (92-NC-0003, J. Abbotts 12/23/91), restated below:

> 3. Combined residues of iprodione are not likely to exceed established tolerances in meat, meat byproducts other than kidney, milk, poultry, and eggs as a result of this Section 18 proposed use. Combined residues of iprodione in fat and kidney of beef cattle may slightly exceed the established tolerances (0.5 and 3.0 ppm, respectively) if additional feed items containing tolerance level residues of iprodione are fed to cattle consuming dried apples treated in accordance with this Section 18 proposed use.

The maximum dietary burden to cattle from this Section 18 use is estimated to be 138 ppm for beef cattle and 69 ppm for dairy cattle.

The maximum dietary burden to beef cattle, considering tolerance level residues of iprodione in/on additional feed items for which uses are registered, could reach 210 ppm. Based on a hypothetical diet of 50% dried apple pomace (138 ppm), 20% peanut vines (30 ppm), 25% peanut hay (38 ppm), and 5% bean vines (4.5 ppm).

A livestock feeding study in which cattle were dosed at 15, 50, and 200 ppm iprodione, indicates that a dietary burden of 210 ppm may

result in iprodione residues of 0.55 ppm in beef fat and 3.01 ppm in beef kidney.

North Carolina accounts for ca. 4.0% of the total U.S. apple production and ca. 0.4% of the number of beef cattle slaughtered in the U.S. (Agricultural Statistics, 1988).

Conclusions (Addendum to 92-NC-0003, J. Abbotts 12/23/91):

1. It is unlikely that the established tolerances for kidney (3.0 ppm) and fat (0.5 ppm) of cattle will be exceeded as a result of this proposed Section 18 because of the conservative nature of the residue estimate, i.e. :

a. Residue estimates for apples were translated from field trials on peaches, reflecting one more application and a shorter PHI from that proposed by this Section 18.

b. Iprodione residues in or on dry apple pomace were derived by utilizing a theoretical concentration factor of 25X (4 lbs dry pomace per 100 lbs of apples).

c. A hypothetical livestock diet consisting of dry apple pomace, peanut hay, peanut vines, and bean hay is very unlikely.

2. DRES should note that North Carolina accounts for ca. 4.0% of the total U.S. apple production. And that North Carolina accounts for ca. 0.4% of the beef cattle slaughtered in the U.S.

Recommendation (Addendum to 92-NC-0003, J. Abbotts, 12/23/91)

Toxicological considerations permitting, CBRS has no objection to this Section 18 exemption. An agreement should be made with FDA regarding the legal status of treated apples, apple processed commodities, and animal commodities, in commerce.

cc:Circ, Abbotts, SACB (E. Saito), Iprodione Section 18 file, SF, RF, PIB/FOD (Furlow)
RDI: EZ:12/31/91
H7509C:CBIIRS:RM810

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

DEC 23 1991

MEMORANDUM:

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: 92-NC-0003. Section 18 Specific Exemption.
Iprodione (Rovral, EPA Reg. Nos. 264-453 and 264-482)
in or on Apples.
No MRID No. DEB No. 9004. DP Barcode No. D171948.

FROM: John Abbotts, Chemist
Special Review Section II
Chemistry Branch II - Reregistration Support
Health Effects Division [H7509C]

THRU: Francis B. Suhre, Section Head
Special Review Section II
Chemistry Branch II - Reregistration Support
Health Effects Division [H7509C]

TO: Susan Stanton, PM Team 41
Emergency Response and Minor Use Section
Registration Support Branch
Registration Division [H7505C]

