UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DEC 15 1976

SUBJECT: PP#6G1850 and FAP#6H5145. Nemacur on pineapples; and PP#6G1863 and FAP#6H5148. Nemacur on apples, cherries, peaches and in meat and milk. Evaluation of analytical methods and residue data.

FROM: William S. Cox, Chemist, Chemistry Branch, RD

TO: Special Registrations Section and Toxicology Branch

THRU: Chief, Chemistry Branch, RD

The Chemagro Agricultural Division of Mobay Chemical Corporation is proposing the establishment of temporary tolerances for residues of the nematocide, ethyl 3-methyl-4-(methylthio) phenyl(1-methyl-ethyl) phosphoramidate(trade name Nemacur) and its cholinesterase-inhibiting metabolites in or on the following agricultural commodities.

0.2 ppm	for pineapple fruit, fresh; 10 ppm (food addivite) for pineapple bran (dried)
1 ppm	for peaches; 10 ppm (food additive) for peaches (dried)
0.02 ppm	for apples and cherries; 0.2 ppm (food additive) for apples, dried and apple pomace (dried)
0.05 ppm	for the meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep
0.002 ppm	for milk

Tolerances have been established (Section 180.349, CFR 40) for residues of Nemacur and its cholinesterase-inhibiting metabolites in or on various commodities at levels ranging from 0.02 to 0.4 ppm.

It should be noted that PP#6F1693 which proposed tolerances for a number of rac's (none of which is involved in the petitions under consideration here) and PP#6F1770 (Nemacur on carrots) are in reject status. In addition, the petitioner is concurrently proposing permanent tolerances (PP#6F1864) for pineapples, its forage and its bran and cannery waste (food additive tolerances). Finally, temporary tolerances for pineapples (at 0.04 ppm) and for pineapple forage at (1 ppm) were established under PP#1G1168; these temporary tolerances expired as of September 25, 1975. The currently proposed use of Nemacur on pineapples differs from both the use contemplated under PP#6F1864 and that considered in connection with PP#1G1168.

The proposed experimental program on pineapples, if approved, will involve the use of 11,370 pounds of active ingredient and the treatment of 100 acres of pineapples in Hawaii over a period of three years.

12 pages

The proposed experimental program on apples, peaches and cherries will involve the treatment of only 38 acres (maximum) distributed in six states (5-8 acres) and New England (5 acres).

Note to SRS and TOX: Our conclusions and recommendations for the subject petition evaluations are listed separately at the end of this memorandum.

Detailed Considerations

Formulations and Uses

The current manufacturing process for Nemacur has not yet been submitted. This deficiency was noted in connection with PP#6F1693. For the purposes of the limited experimental programs only, we are not requiring that this deficiency be resolved. For any permanent tolerances for apples, cherries, peaches or pineapples, the information concerning the current process will be required. The status of one of the inerts in the EC formulation was questioned in connection with PP#6F1693.

All the other inerts are exempted under 180.1001(c) or (d).

For use on Hawaiian pineapples, Nemacur will be applied preplant and soil-incorporated at up to 20 lbs/A as either the 15% granular or as Nemacur 3 emulsifiable, as well as postplant at 3 lbs. Act/A using Nemacur 3 EC only.

There is a 30-day PHI prescribed for the latter use, as well as a restriction against grazing of the forage. For use on apple trees, cherry trees and peach trees, the same formulations will be used: one of the following treatments will be used on the various trees involved in the study--a broadcast application (10 to 20 lbs. Act/A), a band application (4 to 6' band in the orchard row)(at 10 to 20 lbs. Act/A) or an individual (single-tree) application (2.5 to 5' band around the base of each tree at a maximum rate of <2 lbs. Act/A); all the fruit tree applications will be at soil incorporated. A PHI of 75 days is proposed for cherries and one of 150 days is proposed for apples and peaches. There is no grazing restriction for the treated orchards. Such a restriction will be needed to preclude the possibility of illegal residues in meat or milk.

