PP#5E1755

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

FEB 17 1987

EXPEDITE

MEMORANDUM

SUBJECT: PP#7E3495. Methomyl on Imported Hops. Evaluation of Analytical Methods and Residue Data. Accession Numbers 4005690 & 4005691. RCB Number 1827.

FROM: Sami Malak, Ph.D., Chemist
Tolerance Petition Section III
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Charles L. Trichilo, Ph.D., Chief
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

TO: Dennis Edwards, PM #12
Insecticide/Rodenticide Branch
Registration Division (TS-767)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

The petitioner, du Pont de Nemours and Company, Inc., is proposing that a tolerance be established for residues of methomyl in/on imported hops at 4.0 ppm.

Tolerances are currently established for residues of the insecticide methomyl (S-methyl N-[(methylcarbamoyl)oxy] thioacetimidate) in or on several raw agricultural commodities at levels from 0.01 to 40 ppm (40CFR§180.253). No food/feed additive tolerances are currently established for methomyl under 21CFR§193 or §561. No tolerances are currently established for residues of methomyl in/on livestock commodities.

A Registration Standard on methomyl has been issued on May 29, 1981.

Conclusions

1. The metabolism of methomyl in plants is adequately understood. This conclusion may be extended to include hops. The residue of concern for this proposed use on hops is the parent compound, methomyl per se, and its oxime metabolite S-methyl-N-hydroxy thioacetimidate. Both are determined by the enforcement method and expressed as the parent compound, methomyl.

2(a). The metabolism of methomyl in ruminants is presently not adequately understood. Until our deferrals to TOX are addressed, this deficiency remains outstanding [see Conclusion #2(b)].

2(b). It should be noted that TOX has expressed some concern as to the nature of the cyclohexane soluble metabolites in the liver and the magnitude of methyl cyanide (acetonitrile) in milk (see PP#9F2231, RCB deferral by P. V. Errico to TOX on 9/3/81 and TOX's response by W. Dykstra on 9/24/81). RCB's deferral to TOX concerning methyl cyanide (acetonitrile) in milk was again reiterated to TOX since the petitioner did not resolve this issue (PP#9F2231, M. Firestone, 5/24/84). We continue to defer these questions to TOX.

2(c). The presence or absence of acetamide in livestock tissue and milk may be an issue. The presence of this possible metabolite in livestcok tissue or milk may preclude the establishment of tolerances under the "Delaney Clause" appended to Section 409 of FFDCA.

3(a). Adequate analytical methods are available for the determination of methomyl residues in/on hops. The enforcement methodology is PAM II, Method I.

3(b). No adequate methods are available for enforcement of methyl cyanide in milk and/or other as yet unidentified metabolites in liver. If TOX determines that such metabolites should be regulated in the tolerance expression, analytical methodologies adequate for enforcement purposes and method trials will be needed [see Conclusion #2(b)].

3(c). Detailed description of the extraction process from hops samples, information on sample storage prior to analyses, and sample chromatograms are needed.

3(d). The petitioner is requested to clarify the source of contamination in the untreated hops samples.

4. The identity of the formulations could not be ascertained from the submitted labels. The Registration Division should be satisfied that the inerts for both Lannate® 2L and Lannate® 25-WP are cleared.

5. The petitioner should submit a letter stating their intention to register their products in West Germany for this use.

6. The petitioner is advised to revise Section F by proposing tolerances for residues of methomyl in/on fresh and/or dried hops. Furthermore, the petitioner is requested to clarify whether fresh, dried, or both fresh and dried hops will be imported.

7. A revised Section B is needed in which the petitioner must express the dosage in terms of the amount of the active ingredient per acre, as well as the maximum number of applications/dosage per season.

8. At this time, RCB is unable to conclude on the adequacy of the proposed tolerance, since some questions remain unresolved concerning the proposed use (see Conclusion #7).

9(a). Because the dietary intake to cattle for all feeds currently registered exceeded the maximum level of 20 ppm used in the cattle feeding study, RCB is unable to conclude on the magnitude of secondary residues in/on livestock commodities. A dairy cattle feeding study, using up to 80 ppm in the feed is needed prior to establishing further tolerances for residues of methomyl. This feeding study was requested in conjunction with the Registration Standard for methomyl.

9(b). If TOX determines that methyl cyanide in milk and/or the cyclohexane soluble metbolites in liver, once identified, require inclusion in the tolerance expression, additional feeding studies will be needed.

10. A Codex Residue Limit Status Sheet is attached (one page). A Codex temporary limit of 1 ppm for residues of methomyl in/on hops was proposed by 1986 JMPR. This tolerance will be at step 3 in the Codex procedure. No Canadian or Mexican tolernces are currently

established for methomyl in/on hops. Harmonization between US and Codex tolerance in/on imported hops is not possible since methomyl residues in/on hops resulting from the proposed use in this petition exceeded 1 ppm, due perhaps to different use pattern.