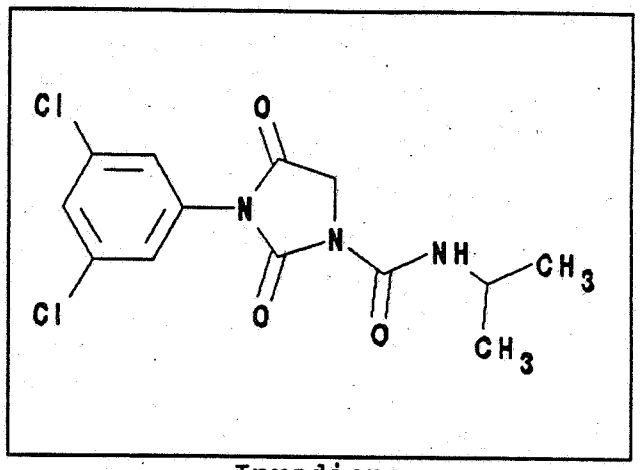
and

Toxicology Branch
Health Effects Division [H7509C]

The North Carolina Department of Agriculture has requested a Section 18 specific exemption for the use of the fungicide Rovral® to control Alternaria mali on apples. The active ingredient is iprodione, 3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide. The request is to use Rhone-Poulenc AG Company products Rovral 50WP, EPA Reg. No. 264-453, and Rovral 4F, EPA Reg. No. 264-482. Up to 6000 acres of apple orchards may be treated. At the maximum use rate on the maximum area treated, up to 18,000 lb ai may be used. The assignment instructions are to estimate residues expected from this proposed use.

Tolerances are established for the combined residues of iprodione, 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 numerous plant commodities, food commodities, and feed commodities, at levels ranging from 0.1 ppm to 300 ppm

(40 CFR 180.399(a), 185.3750, 186.3750). Tolerances are established for the combined residues of iprodione, its isomer, and its metabolites 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide and N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide, all expressed as iprodione equivalents, in or on animal commodities, ranging from 0.5 ppm to 3.0 ppm (40 CFR 180.399(b)). Tolerances have not been established on apples, and no petition is outstanding for a tolerance on apples. Iprodione is a List B Chemical; Phase 4 Review was completed 3/15/91.



Iprodione

Proposed use would allow the application of Rovral 50WP or Rovral 4F at 0.5 to 1.0 lb ai/acre per application. Application will be with an airblast sprayer using 100 to 400 gal of water per acre. Three applications per year will be permitted. The first application will be made during the period 1 June to 15 June; subsequent applications will be made at 2- to 3-week intervals. No applications will be allowed 30 days before harvest. The Section 18 exemption is requested for the period June 1 to September 22, 1992.

Residues of concern. Phase 4 review concluded that similar metabolism on three dissimilar crops has been demonstrated and no further data are required for the purposes of Phase 5 review. Most of the residue was iprodione, but its isomer, two metabolites, and the isomer of one metabolite were also identified in plant metabolism studies. Animal metabolism studies are considered adequate for determination of the metabolites of interest. (Iprodione List B File, C.L. Olinger, 3/15/91) For the purposes of this Section 18 request only, residues of concern are those for which tolerances are presently established: Iprodione, its isomer, and its metabolite 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide for plant commodities; and iprodione, its isomer, and its metabolites 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide and N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide for animal commodities.

Analytical method. An analytical method for plant commodities has been validated by EPA laboratories and published in the Pesticides Analytical Manual, Volume II, and is adequate for enforcement purposes. Residues are extracted from crop samples with acetone. The sample extract is cleaned up by partitioning

with methylene chloride and by column chromatography on Florisil. Iprodione and its isomer are eluted with ethyl acetate:methylene chloride (3:97) and collected as Fraction 1. The dichlorophenyl metabolite is eluted with ethyl acetate:methylene chloride (1:1) and collected as Fraction 2. The three compounds are determined individually on two different columns by GLC with electron capture detection.

Analytical methods are also available for animal commodities. These are Rhone-Poulenc Method 159 for hydroxylated iprodione metabolites in milk, ADC Project 623-A for iprodione and its non-hydroxylated metabolites in milk, and ADC Project 623-B for iprodione and its non-hydroxylated metabolites in bovine tissues. The hydroxylated metabolite is extracted with acetone. Samples are cleaned up using aluminum sulfate precipitation and hexane/acetonitrile partition. Conjugated metabolites are released by mild acid hydrolysis. The hydroxylated metabolites are converted to a common moiety, 4-methoxy-3,5-dichloroaniline, by methylation and basic hydrolysis. The aniline compound is then derivatized to the heptafluorobutyrate. The sample is cleaned up with a Florisil column, and determination is by gas chromatography using electron capture detection.

