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PMSP/TSB



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

SEP 19 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Memorandum:

SUBJECT: FAP#9H5584. Methomyl on Imported Hops.
Evaluation of Analytical and Residue Data.
(DEB #5319, MRID#'s 410404-00, -01)

FROM: Jerry B. Stokes, Chemist
Dietary Exposure Branch
Health Effects Division (H7509C)

Jerry B. Stokes

THRU: Richard D. Schmitt, Ph. D., Chief
Dietary Exposure Branch
Health Effects Division (H7509C)

Richard D. Schmitt

TO: Dennis Edwards, PM-12
Insecticide-Rodenticide Branch
Registration Division (H7505C)

and

Toxicology Branch
Health Effects Division (H7509C)

DEB had previously determined (See PP#7E3495) that green (fresh) hops are not imported into the USA, but that dry hops are imported. A 7.0 ppm tolerance with an expiration date of January 12, 1990 was established (See Federal Register, Vol 52, No. 218, November 12, 1987, p43324).

E. I. Du Pont de Nemours & Company, Inc. has now submitted a cover letter dated March 22, 1989, a revised Section F, and additional residue data in support of this previous request for a methomyl food additive tolerance for imported dry hops. This food additive tolerance request will be evaluated under FAP#9H5584. The petitioner has also requested a permanent 12 ppm methomyl import tolerance in/on dry hops.

Tolerances are established for the insecticide methomyl (S-methyl N-[(methylcarbamoyl)oxy]thioacetamide) in/on a variety of r.a.c's under 40 CFR 180.253 from 0.1 to 40 ppm. A 7.0 ppm food additive tolerance is established under

40 CFR 185.4100 (expiration date 1/12/90) for methomyl in/on the processed commodity dried hops as a result of application to the growing hops. No tolerances are currently established for methomyl residues in/on animal feeds.

A registration standard for methomyl has been issued on May 29, 1981. A FRSTR has been issued in April 1989.

Conclusions:

1. The nature of the residue in plants is adequately understood for the proposed use. The residue of regulatory concern is methomyl.

2a. According to the previous review, PP#7E3495, the nature of the residue in animals is not adequately understood. However, the Assistant Administrator (OPTS) previously decided that the animal metabolism data gaps for methomyl would be addressed in the Methomyl FRSTR and not in the above hops petition.

2b. The FRSTR calls for 1) additional studies depicting the metabolism of methomyl in ruminants and poultry, 2) the distribution and characterization of residues in milk, eggs, liver, kidney, muscle, and fat, and 3) specific analyses for acetonitrile and acetamide. In the only ruminant study submitted, ¹⁴C-residues were not totally characterized in the kidney, liver, or muscle. However, based upon the data submitted, the major metabolism of methomyl in the goat proceeds similar to that of plants: methomyl is oxidized to methomyl oxime, methomyl sulfoxide, acetonitrile, acetamide, and carbon dioxide. These fragments, i.e., acetonitrile, acetamide, and carbon dioxide, can be incorporated into cell constituents. The Guidance Document was released April 1989. Additional metabolism data for the goat study has been submitted to the Agency (3/89), but has not yet been reviewed.

In regards to a poultry metabolism study the due date is October 1990. However, since there are no poultry feed items involved with the proposed use of methomyl on growing hops, this study would not be necessary for the establishment of a methomyl tolerance in/on dry hops only.

2c. The Agency has also determined that acetamide is ubiquitous, already existing at measureable levels in milk and eggs (See Federal Register, Vol 50, No. 197, October 10, 1985, p41341). Although the goat metabolic study did not include the analysis of milk for acetamide residues, based upon the proposed use, the amount of ubiquitous acetamide would mask any expected contribution of acetamide residues in milk from this use. There would be no secondary acetamide residues in/on poultry meat, fat, by-products, or eggs as hops are not a poultry feed item.

2e. According to a recent decision, TOX has recently recommended that acetonitrile residues be included in the tolerance expression

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for thiodicarb (a compound which forms methomyl in vivo as a hydrolysis product), until adequate toxicological data are submitted to the Agency (See memo of 11/8/88, K. C. Swentzel, PP#7F3526). Acetonitrile is a metabolite of thiodicarb and methomyl catabolism in animals.