As a preplant application for pineapples, the 15G or EC formulation will be broadcast at the rate of 10 to 20 lbs. active per acre and soil-incorporated. As postplant applications, 1 to 3 lbs. active

will be diluted in 50 to 250 gallons of water and broadcast sprayed. Such applications are to be made 1 to 3 months after planting and repeated at 1 to 3-month intervals as needed, but not within 30 days of harvest. No more than 40 lbs. active ingredient are to be applied up to the crop harvest regardless of the method of application or formulation used. For the ratoon crop only, the label directs that 1 to 3 lbs. active (in 50-250 gallons of water) is to be applied immediately after the crop harvest and repeated as needed at 1- to 3-month intervals, but again not within 30 days of harvest. For the ratoon crop, not more than 30 lbs. active ingredient is to be used. There is a restriction against the foraging of treated pineapple fields.

Nature of the Residue

Plant Metabolism

The fate of Nemacur in a variety of plants was discussed in detail in connection with PP#6F1693 (memo of D. V. Reed, 3/2/76). To summarize, it was concluded there that the major metabolic path of Nemacur involves thio-oxidation to the corresponding sulfoxide and sulfone, plus hydrolysis to the corresponding phenols. Small amounts (less than 5% of the total activity) of unidentified metabolites retaining the cholinesterase-inhibiting phosphoroamidate structure have been detected in potatoes, cabbage and carrots; these metabolies would not be determined, if present, by the analytical method used for total Nemacur residues. Of some importance is the fact that one of these unidentified metabolites, which has been isolated from potatoes, is some six to seven times more potent than Nemacur per se as a ChE inhibitor. Based on this fact, we have made it a requirement (in connection with PPs#6F1693 and 6F1770) that additional residue data for the crops involved should be submitted--the data should include identification of the unidentified metabolites mentioned above; as an alternate, we stated that we would accept additional and comparative residue data involving the determination of total cholinesterase-inhibiting compounds.

In the present cases, which involve a relatively small acreage of pineapples in Hawaii or small plots of apples, cherries and peaches scattered over the United States, and considering the fact that the data indicate that residues of no more than 0.2 ppm will occur in the harvested crops, we conclude that we can waive the requirements for the additional residue data for these limited experimental programs only. However, for any permanent tolerance or for any significantly expanded experimental program, the requirements outlined

in connection with PP#6F1693 (memo of 3/2/76) must be resolved for any future favorable consideration of tolerance proposals involved with the uses considered here.

Note: The results of one residue study in which residues of over 1 ppm of Nemacur and its ChE-inhibiting metabolites were found in peaches are considered aberrant, as discussed below under Residue Data.

Animal Metabolism

As discussed in connection with PP#6F1693, tracer studies have been conducted on rats, cattle, pigs and poultry. All studies showed that Nemacus is rapidly degraded and excreted, primarily as the conjugated metabolites via the urinary system.

The metabolism study conducted on the cow indicates that when detectable residues present in the tissues and milk, the des-isopropyl analog of Nemacur sulfoxide is also present at ratios of 1:1 and 2:1, respectively, with respect to Nemacur sulfoxide. The des-isopropyl metabolite would not have been detected in the conventional "cold" feeding study on lactating cows. We have, in connection with both PPs#1399 and 6F1693, stated that data on the des-isopropyl metabolites reflecting their potential for transfer to meat and milk and their toxicological significance (i.e., their ChE-inhibiting potency, if any) are needed.

The swine study (using ^{14}C-ring labeled Nemacur) indicated that residues of the sulfoxide phenol and the sulfone phenols were the major components detected in the tissues; the sulfoxide, the sulfone and the phenol of Nemacur were also detected (by TLC). This study did not involve detection of the des-isopropyl metabolite. The swine study was conducted at a level calculated to be the equivalent of 22.5 ppm of the pig diet.

Tracer studies on poultry fed ring-labeled Nemacur at 2, 4 and 10 ppm in the diet resulted in activity levels of 0.03 ppm or less; this activity was not characterized in either the tissues or the eggs.

Although the fate of Nemacur has not yet been characterized to our complete satisfaction, we believe that the low levels of residues, which can reasonably be expected to occur from the proposed uses, and the limited exposures of livestock and poultry to residues in the feed item byproducts, justify a conclusion that the fate of Nemacur

in cattle and poultry has been adequately described. This conclusion pertains to the proposed experimental programs only. For any permanent tolerances or for any significantly expanded experimental program, the question of the presence of residues of the des-isopropyl metabolites of Nemacur sulfoxide and the corresponding sulfone in meet and milk must be resolved.

Analytical Methods

The analytical methods measure Nemacur, its sulfoxide and sulfone by converting all such residues to Nemacur sulfone using potassium permanganate oxidation.

