Vivian Prunier 6-28-96

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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

June 28, 1996

MEMORANDUM:

SUBJECT: Iprodione (109801), Reregistration Case No. 2335. Special Review, Peach Processing Data and Wine Anticipated Residues. Registrant Rhône-Poulenc. CBRS No. 17266, DP Barcode No. D226786, MRID 44020001.

FROM: John Abbotts, Chemist
Special Review Section I
Chemistry Branch II - Reregistration Support
Health Effects Division [7509C]

THRU: Andrew R. Rathman, Section Head
Special Review Section I
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TO: Christina Scheltema
Special Review and Registration Section
Risk Characterization and Analysis Branch
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Registrant Rhône-Poulenc Ag Company has submitted residue data on peach processing. Assignment instructions are to review the peach processing data and, if they are acceptable, to calculate new anticipated residues for canned peaches. Instructions are also to recalculate anticipated residues for wine to reflect information from FDA pertaining to one sample with a high residue level. SRRD requested Expedited Review. CBRS previously determined anticipated residues for iprodione for many commodities (CBRS 15099, 5/1/95, J. Abbotts). Conclusions and Recommendations below pertain only to this assignment.

Conclusions

1. The data in the present submission indicate that iprodione tolerance residues are considerably lower in peaches treated by the lye peeling process than in fresh peaches. However, base hydrolysis of residues could produce compounds that would not be detected as tolerance residues but which could still be of toxicological concern. Data are insufficient to indicate the distribution of tolerance residues between peel and pulp in fresh peaches, or to indicate the nature of the residue in pulp after processing.

2. If the Registrant were to provide convincing data that iprodione residues of concern were negligible in peaches peeled by lye, and if all processed peaches in the U.S. were peeled by lye, then estimated dietary risk from iprodione residues in peaches would be reduced by about 50%. To the extent that peaches are peeled by steam for U.S. consumption, the reduction in dietary risk would be less, or residue data on steam peeled peaches would be required.

3. FDA has advised that high residues reported in a single red wine monitoring sample were most likely due to a clerical error. We have therefore revised anticipated residues without this sample and determine combined iprodione residues, cancer risk, in wine of 0.128 ppm.

Recommendations

In accordance with Conclusion 1, we recommend no modification at this time in anticipated residues previously determined for peaches (CBRS 16521, 2/16/96, J. Abbotts).

To provide convincing evidence that iprodione residues are negligible in canned peaches, data are required on the distribution of tolerance residues between peel and pulp of fresh peaches, or on the nature of the residue in processed peaches. Data on tolerance residues can be generated using a registered formulation as the test substance; data on the nature of the residue should be generated using ^{14}C-iprodione, uniformly labeled in the phenyl ring. At its discretion, the Registrant could combine features of these two types of studies. For example, with the radiolabel study, total radioactive residues in peel and in pulp of fresh harvest peaches could be determined before the processing step. Additional considerations for conducting these studies are described in the Residue Data Needed section of this review. We advise that because of the factors described in Conclusion 2, providing further residue data pertinent to processed peaches may not have a dramatic effect on estimated dietary risk.

We recommend using the value in Conclusion 3 for anticipated residues in wine. Because this value is based on FDA monitoring data, % crop treated has already been taken into account. Therefore, if these revised anticipated residues are used as an input for a DRES run, a value of 100% crop treated should also be used. Anticipated residues are revised for wine only, and any changes in estimated dietary risk from this commodity should be proportional to changes in anticipated residues, provided other parameters have not changed from the previous DRES evaluation.

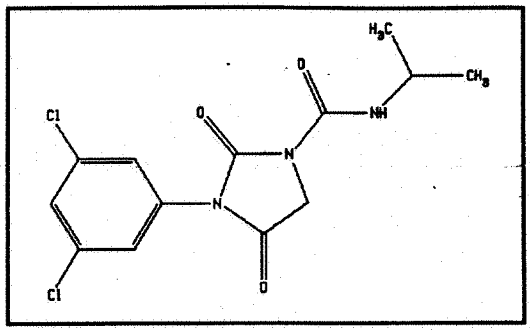
We recommend that a copy of this review be provided to the Registrant. We would be willing to discuss procedures for further studies on peaches if the Registrant desires to submit new residue data.