Hops are only used in the production of beer. Processing data show methomyl residues <0.02 ppm in the final "sud" product and <0.04 ppm in spent hops, the only animal feed item. Therefore, at this present time, since 1) due to the limited use and very low levels of possible methomyl (and metabolite acetonitrile) residues in dry hops and processed commodities, 2) the decision of the Assistant Administrator to address these issues in the FRSTR, the only residue of concern for the proposed use in/on dry hops would be the parent compound methomyl.

3. A revised Section B (a copy of a label for each proposed formulation) must be submitted for the proposed use in which the applications/season (for each proposed dosage level), the between-spraying interval, and the preharvest interval are adequately defined. The submitted data will support a maximum of 5 applications (maximum rate 0.15% a.i.)/season/crop at a 10-day PHI. The petitioner must also clarify whether the "10-day waiting period" is the suggested period between multiple applications and/or the preharvest interval.

4. According to the Methomyl Reg. Std. and the Methomyl FRTRS, additional data are still required for the methomyl product chemistry. However, according to an earlier decision (See memo of 4/21/87, S. Malak) the Assistant Administrator (OPTS) decided that this data gap would be addressed during the FRSTR review. The Guidance Document was released April 1989; the due date for these data are October 1989 and April 1990.

5a. In the previous petition, PP#7E3495, adequate residue data for dry hops were collected by the PAM II analytical methomyl enforcement methodology. In this petition, FAP#9H5584, the submitted GLC/MS analytical methodology used for data collection is quite different from the PAM II analytical methomyl enforcement methodology. However, the residue data is adequately supported by recovery data using this GLC/MS method for methomyl-fortified hops samples.

5b. Methomyl residues are adequately recovered (>80%) by the FDA's multiresidue Protocol III (PAM I, Sec. 232.4). According to Agency guidelines, data must be submitted for the other multiresidue protocols I, II, and IV. However, based upon the limited use on the minor crop of dry hops, additional data for the other multiresidue protocols will not be needed before the establishment of any tolerances for dry hops only.

6. The petitioner must clarify the conditions for the submitted storage stability data, e.g., the length of storage in months

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and dates of analyses should be submitted for all samples of hops, both green and dry. Similar data must be provided for the two processed commodities, "sud" and spent hops.

7. The residue data are adequate to support the proposed use and the proposed 12 ppm tolerance for dry hops for both formulations, LANNATE®20 L and LANNATE®25 WP.

8. A Codex limit of 2 ppm is established on dry hops for the sum of the parent methomyl and its metabolite methomyl oxime. No Canadian or Mexican limits are currently established. Comparability is not possible since this petition proposes a 12 ppm tolerance in/on dry hops and the supporting residue data show the methomyl residues to exceed the 2.0 ppm Codex tolerance.

Recommendations:

DEB cannot recommend the proposed 12 ppm tolerance in/on dry hops because of deficiencies 3 and 6.

Detailed Considerations:

Manufacturing Process/Formulations:

The manufacturing process of methomyl is discussed in the Methomyl Registration Standard (5/29/81) and the Methomyl FRSTR (4/89). According to the both of the above, additional data are still required for the nature of the process, the relative amounts of beginning materials, the production equipment, the duration of each step, purification procedures, and/or quality control measures. Additional data are needed for the manufacturer, producer, or supplier of each beginning material and/or information in regards to the properties of each beginning material.

However, according to an earlier decision (See memo of 4/21/87, S. Malak) the Assistant Administrator (OPTS) decided that this data gap would be addressed during the FRSTR review. DEB has not as yet received or reviewed the requested data. The Guidance Document was released April 1989; the due date for these data are October 1989 and April 1990.