The basic method consists of acetone extraction, chloroform partitioning, evaporation, permanganate oxidation in aqueous solution, extraction into chloroform and analysis using GLC with thermionic detection. For some crop and animal substrates, additional clean-up steps, i.e., acetonitrile partitioning before oxidation or Florisil column cleanup after oxidation, are employed.

The method for crops (Chemagro Report 25402) was successfully tested on peanuts by AMS (PP#0F0982, memo C. P. Makhijani, 12/1/71).

For crops in these petitions, the petitioner reports recoveries ranging from 72 to 134% for fortification levels of 0.05 and 0.10 ppm with Nemacur, its sulfoxide or its sulfone. Controls were all less than 0.01 ppm.

The sensitivity of the method on crops appears to be at the 0.02 ppm level for combined residues of Nemacur, its sulfoxide and its sulfone. Interference studies have been conducted for a number of the other organophosphorus pesticides tolerated on the various crops. No severe interferences have been noted; however, the Nemacur sulfone (the oxidative form in which the combined residues are determined) occurs as a shoulder on the peaks of Diazinon and the sulfone of Di-Syston. A confirmatory method employing an alternate column has been submitted; thus, we consider the specificity problem one that has been resolved.

The GLC methods used for determining residues of Nemacur, its sulfoxide and sulfone in animal tissues and milk are similar to the above method but employ a more rigorous clean-up. The methods appear sensitive to 0.002 ppm in milk and 0.02 ppm in tissues. Adequate recoveries ranging

from 70-110% were obtained for fortifications with all three compounds in tissues and milk.

For the purposes of the proposed temporary tolerances, we conclude that adequate methods are available for enforcement. However, should further studies indicate that other components of the residue are of toxicological importance (the phenolic metabolites or other ChE-inhibitors), additional methods will be required for any permanent tolerances.

Residue Data (pineapples)

The number of studies is somewhat limited--a total of five pertinent studies is submitted. However, two of these reflect exaggerated rates, 1.67X the maximum proposed for the foliar applications only. In addition, another study involves both a preplant application at the recommended maximum and an exaggerated (1.67X) rate for the postplant applications. For the purposes of the proposed experimental program, we find the number studies to be adequate. For any future tolerance or for a greatly expanded experimental program, a larger number of studies will be required.

For the studies reflecting the proposed PHI (or essentially so) and the exaggerated postplant rates only, residues in the fruit are reported as being 0.02 ppm and 0.03 ppm. For studies reflecting a rate equivalent to 0.83 X the maximum recommended, residues are essentially nondetectable (i.e., equivalent to background level of 0.01 ppm or less). Only in the case of pineapples treated both preplant at the maximum rate recommended and postplant at 1.67X the maximum rate recommended were residues of 0.14 ppm found at 31 days after the last of six treatments.

There are no data reflecting the ratoon crop use; however, considering the fact that lower rates are used in that case, we are translating from the available data to the ratoon crop.

Companion analyses of fresh and dried bran indicate that there are significant residues of Nemacur and/or its metabolites in the "peel" fraction of pineapples. These ranged from 0.31 to 1.07 ppm for the wet bran processed from pineapples harvested 31 or 32 days after the last of 6 postplant applications. When dried, the resulting animal feed item had maximum residues of almost 7 ppm, which when adjusted for rate of application indicates that residues in the bran (dried) would be slightly below 5 ppm. (See below for Residues in Processed Byproducts.)

The limited data indicate that a tolerance of 0.1 ppm would probably be adequate (after adjusting for rate of application); however, for the purposes at hand, we find the proposed tolerance level of 0.2 ppm for pineapples to be adequate and appropriate.

There is a restriction against the grazing or feeding of pineapple forage and we need not concern ourselves with residues in the foliage.

Note: A storage stability study on Nemacur sulfoxide residues in pineapple is presented in this petition. The data indicate only minor losses over long periods of storage at 0 to 10°F.

Residue Data (Apples, Cherries, Peaches)

The petitioner presents 12 studies on apples (six for each formulation), nine studies on cherries (five for the granular and four for the EC), and eleven on peaches (five for the EC and six for the EC). After elimination of studies which reflect samples taken at post-treatment intervals of over 190 days (i.e., the second growing season after treatment), we have a total of 26 studies reflecting the proposed treatment.

