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PP# 7F1954 and the amendments of 4/28/78 and 5/12/78 Oxamyl on apples.  
Comments on the analytical method and residue data.

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Thru: Chief, Chemistry Branch

E. I. Du Pont de Nemours and Company proposes that a tolerance of 2 ppm be established for the combined residues of oxamyl, methyl N,N-dimethyl-N-[(methylcarbamoyl)oxy]-1-thiooxamimidate and its metabolite N,N-dimethyl-1-cyanoformamide in or on apples.

A tolerance of 3 ppm for residues of oxamyl in or on celery was established pursuant to PP#5F1650 (Sec. 180.303). PP#6F1696, PP#7F1907 and PP#1909 proposing tolerances for residues in or on potatoes, citrus and cottonseed, respectively, are currently in reject status. PP#7F1937 and PP#7F2000 proposing tolerances in or on root crops and pineapples, respectively, are currently pending.

#### Conclusions

1. The fate of oxamyl on apples has been adequately delineated. Oxamyl, per se, is considered the residue of concern.
2. The available analytical methodology is suitable for enforcement.
- 3a. The residue data demonstrate that residue levels resulting from the proposed use will not exceed the proposed 2 ppm tolerance.
- 3b. The apple processing data demonstrate that residues do not concentrate upon processing, and that no food additive tolerances are needed.
4. There is no reasonable expectation of secondary residues in meat, milk, poultry or eggs from the proposed use.
5. The petitioner has proposed that the metabolite, DMCF, be included in the tolerance expression. Toxicology branch has determined that DMCF is not of toxicological concern; and therefore, it should be deleted from the proposed tolerance.

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Recommendations

1. Contingent upon the deletion of DMCF from the proposed tolerance, so that it conforms to the form of the established oxamyl tolerance, Section 180.303, we recommend that the proposed 2 ppm tolerance for residues of oxamyl on apples be established.

Formulation

The oxamyl formulation proposed for use on apples in Vydate L, a liquid concentrate, containing 24% active ingredient (or 2 lbs a.i. per gal.). The inert ingredients of this formulation are all cleared under Section 180.1001.

The manufacturing process for oxamyl was discussed in detail in the review of PP#5F1650. (See Dr. R. Hummel's memo of 12/17/75). The possibility of dialkyl-N-nitrosamines being present in the Vydate L formulation at low levels was discussed in detail in our reviews of PP#5G1811 and PP#7F1907. The petitioner has submitted additional analyses of Vydate L samples by GLC-MS. The additional studies show that less than 1 ppm (method sensitivity) N,N-dimethyl nitrosamine is present in the formulated product. Technical oxamyl is a minimum of 95% active material.

[REDACTED] We do not anticipate any residue problems from these impurities at the above levels.

Proposed Use

Oxamyl, as Vydate L, is recommended for use on apples at rates ranging from 0.0625 to 0.50 lbs a.i. per 100 gals for the control of European red mites and two spotted spider mites. Sufficient spray solution is to be applied to obtain thorough coverage (runoff), but not more than 400 gals per acre. Proportionally less spray solution is to be applied for concentrate sprayers. Applications are not to be made within 30 days after bloom or within 14 days of harvest. The feeding or grazing of livestock in treated orchards is prohibited. There is no restriction on the number of applications permitted.

Nature of the Residue

Plant Metabolism: The fate of oxamyl in plants was discussed in detail in connection with PP#3G1316, 3G1349 and 5F1650 (see memos of 12/12/72, 5/13/73, 2/7/74 and 2/28/75 by D. Duffy and 10/17/75 by Dr. R. Hummel). Metabolism studies have been carried out on tobacco, peanuts, oranges, apples, potatoes and recently on tomatoes. The results of these studies are briefly discussed below.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

The apple study involved the brushing of young apples with a labeled oxamyl solution equivalent to 1 lb a.i./100 gal. (or about 2X the maximum recommended rate). The ripe apples were harvested about 47 days later. An aqueous surface wash of the treated apples removed only a trace of activity (<0.3%). Peel and interior portions of the washed apples were then extracted separately with methanol. The pulp remaining after extraction was dried and analyzed for <sup>14</sup>C content, by combustion. Levels of total activity (as oxamyl) ranged from 0.8-2.0 ppm and were similar in peel and interior fractions. Almost all of the activity (98%) was extracted by the methanol.