DETAILED CONSIDERATIONS

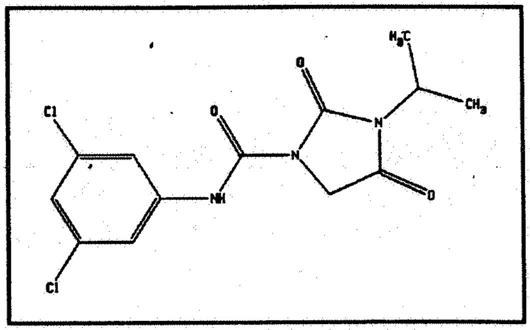
Background

Tolerances are established for the combined residues of the fungicide iprodione, 3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidine-carboxamide, its isomer, 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide, and its metabolite, 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide, in or on plant commodities, food commodities, and feed commodities (40 CFR 180.399(a) and (c), 185.3750, 186.3750). The isomer and metabolite are designated RP-30228 and RP-32490, respectively. Tolerances are established for combined residues of the same residues as for plant tolerances, plus the metabolite N-(3,5-dichloro-4-hydroxyphenyl)-ureido-carboxamide, all expressed as iprodione equivalents, in or on animal commodities (40 CFR 180.399(b)). The additional animal metabolite is designated RP-36114. Chemical structures of residues in tolerance expressions are given in Figure 1. Iprodione is a List B Chemical; Phase 4 Review was completed 3/15/91.

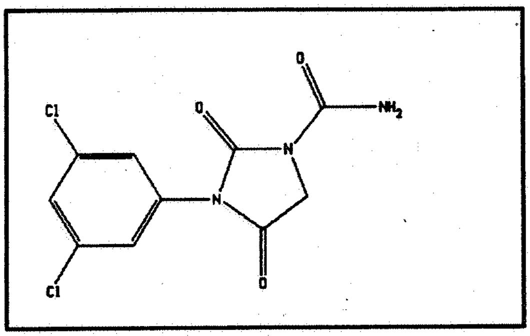
Figure 1. Iprodione Tolerance Residues:



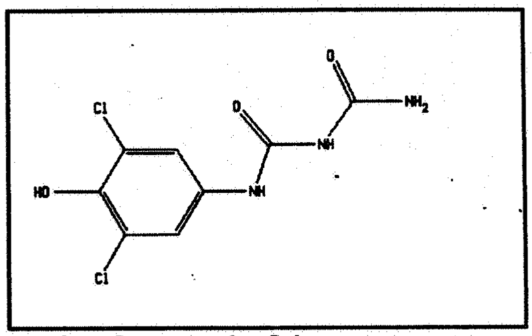
Parent



Isomer, RP-30228

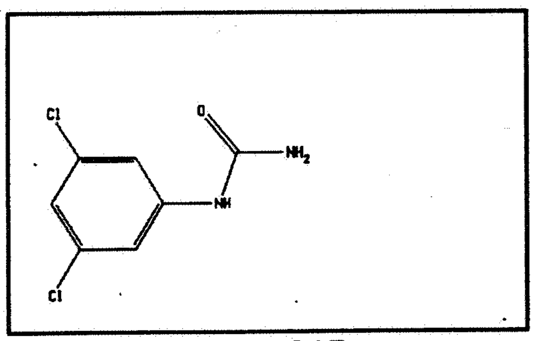


RP-32490

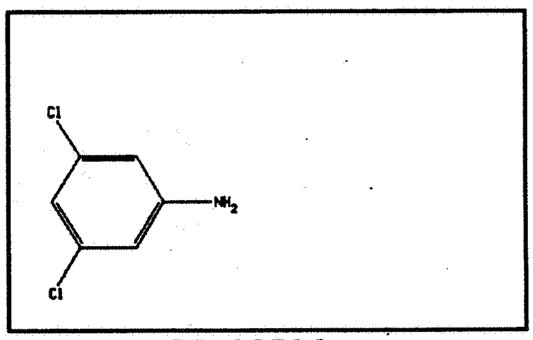


Animal metabolite RP-36114

Figure 2. Additional metabolites:



RP-44247



RP-32596,
3,5-dichloroaniline

CBRS previously determined anticipated residues for iprodione for many commodities; anticipated residues for peaches were based on FDA and FOODCONTAM monitoring data (CBRS 15099, 5/1/95, J. Abbotts). Anticipated residues for a few commodities, including peaches, were subsequently revised based on monitoring data from the USDA Pesticide Data Program (PDP); this resulted in higher anticipated residues in peaches (CBRS 16521, 2/16/96, J. Abbotts). Review of a dietary risk assessment submitted by Registrant Rhône-Poulenc noted that the Registrant used half the limit of quantitation for anticipated residues in canned peaches. However, this value was not well supported by residue data, and CBRS did not accept lower anticipated residues for the sub-category canned peaches. CBRS further noted that even if the Registrant's value for canned peaches were to be accepted, the Registrant's estimated dietary risk, cancer, from peaches alone would be close to 10^{-6}. (CBRS 16838, 2/15/96, J. Abbotts)

The Registrant subsequently submitted hydrolysis data to support the claim that the lye peeling process degrades iprodione residues in peaches. Review concluded that at pH 9, the most alkaline conditions for which data were reported, nearly all residues of parent were converted to the isomer RP-30228, which is also a tolerance residue (see Figure 1). These data by themselves did not support the idea that the lye peeling process degraded iprodione residues of concern in or on peaches. (Memo, 3/7/96, J. Abbotts). At a subsequent meeting with Agency personnel on April 12, 1996, Registrant representatives provided summary data on peach processed commodities, with an explanation that the data were generated before Agency requirements on Good Laboratory Practice Standards were in effect. CBRS advised that these data should be submitted for formal review. In response, the Registrant has provided the present submission:

Iprodione Residue Data for Whole Peaches, Skinned Peaches, and Peach Cannery Waste, Report ASD No. 84/071, Completion Date February 9, 1984, Rhône-Poulenc Ag Company (MRID 44020001).

Peach Processing Data

With the present submission, peach trees at two CA locations were sprayed with a 50% WP formulation, once at 7 days pre-harvest and once at 0 days pre-harvest. The rate was 2 x 1.0 lb ai/A, and 2 x 2.0 lb ai/A at one location. A portion of fresh fruit was saved for residue testing, and another portion was used for processing at a cannery pilot plant operated by Tech S Corporation. At the pilot plant, fruit was immersed in 1.5% caustic solution (not otherwise described) for 1.5 min at 190°F. Fruit was dipped in water for about 10 sec to cool, then peel was wiped from fruit by hand. Samples of cannery waste (peel sludge), skinned fruit, and fresh fruit were frozen and shipped to Morse Laboratories, Sacramento CA, for residue analysis.

Samples were analyzed for tolerance residues (Figure 1) according to Registrant Method No. 151. The method consists of extraction with organic solvents, gel permeation chromatography, clean up on a Florisil column, and analysis by gas chromatography with electron capture detection. The method was validated with fortified control samples for each individual residue. Residue data are summarized in Table 1:

Table 1. Peach processing residue data.

Sample	Rate, lb ai/A	Iprodione residues, ppm:			
		Parent	RP-30228	RP-32490	Total
Test 1:					
Whole fruit	2 x 1.0	0.86	≤0.05	≤0.05	≤0.96
Skinned fruit		≤0.05	≤0.05	≤0.05	≤0.15
Cannery waste		0.08	≤0.05	≤0.05	≤0.18
Test 2:					
Whole fruit	2 x 1.0	0.99	≤0.05	≤0.05	≤1.09
Skinned fruit		≤0.05	≤0.05	≤0.05	≤0.15
Cannery waste		≤0.05	0.15	≤0.05	≤0.25
Whole fruit	2 x 2.0	1.50	≤0.05	≤0.05	≤1.60
Skinned fruit		0.10	≤0.05	≤0.05	≤0.20
Cannery waste		0.21	0.92	≤0.05	≤1.18

Table notes: Both tests were in CA, at different locations. Pre-harvest interval was 0 days for all trials.