In all cases, save those where samples were taken at PHI's considerably earlier than those proposed or an exaggerated application rate was used, the reported residues are less than 0.01 ppm. At exaggerated rates of 1.5 or 2X the proposed rate, only one sample reflected detectable residues of 0.04 ppm when the proposed PHI's were observed. Even when earlier PHI's were observed for apples, the one sample taken at 66 days following a 1X treatment had reported residues of 0.26 ppm (this value was actually calculated from residue data generated during a processing study, based on the levels found in the wet pomace and the juice). However, in another apple study reflecting a 2X treatment, no detectable residues were reported at 31, 51, 41 or 23 days post-treatment. For cherries, all except one sample were reported as bearing residues of less than 0.01 ppm; the one exception was at the 0.01 ppm level (which is pushing the limit of sensitivity)--the cherry samples were taken at PHI's of 29 to 70 days.

For peaches, all studies involving the proposed PHI of 150 days (or approximately that length of time) were reported as having non-detectable residues (less than 0.01 ppm), including one at an exaggerated application rate (1.5X that recommended). One study, at the 1X application rate, reflected a PHI of only 73 days vs. the recommended 150 days--this sample was reported as having total Nemacur residues of 0.02 ppm. Another study, reflecting a 1.5X rate and a PHI of 104 days, reported a residue level of 1.16 ppm (check analysis

was 1.06 ppm). This one value is the only one of the available (32) studies for apples, peaches and cherries which is above the trace level (i.e., over 0.05 ppm). While we have no ready explanation for this one value, we think it appropriate to consider it aberrant, particularly since it involves both an exaggerated application rate and a PHI about half that recommended on the label, and in view of the results of other fruit tree studies involving exaggerated rates, reduced PHI's or both. For these reasons, we conclude that the proposed tolerance level of 0.02 ppm for residues of Nemacur in apples and cherries is adequate and appropriate, not only for these crops, but for peaches as well.

For permanent tolerances or for greatly expanded experimental programs, we will require additional residue studies reflecting broader geographical representation.

Residues in Processed Byproducts

An apple processing study was conducted on apples harvested 66 days after a 1X application. The apples were processed into wet pomace, juice and the wet pomace then dried. These data show an overall concentration factor of 10X between fresh fruit and dried pomace--thus, an appropriate food additive tolerance for apple pomace (dried) is 0.2 ppm, as proposed by the petitioner.

In addition, the petitioner is requesting a food additive tolerance for dried apples and dried peaches. There are no data for such a tolerance; the petitioner is relying on the same (10X) factor as that noted in the drying of wet apple pomace to dried apple pomace. While we do set food additive tolerances for certain dried fruits (prunes, raisins, figs and dates), we do not set tolerances on the other dried fruits since these others are normally reconstituted before consumption. Thus, we find there is no need for the proposed food additive tolerance of 10 ppm for dried peaches or the one of 0.2 ppm for dried apples.

As to pineapples, the petitioner is proposing a food additive tolerance of 10 ppm for pineapple bran. The studies on the processing of treated pineapples indicated that residues in the resulting bran could be quite high (up to 6.55 ppm) from foliar (postplant) applications at an exaggerated rate (1.67X the maximum recommended), even though residues in the resulting edible pulp are quite low (0.14 ppm or less). These data indicate that the foliar applications of the treated pineapples do not result in significant translocation of the surface residues.

Based on the somewhat limited data, we believe that a food additive tolerance of 5 ppm would be adequate (after adjusting for the rate applied); however, for a temporary tolerance we are not objecting to the 10 ppm level proposed for pineapple bran (dried).

Residues in Meat, Milk, Poultry and Eggs

There are no feed items involved in these petitions which involve common or usual items of feed for poultry; the proposed uses, therefore, fall into category 3 of Section 180.6(a) with respect to poultry and eggs, and tolerances are not needed for these commodities.

Apple pomace is a major feed item for cattle; however, for the fruit tree uses, we consider them to be trace residue situations and, even at the tolerance level, no more than about 0.07 ppm of Nemacur residues could occur in the cattle diet from the use of treated apples as a source of the pomace. Even at 40 ppm in the diet, no detectable residues (<0.01 ppm for tissues; <0.001 ppm for milk) of Nemacur were detected in a conventional 28-day feeding study on lactating cattle. Thus, we need not consider the proposed use on apples to a significant source of residues in the diet of cattle.