Iprodione and nonhydroxylated metabolites are extracted with acetone. Samples are cleaned up using aluminum sulfate precipitation and hexane/acetonitrile partition. Parent and metabolites are converted to a common moiety, 3,5-dichloroaniline, by basic hydrolysis. The aniline is derivatized to the heptafluorobutyrate, cleaned up on a Florisil column, and determination is by gas chromatography using electron capture detection. These methods have been found to be adequate for enforcement purposes (PP 2F2728, M.F. Kovacs, 5/24/83); and have been submitted to FDA for Publication in PAM, Volume II (M. Bradley, 2/27/87).

Residue data. The North Carolina Department of Agriculture reported that no residue data were available for iprodione on apples in the U.S. The Department submitted residue data from field trials in Japan and France. The highest residues reported are 6.5 ppm iprodione at an application rate of 5 kg/ha (4.4 lb ai/A) in Japan. These data are not acceptable for the purposes of this Section 18 request. Data are submitted in a summary table and no further explanation is given of the data or the field trials which generated the data. Ten treatments are indicated for the trial with the highest residues; it is not clear from the table whether 4.4 lb ai/A represents the amount applied with each treatment, or the total amount applied. Since Codex maximum residue levels (MRLs) are established for iprodione parent only, it is not clear if the residue data are for parent only or for parent plus metabolites.

Applicant North Carolina notes that apples, pears, and peaches have comparable Codex MRLs for iprodione, 10 mg/kg. No residue data are available for pears, a member with apples of the pome fruit crop group. For the purposes of this Section 18 request only, residue data from peaches will be translated for apples. Residue data for peaches, including data from field trials in NC, were submitted in support of PP 2F2596. Data were provided for four applications by ground spray at 1.0 lb ai/A, and a PHI of 0 days. This represents one more application and a shorter PHI than the proposed use for apples, so translating these residue data from peaches is not likely to underestimate residues on apples from this Section 18 proposed use. Data were provided for iprodione (RP26019), its isomer (RP30228), and its dichlorophenyl metabolite (RP32490), and are summarized in Table 1. These data were generated by Rhone-Poulenc AG:

Table 1. Summary of Field Trial Data, Iprodione on Peaches.

Location	Iprodione residues, ppm			
	RP26019	RP30228	RP32490	Combined
CA	1.65	0.09	<0.05	1.79
CA	2.69	0.10	<0.05	2.84
NC	8.10	0.17	<0.05	8.32
NC	9.57	0.23	<0.05	9.85
SC	10.24	0.16	<0.05	10.45

Table notes:
Applications in all cases were 4 x 1.0 lb ai/A by ground spray; PHI in all cases was 0 days.

Review of these data, and other residue data for up to 7 applications, concluded that provided the proposed use limited the number of applications to 5, combined iprodione residues were not likely to exceed 20 ppm. Storage stability data were adequate for peaches, and the analytical method used was that which is presently published in PAM Vol. II. (PP 2F2596, R.B. Perfetti, 5/13/82). Based on the data in Table 1, combined residues of iprodione resulting from this Section 18 proposed use are not likely to exceed 11 ppm in or on apples.

Processing data. No apple processing data were submitted with this Section 18 request. Information in the CBRS Apple Cultural Practices File indicates that 100 lb of apples can be processed to 80 lb cider and 20 lb wet pomace, which is dried to 4 lb dry pomace, of average moisture content of 10%. This information allows an estimate of maximum residues in apple processed commodities. If iprodione were to concentrate in apple juice,

the concentration factor would be 1.25, and combined residues in juice would not be expected to exceed 14 ppm. If iprodione were to concentrate instead in pomace, combined residues would not be expected to exceed 55 ppm in wet pomace or 275 ppm in dry pomace.