On behalf of the Registrant, Technical Assessment Systems, Inc., Washington, D.C., transmitted the following information on peach processing to CBRS by facsimile on March 8, 1996:

Peaches are washed upon arrival at the cannery through a series of revolving screens, soaking tanks, and high pressure sprays. Once the peaches have been graded by size, they are lye-peeled and the pits are removed mechanically. Typically, a 2% to 3% lye solution (although solutions up to 11% may be used) is used in conjunction with specified temperatures. The amount of time (usually 45 to 60 seconds) that the peach is exposed to the lye will depend on the concentration of the solution and the temperature. These factors are, in turn, dependent on the maturity of the fruit. Following the lye bath/spray, the peaches are thoroughly sprayed with cold water to completely remove the peel and any lye residue.

Freestone peaches may be peeled by steam. Depending on the size and maturity of the fruit, steaming for 1/2 to 2 minutes is sufficient to remove the peel.

Peeled peaches are placed into sterilized cans, which are then filled with syrup or juice. The filled cans are heated to boiling before being sealed. The cans are then cooled to prevent further cooking of the fruit.

CBRS Comments, Peach Processing

The data in the present submission indicate that iprodione tolerance residues are considerably lower in peaches treated by the lye peeling process than in fresh peaches. However, the alkaline hydrolysis data previously reviewed (see Background section) suggest the possibility that treating peaches with base could generate molecules other than the tolerance residues which would still be of toxicological concern.

Other data pertaining to treatment of iprodione residues in base reinforce this concern. A submission on confined rotational crops included data on hydrolysis of iprodione and its metabolites (CBRS 15422, 6/9/95, S.A. Knizner). Acid and base hydrolysis of iprodione resulted in the formation of RP-32490 and RP-44247. RP-44247 was also formed from hydrolysis of RP-32490. Review also noted that the Registrant has submitted an analytical method that converts iprodione tolerance residues to 3,5-dichloroaniline, RP-32596, through overnight hydrolysis in 3 N KOH at 100°C (Ibid.) (see Figure 2 for structures).

The present submission did not provide data on the distribution of tolerance residues between peach peel and pulp before processing. Moreover, the data in Table 1 do not allow calculations on a mass balance basis to determine that distribution. Information in the Cultural Practices file indicates that peel and pit combined represent about 12% of the total weight of a peach. Peel would be expected to represent a smaller portion of the peach than pit, but if iprodione residues were concentrated in the peel, then residues on a ppm basis should be at least an order of magnitude higher than residues in whole fruit. This is not seen in Table 1, which could be due to degradation of residues in the peels from treatment in base. The considerations above lead to the following comment:

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Conclusion 1: The data in the present submission indicate that iprodione tolerance residues are considerably lower in peaches treated by the lye peeling process than in fresh peaches. However, base hydrolysis of residues could produce compounds that would not be detected as tolerance residues but which could still be of toxicological concern. Data are insufficient to indicate the distribution of tolerance residues between peel and pulp in fresh peaches, or to indicate the nature of the residue in pulp after processing.

Recommendation: In accordance with Conclusion 1, we recommend no modification at this time in anticipated residues previously determined for peaches (CBRS 16521, 2/16/96, J. Abbotts).

Peach Utilization Data

Data on the production and utilization of peaches in the U.S. are contained in Agricultural Statistics, 1993, U.S. Department of Agriculture (USDA). For 1991, the last full year for which data were available, utilized production of peaches in the U.S. was 2,506 million pounds (2.5 billion pounds). Exports were 108,063 metric tons, or 238 million pounds. The publication Foreign Agricultural Trade of the United States, Calendar Year 1993 Supplement, USDA, reported for 1992 that U.S. imports of peaches were 53,701 metric tons, or 118 million pounds. Thus, domestic production represents the large majority of U.S. consumption of peaches.