In the case of pineapple bran, this may be fed at up to 40% of the diet of beef and dairy cattle (according to Harris' Compendium). Based on the proposed food additive tolerance level of 10 ppm, this would translate to 4 ppm of the cattle diet. Considering that no residues were detected from the 40 ppm feeding, we can conclude that there will be no detectable residues of Nemacur as determined by the current enforcement method.

The question of the possibility of the des-isopropyl metabolite being a component of concern in meat and milk has not yet been resolved. However, considering the fact that much of the pineapple to be harvested would be consumed fresh or would be extensively commingled with untreated fruit during processing, we conclude that for the limited programs considered here, there is no likelihood of any significant exposure of cattle to residues of Nemacur. This is further supported by the metabolism study involving a dose equivalent to 1000 ppm in the diet, which resulted in a maximum of 0.06 ppm total ^{14}C-activity in the milk; the fat and liver samples taken after sacrifice had activity levels equivalent to 0.015 and 0.099 ppm, respectively, whereas the kidney had an activity level of 1.66 ppm--much of this (in the kidney) would have been present as the conjugated phenolic metabolites.

Based on all the data, we place the proposed (limited) uses in category 3 of Section 180.6(a), with respect to meat and milk. As indicated above under Nature of the Residue, for any permanent tolerances, the fate of Nemacur in cattle must be clarified with respect to the presence or absence of the des-isopropyl metabolite during a conventional feeding study.

W. S. Cox

PP#6G1863 and FAP#6H5148. Nemacur on apples, cherries and peaches.

Conclusions

1. For the purposes of the limited experimental program, the fate of Nemacur in animals and plants has been adequately described.

2. The available analytical method is adequate to enforce the proposed tolerances in terms of Nemacur and its ChE-inhibiting metabolites.

3. There is a grazing restriction for the proposed uses in fruit orchards.

4. (a) The proposed tolerance level of 0.02 ppm for apples and cherries is adequate. The proposed food additive tolerance for apple pomace is adequate and appropriate.

(b) The proposed tolerance for peaches and the proposed food additive tolerance for dried peaches are unnecessarily high: the latter is inappropriate. Section F should be revised to propose a common tolerance level of 0.02 ppm for apples, cherries and peaches and to delete the proposed food additive tolerances for dried apples and dried peaches.

(c) Contingent upon petitioner amending the label to include a restriction against the grazing of treated orchards, we can place the proposed uses of Nemacur in Category 3 of Section 180.6(a); if this is done, the proposed tolerances for meat and milk will be unnecessary and Section F should be amended by withdrawing these proposals at the time that Section 8 (the label) is amended to include the grazing restriction.

Recommendation

Contingent upon the petitioner's amending of Sections B and F (as discussed in Conclusions 3, 4(b) and 4(c), we recommend that the proposed temporary tolerances for apples, cherries and peaches be established along with a temporary food additive tolerance of 0.2 ppm for apple pomace.

The petitioner should be notified that, for any permanent tolerances or for any expanded experimental program(s), the following will be needed:

(1) Additional residue data for the fruits reflecting a broader geographical representation and studies reflecting irrigated orchards.

(2) Resolution of deficiencies 1 through 5 outlines to the petitioner in connection with PP#6F1693 (reject letter dated April 2, 1976).

PP#6G1850 & FAP#6H5145; Nemacur on Pineapples

Conclusions

1. For the purposes of the limited experimental program, the fate of Nemacur in plants and animals has been adequately described.

2. The available analytical method is adequate to determine residues of Nemacur as such, or as the corresponding sulfoxide and sulfone and to enforce the proposed tolerances in terms of Nemacur and its ChE-inhibiting metabolites.

3. The proposed tolerance levels of 0.2 ppm for pineapples and of 10 ppm for pineapple bran are adequate.

4. For the purposes of the limited experimental program, we categorize the proposed use as being in subparagraph 3 of Section 180.6(a).

Recommendation

We recommend that the proposed temporary tolerances be established. The petitioner should be notified that, for any permanent tolerances or for any expanded experimental programs based on the proposed use, the following will be required:

1. Additional residue data reflecting the proposed use in Hawaii.

2. A description of the process used in the manufacture of pineapple bran from treated pineapples.

3. Resolution of the deficiencies 1 through 5 outlined to the petitioner in connection with PP#6F1693 (reject letter dated April 2, 1976).