Meat, milk, poultry, and eggs. Dehydrated apple pomace can represent up to 50 percent of the diet for beef cattle, 25 percent for dairy cattle, 5 percent for turkeys and broiler poultry, and is not used in the diet for laying hens and swine. Dehydrated apple pomace contains a wet weight of about 11 percent, so potential residues are likely to be the same as dry pomace, 275 ppm. The maximum dietary burden of combined iprodione residues from this Section 18 use would then be 138 ppm for beef cattle, 69 ppm for dairy cattle, and 13.75 ppm for turkeys and broilers. Other commodities which could contribute significant iprodione dietary burdens in cattle and poultry are indicated in Table 2:

Table 2. Iprodione Feed Commodities.

Commodity	Tolerance, ppm	Dietary burden, (%) x tolerance = burden, ppm in:		
		Beef cattle	Dairy cattle	Turkeys/ Broilers
Beans, vine hay	90	(20%)=18	(35%)=31.5	NU
Peanut forage (vines)	150	(20%)=30	(40%)=60	NU
Peanut hay	150	(25%)=38	(60%)=90	NU
Grapes, pumace, dried	225	(30%)=68	(20%)=45	(5%)=11.3
Raisins, waste	300	(10%)=30	(10%)=30	NU
Apple pumace, dry (This Section 18)	275 (estimated)	(50%)=138	(25%)=69	(5%)=13.75

Of the commodities in Table 2, grapes and raisins are not likely to be part of the local feed diet in NC. Ensminger and Olentine, Feeds and Nutrition, 1978, identify three major categories for beef and dairy cattle feed: 1) grains, byproduct feeds, roots and

tubers; 2) protein supplements; and 3) dry forages and silages. Apple pumace falls into category 1, bean and legume hay fall into category 3. In the event that beef cattle were fed the rather unlikely diet of 50% dry apple pumace (138 ppm), 20% peanut vines (30 ppm), 25% peanut hay (38 ppm), and 5% bean vines (4.5 ppm), the dietary burden could reach 210 ppm. If dairy cattle were fed a diet of 60% peanut hay (90 ppm), 25% dry apple pumace (69 ppm), and 15% peanut vines (22 ppm), the dietary burden could reach 191 ppm.

Animal feeding studies have been submitted in support of previous petitions. A cattle feeding study was submitted in support of petition PP 2F2728. Lactating cows were fed iprodione at 5, 15, 50, and 200 ppm in the diet for 28 days. Maximum combined residues of iprodione in cattle tissues and milk at the three higher feeding levels are summarized in Table 3 (PP 2F2728, M.F. Kovacs, 10/25/82):

Table 3. Summary of Iprodione Residues in Cattle Feeding Study.

Sample	Combined residues, ppm, at feeding levels of:			Established Tolerance, ppm
	15 ppm	50 ppm	200 ppm	
Meat	<0.05	0.07	0.13	0.5
Kidney	0.16	0.80	2.87	3.0
Fat	0.05	0.21	0.52	0.5
Liver	0.13	0.66	1.95	3.0
Milk	0.10	0.20	0.39	0.5

The maximum estimated dietary burden from this Section 18 proposed use would be 191 ppm for dairy cattle, and 210 ppm for beef cattle. Combined iprodione residues would not be expected to exceed established tolerances for meat, meat byproducts other than kidney, and milk. Combined iprodione residues could slightly exceed tolerances in kidney and fat. The diets that could cause over-tolerance residues seem unlikely.

A poultry feeding study was submitted in support of petition PP 4F3129. Hens were fed iprodione at 2, 20, and 100 ppm in the diet for 28 days. The combined iprodione residues recovered from poultry tissues and eggs are summarized in Table 4. Methods used to determine the residues in animal tissues from the feeding studies in cattle and poultry were the same ones which have been approved for publication in PAM II. Storage stability data were adequate for animal tissues. (PP 4F3129, R.W. Cook, 2/15/85, RCB Nos. 225, 226):

Table 4. Summary, Iprodione Residues in Poultry Feeding Study.