Recommendations

We recommend against the propsed tolerance for residues of methomyl in/on hops for the reasons cited in Conclsuions 2(a), 2(b), 2(c), 3(b), 3(c), 3(d), 4, 5, 6, 7, 8, 9(a), and 9(b). Also, note our deferral to TOX in Conclusion 2(b) and to the Registration Division in Conclsuion 4.

DETAILED CONSIDERATIONS

Manufacturing Process

The manufacturing process of methomyl is discussed in the Methomyl Registration Standard (5/29/81).

Detailed description of the manufacturing process including the amount of starting materials; also data on the composition of starting and intermediate materials used in the synthesis were cited by the Registration Standard as data gaps. For the purpose of this use on hops, RCB will defer this data requirements to be addressed in connection with the Methomyl Registration Standard.

Technical methomyl is manufactured by du Pont and Shell companies, both technicals were reported by the Registration Standard as containing 97-99% active methomyl.

Formulations

Two formulations are recommended for use on hops which are: du Pont Lannate® 20L Insecticide and du Pont Lannate® 25-WP Insecticide. Both labels carry West Germany's identifications as "BBA triangle No. 03113, containing 200 g/l water soluble methomyl", for Lannate® 20L; and "BBA triangle No. 1878, containing 25% methomyl", for Lannate® 25-WP.

The Methomyl Registration Standard lists four liquid formulations with a minimum active ingredient of 24.4% which is not du Pont's formulation (Reg. No. 201-349); and one wettable powder formulation containing 26.4% active ingredient which is du Pont's formulation (Reg. No. 352-362). Because the identity of the formulations could not be ascertained from the submitted labels. The Registration Division should be satisfied that the inerts for both Lannate® 20L and Lannate® 25-WP are cleared. The petitioner should submit a letter stating their intention to register their products in West Germany for this use.

Proposed Use

The proposed use on hops calls for multiple applications of methomyl at a maximum rate of 0.15% solution, "To obtain an equal distribution of the spray liquid, use an efficient amount of water, depending on equipment and leaf density" [sic]. There is a 10 day PHI.

A revised Section B is needed in which the petitioner must express the dosage in terms of the amount of the active ingredient per acre, as well as the maximum number of applications/dosage per season.

Nature of Residues

Plant Metabolism

No additional plant metabolism studies were submitted with this petition.

The metabolism of ^{14}C-methomyl in corn, cabbage and tobacco plants is discussed in several petitions and the Methomyl Registration Standard (5/29/81). To summarize, methomyl is absorbed by plants from soil and foliar applications, translocated and metabolized into naturally occurring compounds. Compounds lost through volatilization include carbon dioxide and possibly acetonitrile.

We conclude that the fate of methomyl in plants is adequately understood. This conclusion may be extended to include hops. The residue of concern for this proposed use on hops is the parent compound, methomyl per se, and its oxime metabolite S-methyl-N-hydroxy thioacetimidate. Both are determined by the enforcement method and expressed as the parent compound, methomyl.

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Animal Metabolims

No animal metabolism studies were submitted with this petition.

Animal metabolism studies have been discussed in several petitions and in the Methomyl Registration Standard (5/29/81).

In the rat, almost all the administered radiolabeled methomyl was excreted in 24 hours as carbon dioxide, acetonitrile and unidentified urinary products. When dairy cows were fed unlabeled methomyl at 2 ppm and 20 ppm of their daily diet, no residues were found (<0.02 ppm) in milk or tissues. Additionally, no residues were reported (<0.02 ppm) in liver, fat, urine, kidney or muscle from dogs fed unlabeled methomyl for one year at 1000 ppm.

The metabolism of methomyl in the goat was recently discussed in PP#9F2231 (memo of P. V. Errico, 9/3/81). In this study, three lactating goats, each was fed ^{14}C-methomyl for 10 to

10 1/2 days, twice daily in their diet, at a rate equivalent to 20 ppm. It was apparent from this study that up to 8.4% of the radiolabeled methomyl was reincorporated into biomolecules or excreted as acetonitrile in milk. The major residue in heart, kidney and liver is acetonitrile with <2% present as the parent or its oximino compound. Blood residues are ^{14}C-acetonitrile and probably a small amount of ^{14}C-acetic acid. Excretion via urine, feces and respiration amounts for up to 65% of the label. The remaining labeled materials was accounted for by the petitioner as too volatile to collect and is probably $^{14}CO_2$ and ^{14}C-acetonitrile. Little or no label migrated to the fat tissue. Identification was not reported for label found in muscle tissue.