Agricultural Statistics, 1993 reported for 1991 that fresh peaches utilized were 1,232 million pounds, or 49% of total utilized peaches. Processed peaches represented 51% of total utilized peaches, and canned peaches were 987 million pounds, or 39% of the total utilized. Freestone peaches produced and utilized in 1991 were 627 million pounds, 25% of total utilized. As noted above, Freestone peaches may be peeled by steam. The considerations above lead to the following comment:

Conclusion 2: If the Registrant were to provide convincing data that iprodione residues of concern were negligible in peaches peeled by lye, and if all processed peaches in the U.S. were peeled by lye, then estimated dietary risk from iprodione residues in peaches would be reduced by about 50%. To the extent that peaches are peeled by steam for U.S. consumption, the reduction in dietary risk would be less, or residue data on steam peeled peaches would be required.

Residue Data Needed

To provide convincing evidence that iprodione residues are negligible in canned peaches, data are required on the distribution of tolerance residues between peel and pulp of fresh peaches, or on the nature of the residue in processed peaches.

Data on tolerance residues can be generated using a registered formulation as the test substance; data on the nature of the residue should be generated using ^{14}C-iprodione, uniformly labeled in the phenyl ring. Because the parameters of concern are related to the relative distribution of residues between peel and pulp, geographical representation would not be necessary, and either study could be conducted in a greenhouse.

Iprodione should be applied at the maximum label conditions for foliar application, in effect before the interim risk reduction measures to which the Registrant recently agreed. Because the effects of the interim measures on residue levels cannot be definitively predicted, application should be at the previous conditions to maximize residues. For peaches, the previous maximum label conditions were 5 x 1.0 lb ai/A, with a 0 day PHI. Data on tolerance residues can be provided for peel and pulp. Care should be taken in peeling samples to minimize the portion of the pulp that is removed with peel.

Alternatively, or in addition to data on fresh peaches, the Registrant could provide nature of the residue data on processed peaches. Such a study should be conducted with ^{14}C-iprodione, applied at the previous maximum label conditions described above. At least the total radioactive residues (TRR) in fresh peaches should be determined. The nature of the residue in pulp from processed peaches should be determined; if metabolites cannot be identified, then at least TRR in processed pulp should be determined. Because these studies will be conducted with radiolabeled peaches, we will not require processing at a pilot facility; laboratory procedures which simulate the lye peeling process as closely as feasible should be used. Care should be taken that peach pulp not be exposed to alkali conditions for longer than would be the case with commercial processing. That is, after immersion in lye, peaches should be extensively sprayed with water or placed in pH 7 buffer for an extended time before preparation for storage or analysis. If the Registrant desires to demonstrate that steam peeling reduces residues in pulp, then similar data should be provided on peaches peeled by steam. These considerations lead to the following comment:

Recommendations: To provide convincing evidence that iprodione residues are negligible in canned peaches, data are required on the distribution of tolerance residues between peel and pulp of fresh peaches, or on the nature of the residue in processed peaches. Data on tolerance residues can be generated using a registered formulation as the test substance; data on the nature of the residue should be generated using ^{14}C-iprodione, uniformly labeled in the phenyl ring. At its discretion, the Registrant could combine features of these two types of studies. For example, with the radiolabel study, TRR in peel and in pulp of fresh harvest peaches could be determined before the processing step. Additional considerations for conducting these studies are described in the Residue Data Needed section of this review. We advise that because of the factors described in Conclusion 2, providing further residue data pertinent to processed peaches may not have a dramatic effect on estimated dietary risk.