Sample	Combined residues, ppm, at feeding levels of:			Established Tolerance, ppm
	2 ppm	20 ppm	100 ppm	
Meat	<0.05	0.32	1.68	1.0
Fat	0.18	2.57	8.62	3.5
Kidney	0.33	2.30	6.87	1.0 (MBYP)
Liver	0.61	4.10	13.40	5.0
Eggs	0.14	0.75	2.17	1.5

The maximum dietary burden of combined residues of iprodione for turkey and broilers from this Section 18 proposed use is 13.75 ppm. This dietary burden is the result of conservative assumptions: Residue data were translated to apples from peaches, which received four applications with a PHI of 0 days, compared to the proposed use of three applications with a 30 day PHI. In addition, maximum concentration of iprodione in apple processing fractions was assumed. Recognizing the conservative nature of these assumptions, and applying linear regression analysis to the poultry feeding data, CBRS concludes that combined iprodione residues in poultry tissues and eggs are not likely to exceeded established tolerances as a result of this Section 18 proposed use.

Conclusions

1a. For the purposes of this Section 18 request only, residues of concern in plant commodities are those for which tolerances are presently established: iprodione, its isomer, and its metabolite
3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide.

1b. For the purposes of this Section 18 request only, residues of concern in animal commodities are those for which tolerances are presently established: iprodione, its isomer, and its metabolites
3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide and
N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide.

2a. The submitted residue data were not acceptable to support the proposed use. For the purposes of this Section 18 request only, residue data from peaches were translated to apples. Using the translated data, CBRS estimates that combined residues of iprodione resulting from this Section 18 proposed use are not likely to exceed 11 ppm in or on apples.

2b. No residue data were submitted on apple processed commodities. For the purposes of this Section 18 request only, combined residues of iprodione resulting from this Section 18 proposed use are not likely to exceed 14 ppm in apple juice, 55 ppm in wet apple pomace, or 275 ppm in dry apple pomace.

3. Combined residues of iprodione are not likely to exceed established tolerances in meat, meat byproducts other than kidney, milk, poultry, and eggs as a result of this Section 18 proposed use. (Combined residues of iprodione in fat and kidney of beef cattle may slightly exceed the established tolerances (0.5 and 3.0 ppm, respectively) if additional feed items containing tolerance level residues of iprodione are fed to cattle consuming dried apple pumace from apples treated in accordance with this Section 18 proposed use.) will be revised assume wor exceed tole

4. The method published in Pesticides Analytical Manual, Volume II, is adequate for enforcement purposes for combined residues of iprodione in plants. Rhone-Poulenc Method 159, ADC Project 623-A, and ADC Project 623-B are adequate for enforcement purposes for combined residues of iprodione in animal commodities.

5. Analytical reference standards are available from the Pesticides and Industrial Chemicals Repository at RTP, NC.

6. Residue data used to estimate expected residues were generated by laboratories of Rhone-Poulenc AG Company or Analytical Development Corporation (CO). No data from Craven Laboratories were used in estimating residues expected from this Section 18 proposed use.

Recommendation

Toxicological considerations permitting, and with the additional consideration that this proposed use may result in combined iprodione residues in kidney and fat which exceed established tolerances, CBRS has no objections to the issuance of this Section 18 exemption. An agreement should be made with FDA regarding the legal status of treated apples, apple processed commodities, and animal commodities, in commerce.

cc:Circ, Abbotts, SACB (E.Saito), Iprodione Section 18,
Iprodione SF, RF, PIB/FOD (C. Furlow)
RDI:FBSuhre:12/17/91:DFEdwards:12/18/91:EZager:12/20/91
H7509C:CBII-RS:JAbbotts:CM-2:Rm812A:305-6230:12/20/91