After removal of the methanol by evaporation, 77% of the activity in the resultant aqueous concentrate partitioned into ethyl acetate. TLC analysis of the ethyl acetate fraction revealed the following composition: 21% oxamyl, per se, 55% oxime, 22% N,N-dimethyl-1-cyanoformamide, (DMCF) and 2% unidentified residue. The polar fraction (21% of the total activity) was purified by column chromatography and analyzed by TLC. No evidence of the mono-glucose conjugate of the oxime (Metabolite A) or its monomethyl analog (Metabolite A') were detected. However, after hydrolysis with  $\beta$ -glucosidase 36% of this activity was shown to be Metabolite A.

Thus, 16% of the total activity after 47 days was present as parent compound. Approximately 42% and 17% of the total activity was present as the oxime and DMCF, respectively. Of the remaining 25% at least 8% was shown to be polyglucose conjugates of the oxime.

The orange metabolism study showed that six weeks after treatment about 9% of the activity was present as parent compound, 4% as free oxime (N,N-dimethyl-2-hydroximino-2-mercaptomethyl-acetamide) and 29% DMCF (N,N-dimethyl-1-cyano-formamide). The remaining 63% has been shown to consist principally of various conjugates of the oxime and its mono- and of demethylated derivatives.

In potatoes 14 days after treatment only 3% of the activity could be extracted with solvents of various polarity. Acid and enzymatic hydrolysis experiments released as much as 78% of the original activity. The studies showed that the oxime and its demethylated derivatives comprise a major portion of the residue in potatoes and that these residues are largely present as polysaccharide type conjugates.

The results from the orange, and potato studies, as well as studies done previously on peanuts and tobacco are consistent with the study on apples.

In conclusion the metabolism studies show a degradation of oxamyl residues to its oxime and its mono- and di-demethylated derivatives of their various conjugates. Residues of DMCF in apples were detected in the cold studies (which involved shorter preharvest intervals) at levels as high as 15% of the levels of oxamyl, per se. In a personal conversation between Dr. George Whitmore and J. Northington on 5/2/78, Toxicology Branch indicated that there was no toxicological concern for

residues of DMCF, the demethylated oxime metabolites or their conjugates and that these compounds need not be included in the tolerance expression. Therefore, we reiterate our previous conclusion that the fate of oxamyl in plants has been adequately delineated. Oxamyl, per se, is the residue of concern.

**Animal Metabolism:** The fate of oxamyl in animals has been discussed in detail most recently in our review of PP47F1907 (see memo 10/14/77). The rat metabolism studies showed that approximately 75% of the ingested oxamyl was excreted within 72 hrs (principally via the urine). About 80% of the eliminated activity was present as conjugates of the oxime, its mono- and di-demethylated derivatives, N,N-dimethylloxamic and N-methyl oxamic acid. No intact oxamyl or free oxime or any other organo-soluble radiolabeled metabolites were detected. Approximately 50% of the activity remaining in the tissues was incorporated into natural amino acids. The remaining activity remains unidentified, but was shown not to be present as any of the organo-soluble metabolites or their conjugates. Thus, we conclude that metabolism of oxamyl residues and re-incorporation of the fragments into natural products has been demonstrated, the fate of oxamyl, per se, in rats is adequately delineated.

A third labeled metabolism study investigating the fate of the monoglucose conjugate of the oxime, Metabolite A, was also submitted. This study shows that the fate of the conjugate upon ingestion by the rat was essentially the same as the parent compound.

A ruminant metabolism study has been submitted in which two lactating goats were maintained on a diet containing 10 ppm <sup>14</sup>C labeled oxamyl for 10 and 20 days, respectively. Approximately 65% of the administered dose was eliminated via the urine and feces within 72 hours. Blood and tissue samples contained residues equivalent to 1 ppm (calculated as oxamyl). 40-70% of this activity was shown to be present as amino acids. Samples of muscle, blood, and liver were subjected to further extractions with solvents of various polarity. Only trace levels of activity (<0.02 ppm) were recovered in the hexane and chloroform extracts. With the exception of the blood sample, no significant residues were detected in the more polar solvents either. A single compound accounted for the majority of the activity found in blood. It was shown not to be the parent compound or any of its metabolites or their conjugates. The available evidence indicates that the compound is polar and has a relatively low molecular weight. The majority of the activity in tissues remained unextracted. However, after hydrolysis with Pronase (R) (an enzyme which reportedly hydrolyzes almost all proteins with almost complete liberation of the constituent amino acids), 83-90% of the activity was solubilized and analyzed by GLC. The retention times were the same as those for the amino acid standards.

Approximately 47% of the 1.3 ppm activity in milk was shown to be incorporated into casein, lactose and triglyceride fats. An additional 6% of the activity in milk was incorporated into milk proteins other than casein. Two additional labeled compounds were detected in milk. However, it was shown that these compounds did not contain a structural moiety related to oxamyl.