The following is RCB's comments on the goat metabolism (P. V. Errico, 9/3/81): "In the ruminant, methomyl is metabolized to acetonitrile and carbon dioxide, and the acetimidate carbon is incorporated into cellular biomolecules. Residues in milk were reported as up to 29% acetonitrile. No trace (<0.002 ppm) of methomyl or its oximino metabolite was found in the insoluble freeze-dried milk samples. No methomyl or its oximino metabolite was reported in heart, kidney or liver (<0.02 ppm). The identity of labeled meterial in muscle tissue was not identified. Apparently the petitioner felt this radioactive material is similar

to or the same as any labeled components found in the heart, kidney or liver. No ^{14}C compounds (<0.01 ppm) were detected in fat for the experimental period. Up to 2.4% of the total label was found in milk as acetonitrile (reported as equivalent methomyl). Equivalent methomyl in milk reportedly ranged from 0.8 to 2.7 ppm. In the present case acetonitrile ranged from 0.059 ppm to 0.20 ppm over the experimental period (0.23 ppm - 0.78 ppm equivalent methomyl). When freeze dried tissue of liver, heart and kidney are each sequentially extracted with ethyl acetate and methanol much of the radioactivity is dissolved. When this labeled material is partitioned between cyclohexane/water, 98% of the radioactivity remains in the organic phase. This behavior indicates the labeled material is not methomyl or its oximino metabolite. No further characterization of this organic solvent soluble radioactive material was reported."

A deferral to TOX was made as to their concern for methyl cyanide in milk. If TOX is concerned we will need residue data for methyl cyanide in milk reflecting the feeding of methomyl at appropriate levels and validated analytical methodology adequate for enforcement puropses.

It should be noted that TOX has expressed some concern as to the nature of the cyclohexane soluble metabolites in the liver and the magnitude of acetonitrile in milk (see PP#9F2231, RCB deferral by P. V. Errico to TOX on 9/3/81 and TOX's response by W. Dykstra on 9/24/81). RCB's deferral to TOX concerning acetonitrile in milk was again reiterated to TOX since the petitioner did not resolve this issue (PP#9F2231, M. Firestone, 5/24/84). Furthermore, RCB reiterated the need for identifying the nature of the cyclohexane soluble ^{14}C-activities extracted from the liver which was found to be equal to 5.8 ppm resulting from a 20 ppm feeding level for 10.5 days (PP#9F2231, M. Firestone, 5/24/84). In the same petition, P. V. Errico (9/3/81) found that 8% of radiolabeled methomyl was found in animal tissues in the form of cyclohexane soluble compounds and that 2.4% of the administered radiolabeled methomyl was found in milk as acetonitrile. Acetonitrile was reported at 29% of the total residues in the goat milk resulting from a feeding level of 20 ppm for 10 days (PP#9F2231, P.V. Errico, 9/3/81).

We continue to defer these questions to TOX. Until our deferral to TOX is addressed, RCB is unable to conclude on the metabolism of methomyl in ruminants.

Analytical Methods

The residue determination in this submission follows the method of Pease, H. L., and Kirkland, J. J., 1968. Determination of Methomyl Residues Using Microcoulometric Gas Chromatography, J. Agr. Food Chem., 16:554-557. This method is the same as that outlined in PAM II as Method I.

In this method, methomyl is extracted by blending the sample with ethyl acetate. The methomyl residues are partitioned into water, acidified, and then washed with hexane. The residues are extracted with chloroform, concentrated, and base hydrolyzed to the oxime, S-methyl-N-hydroxy thioacetimidate. The solution is then acidified, and the residue extracted into ethyl acetate, concentrated and the residue determined by flame photometric detection sensitive to sulfur. Using 5 microliter sample, the sensitivity of the method was reported at 0.02 ppm.

Untreated control samples of hops were reported to contain methomyl residues ranging from 0.2 to 0.39 ppm. Apparnetly, these samples were contaminated, however, the source of contamination was not determined. The petitioner is requested to clarify the source of contamination in the untreated hops samples.

A recovery study is included, apparently on the 1979 samples, in which hops were fortfied at 0.04 to 20 ppm levels, and recoveries were reported in the range of 67 to 100%, averaging 83%. No information was provided on the storage of the samples. Information on sample storage prior to analyses is needed.

Detailed description of the extraction process from hops samples and sample chromatograms are needed.

Adequate analytical methods are available for the determination of methomyl residues in/on hops. The enforcement methodology is PAM II, Method I.

If TOX determines that methyl cyanide residues in milk and/or other as yet unidentified metabolites in liver should be included in the tolerance expression, additional analytical methodologies adequate for enforcement and method trials will be needed.