Wine Anticipated Residues

Anticipated residues for wine were determined on the basis of FDA monitoring data (CBRS 15099, 5/1/95, J. Abbotts). One red wine sample, with over-tolerance residues of 100 ppm, heavily influenced the anticipated residues for this commodity. This monitoring sample, designated 91083835, was collected on 4/9/91 in OR, and was reported from the Seattle district.

To further evaluate the validity of this single sample, this reviewer contacted the Food and Drug Administration, and was eventually referred to Mr. Fred Krick, with the FDA laboratory in Seattle WA. After some investigation, Mr. Krick reported that FDA was unable to locate the original chromatogram for this sample at the Oregon lab; presumably those records have been discarded. Mr. Krick advised, however, that 100 ppm must have been a keypunch error. He was working in the Seattle lab at the time, and a determination at that magnitude would have received widespread attention. He generally does not recall iprodione residues on any commodity at more than 5 ppm, and 100 ppm would have been off the chart on the chromatogram. Mr. Krick estimated that the actual level would have been 1.0 or 0.1 ppm, but in the absence of the original chromatogram, the actual level is unknown. He recommended discarding that one sample from the data set entirely (personal communication, 4/29/96).

This recommendation from FDA seems appropriate, and anticipated residues will be determined without this single sample. Derivation of an expression for anticipated residues, cancer risk, based on monitoring data has previously been described (CBRS 15099, 5/1/95, J. Abbotts):

$$a = [(np-d)(\tfrac{1}{2}L) + \Sigma^d]/n \qquad (1)$$

where a = average anticipated residues in ppm,
n = the total number of samples, with or without detectable residues,
p = the portion of the crop treated, expressed as a decimal,
d = the number of samples with detectable residues,
L = the limit of determination for the analytical method used,
Σ^d = the sum of all residues in ppm over d samples.

We note that if the number of samples with detectable residues is greater than would be predicted by the estimated percent crop treated (i.e., d > np), then the first term of equation (1) would be negative. Since this result does not make sense, in that case

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the first term is dropped and the samples with detects are assumed to represent the percent crop treated.

In the previous determination, anticipated residues based on monitoring data were adjusted for percent crop treated data; where percent treated was reported as a range, the higher limit of the range was used (Ibid.). In the previous determination, the higher limit for wine grapes was 19% crop treated. BEAD has since updated percent crop treated data, but the higher limit for wine grapes remains 19% (Memo, 12/95, Alan Halvorson). In the previous determination, anticipated residues were based on FDA domestic samples, because imports account for approximately 10% of U.S. wine consumption and residues were lower in FDA import samples (CBRS 15099, 5/1/95, J. Abbotts). Domestic samples with detectable residues were 34/62 for white wine, and 30/81 for red wine. Because the frequency of detects is higher than 19%, the detect samples will be assumed to represent the portion of the crop that is treated.

In the previous determination, the sum of residues over samples with detectable residues was 12.702 ppm for white wine, and 105.481 ppm for red wine. Discarding the single red wine sample with 100 ppm and substituting into equation (1) above gives:

a = [12.702 + 5.481]/142 = 0.128 ppm. The considerations above lead to the following comments:

Conclusion 3: FDA has advised that high residues reported in a single red wine monitoring sample were most likely due to a clerical error. We have therefore revised anticipated residues without this sample and determine combined iprodione residues, cancer risk, in wine of 0.128 ppm.

Recommendations: We recommend using the value in Conclusion 3 for anticipated residues in wine. Because this value is based on FDA monitoring data, % crop treated has already been taken into account. Therefore, if these revised anticipated residues are used as an input for a DRES run, a value of 100% crop treated should also be used. Anticipated residues are revised for wine only, and any changes in estimated dietary risk from this commodity should be proportional to changes in anticipated residues, provided other parameters have not changed from the previous DRES evaluation.

cc:Circ, Abbotts, RF, Iprodione List B File, SF, E. Doyle (DRES), Vivian Prunier (SRRD)
RDI:ARRathman:6/25/96:RBPerfetti:6/26/96:EZager:6/26/96
7509C:CBII-RS:JAbbotts:CM-2:Rm805A:305-6230:6/28/96
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