It is our judgement that these studies show that oxamyl is rapidly metabolized and excreted by ruminants and non-ruminants. The residues that remain in tissues are apparently fragmented and incorporated in natural tissue constituents. Therefore, we conclude that the fate of oxamyl in animals has been adequately delineated. Oxamyl, per se is the residue of concern.

#### Analytical Methods

The method recommended for enforcement is that of Pease and Holt. It has been used for a variety of commodities including apples. The procedure is based on an alkaline hydrolysis of oxamyl to its more volatile oxime; and thus, the method determines both the parent compound and its free oxime.

Oxamyl residues are extracted into ethyl acetate, water added and the ethyl acetate evaporated off. The aqueous solution is then washed with hexane and made basic with 1N sodium hydroxide. After a chloroform wash the solution is heated on a steam bath to convert oxamyl to its oxime. The mixture is then saturated with sodium chloride and extracted with ethyl acetate. After concentration the residues are determined by GLC using a flame photometric detector operating in the sulfur mode.

Validation data have been submitted for the proposed procedure on apples fortified at levels ranging from 0.04-2 ppm. Recoveries ranged from 78-96%. With the exception of one value which was 0.04 ppm, all of the control values were reported as <0.02 ppm. No validation data for the recovery of residues of the oxime from apples has been submitted; however, adequate recoveries of the oxime from peanuts, peanut hulls and tobacco have also been demonstrated.

Successful method trials were conducted for celery and cottonseed. Recovery values from celery samples fortified at 3 and 6 ppm ranged from 77-82%. Control values were reported as <0.02 ppm. Recovery values of oxamyl from cottonseed fortified at levels of 0.2 and 0.4 ppm ranged from 89-110%. The cottonseed control values were reported as none detected.

A method for the determination of DMCF is also available, and has been discussed in previous reviews. (See the review of PP#7F1909 by J. Worthington). However, TOX has concluded that DMCF is not of toxicological concern and that it need not be included in the tolerance. Therefore, no enforcement methodology for DMCF is needed.

In conclusion, adequate enforcement methodology for the determination of oxaryl residues in or on apples is available.

#### Residue Data

A total of 19 residue studies from nine states reflecting application rates ranging from the lowest recommended rate up to 2 times the maximum recommended spray concentration are submitted. The studies reflect single and multiple (up to 7) ground applications and preharvest intervals ranging from 2-21 days. The highest residue level reported was 1.9 ppm found 3 days after a single 2X application. The highest levels reported from the maximum proposed rate at least 14 days after harvest was 1.1 ppm. The 1.1 ppm was detected 21 days after a single application. The above residue levels are from Wapato, Washington, which had no rainfall during the studies conducted there. The highest level reported in the remaining studies was 0.7 ppm, which was detected 2 days after a third treatment.

The data submitted for apples do not demonstrate the relatively rapid rate of decline oxaryl residues usually exhibit. However, it is our judgment that the proposed 2 ppm tolerance level is adequate to cover residue levels resulting in or on apples from the proposed use.

Residue data for dried apple pomace <sup>- pp # 1349</sup> have also been submitted. These data indicate that dried pomace contains approximately 1/6 the level present in the fresh fruit. Therefore, we can conclude that no food additive tolerance to cover the residues in apple pomace is needed.

In conclusion, the available residue data demonstrate that the proposed 2 ppm tolerance level for residues of oxaryl in or on apples is adequate to cover residues resulting from the proposed use.

#### Meat, Milk, Poultry and Eggs

The available ruminant feeding study was discussed in detail in connection with PP#361349 (see memo of 3/5/73 by D. Duffy). Eight lactating dairy cows (two at each level) were fed unlabeled oxaryl at levels of 0, 0.2, 10 and 20 ppm for 30 days. One animal from each level was sacrificed at the end of the dosing period. The remaining animals were sacrificed 7 days later. Milk was sampled periodically throughout the study. Analyses of the milk, milk fat, muscle, liver, kidney and fat samples showed no detectable residues (<0.02 ppm) of oxaryl or its oxime.

Dried apple pomace may be fed to beef and dairy cattle at rates up to 50 and 25% of the diet, respectively. Therefore, the treated apples could contribute approximately 0.17 and 0.08 ppm to the beef and dairy cattle diets, respectively. (2 ppm x 17% for processing losses x 50% of the diet = 0.17 ppm).

The feeding data demonstrate that there is no reasonable expectation of oxamyl residues in meat, fat, meat byproducts or milk from the feeding of apple pomace derived from treated apples. We do not consider apple pomace a poultry feed item; therefore, we can also conclude there is no expectation of secondary in poultry or eggs.

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