Residue Data

Residue data submitted reflect 3 field trials grown near Frankfurt, West Germany in 1979. As requested under Analytical Methods, information on the storage of the samples prior to analyses are needed.

In the field trials, methomyl was applied to hops at rates trial ranging from 0.53 to 1.61 lb act/A. At 10 day PHI, methomyl residues in fresh hop samples ranged from 0.37 to 1.7 ppm, averaging 0.94 ppm (6 samples). At zero and 21 day-PHI's methomyl residues were reported at a maximum of 20 and 0.13 ppm, respectively. In two samples of dry hops, methomyl residues were reported at 0.45 and 1.2 ppm reflecting 10 day PHI; 13 and 21 ppm at 0-day PHI; and 0.03 and 0.11 ppm at 21 day PHI.

The petitioner is advised to revise Section F by proposing tolerances for residues of methomyl in/on fresh and/or dried hops. Furthermore, the petitioner is requested to clarify whether fresh, dried, or both fresh and dried hops will be imported.

At this time, RCB is unable to conclude on the adequacy of the proposed tolerance, since some questions remain unresolved concerning the proposed use (see Proposed Use).

Storage conditions of the samples and a detailed description of the extraction procedures are needed (see Analytical methods).

Meat, Milk, Poultry and Eggs

No poultry feed items are involved in this petition. Therefore, there will be no problem with secondary residues of methomyl in poultry tissues and eggs from the proposed use.

The feed item involved in this petition is spent hops contributing up to 5% of the dietary intake to dairy and beef cattle. Assuming that methomyl residues in this commodity are not expected to be higher than in the rac, "4.0 ppm", and after considerations are given to other feed items for which there are tolerances, the maximum dietary intake to dairy cattle was calculated at 28.45 ppm as follow:

Feed Items	Tolerances in ppm	Percent in Feed	Maximum Dietary Intake in ppm
Grass hay, Bermuda	40	70	28.00
Hops	4[1]/	5	0.20
Grains, small	1	25	0.25
		Total	28.45

1/ Assumed level.

Because the dietary intake to cattle exceeded the maximum level of 20 ppm used in the cattle feeding study (see Animal Metabolism), RCB is unable to conclude on the magnitude of secondary residues in/on livestock commodities. A dairy cattle feeding study, using up to 80 ppm in the feed is needed prior to establishing further tolerances for residues of methomyl. This study was cited by the Methomyl Registration Standard as a significant data gap.

If TOX determines that methyl cyanide in milk and/or the cyclohexane soluble metbolites in liver, once identified, require inclusion in the tolerance expression, additional feeding studies will be needed.

The presence or absence of acetamide in livestock tissue and milk may be an issue. The presence of this possible metabolite in livestcok tissue or milk may preclude the establishment of tolerances under the "Delaney Clause" appended to Section 409 of FFDCA.

Other Considerations

A Codex Residue Limit Status Sheet is attached (one page). A Codex temporary limit of 1 ppm for residues of methomyl in/on hops was proposed by 1986 JMPR. This tolerance will be at step 3 in the Codex procedure. No Canadian or Mexican tolernces are currently established for methomyl in/on hops. Harmonization between US and Codex tolerance in/on imported hops is not possible since methomyl residues in/on hops resulting from the proposed use in this petition exceeded 1 ppm, due perhaps to different use pattern.

Attachment 1: Codex Sheet (one page).

cc: RF, Circu, SF (methomyl), PP#7E3495, S. Malak, EAB, EEB, FDA, Anne Lindsay/PSPS, Anne Barton/HED, James Akerman/ RD, and PMSD/ISB.
RDI: P.V.Errico:2/12/87:R.D.Schmitt:2/12/87
TS-769:RCB/HED:CM#2:RM:6814A:S.Malak:X557-4379:2/11/87

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Methomyl

CODEX NO. 94

Fred Suhre 2/11/87

CODEX STATUS:

[ ] No Codex Proposal Step 6 or above

Residue(if Step 8): Methomyl

Crop(s)	Limit (mg/kg)
hops	1*

PROPOSED U.S. TOLERANCES:

Petition No. 7E3495

RCB Reviewer Jami Malek

Residue: Methomyl (S-methyl N-[(methyl-carbamoyl)oxy]thioacetimidate

Crop(s)	Limit (mg/kg)
Imported hops	4.0

CANADIAN LIMITS:

[x] No Canadian limit (on hops)

Residue:

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

[x] No Mexican limit (on hops)

Residue:

Crop(s)	Limit (mg/kg)

NOTES: * Temporary limit proposed by 1986 JMPR. Will be at Step 3 in the Codex Procedure.

Form revised 1986