Proposed Use:

The proposed use on hops calls for application of above methomyl formulations, LANNATE 20 L (watersoluble concentrate 200g a.i./l) and LANNATE 25-WP (wetttable powder, 25% a.i.), at a maximum rate of 0.15% (150g in 100 liters of water) with a 10-day "waiting period". The submitted labels in this packet dated 3/23/89 do not specify the maximum a.i. and/or maximum applications/season. The frequency of each application is specified for LANNATE®20 L only: 10 to 14-day interval.

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This interval is not defined on the LANNATE®25 WP label. Neither is it clear whether this "waiting period" is the suggested period between multiple applications and/or the preharvest interval (PHI).

The submitted data will support a maximum of 5 applications (maximum rate 0.15% a.i.)/season/crop at a 10-day PHI. Under PP#7E3495, additional label application directions were submitted dated 3/12/87 in which both formulations at the proposed 0.15% rate were limited to five applications/season. The petitioner must also clarify whether the "10-day waiting period" is the suggested period between multiple applications and/or the preharvest interval. These directions should be clearly stated on the labels. Therefore a revised Section B (a copy of a label for each proposed formulation) must be submitted for the proposed use in which the maximum a.i./season, the maximum applications/season (for each proposed dosage level), the between-spraying interval, and the preharvest interval are adequately defined.

Nature of the Residue:

Plants: The metabolism of methomyl in plants is adequately understood based upon studies in corn, cabbage, and tobacco. The metabolic pathway involves the conversion of the parent methomyl to methomyl oxime which is subsequently degraded to acetonitrile (and possibly to acetamide) and carbon dioxide. Methomyl may also be oxidized to methomyl sulfoxide. Methomyl, methomyl oxime, and methomyl sulfoxide may form glucosides and other conjugates. Methomyl and metabolites can be incorporated into natural constituents, e.g., organic acids, amino acids, sugars, and lipids.

Therefore, the residue of regulatory concern for the proposed use in/on growing hops is the parent, methomyl.

Animals: According to the previous review, PP#7E3495, and the Methomyl FRSTR, the nature of the residue in ruminants is not adequately understood. The only animal metabolism submitted to date is a lactating goat study with 14C-methomyl. Although the 14C-residues are not totally characterized in kidney, liver, and muscle, based upon the data submitted, the major metabolism of methomyl in the goat proceeds similar to that of plants: methomyl is oxidized to methomyl oxime, methomyl sulfoxide, acetonitrile, acetamide, and carbon dioxide. These fragments are then incorporated into cell constituents.

The FRSTR still calls for 1) additional studies depicting the metabolism of methomyl in ruminants and poultry, 2) the distribution and characterization of residues in milk, eggs, liver, kidney, muscle, and fat, and 3) specific analyses for acetonitrile and acetamide. However, due to 1) the very low

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levels of possible methomyl residues in food/feed products, and 2) the Assistant Administrator's (OPTS) decision that this data gap will be addressed in the Methomyl FRSTR methomyl, metabolism of methomyl in animals is adequately understood for the proposed use in/on dry hops only. The Guidance Document was released April 1989. Additional metabolism data for the goat study has submitted to the Agency (3/89), but has not yet been reviewed.

In regards to a poultry metabolism study the due date is October 1990. However, since there are no poultry feed items involved with the proposed use of methomyl on growing hops, this study would not be necessary for the establishment of a methomyl tolerance in/on dry hops only.

The Agency has also determined that acetamide is ubiquitous, already existing at measureable levels in milk and eggs (See Federal Register, Vol 50, No. 197, October 10, 1985, p41341). Although the goat metabolic study did not include the analysis of milk for acetamide residues, based upon the proposed use, the amount of ubiquitous acetamide would mask any expected contribution of acetamide residues in milk from this use. (There would be no secondary acetamide residues in/on poultry meat, fat, by-products, or eggs as hops are not a poultry feed item.)

The above goat metabolism showed that acetonitrile formed in milk (approximately 25 to 35% of TRR; 0.5 or 0.7 ppm) when the animal was fed a diet containing 20 ppm of methomyl. TOX has recently recommended that acetonitrile residues be included in the tolerance expression for thiodicarb (compound which forms methomyl in vivo as a hydrolysis product), until adequate toxicological data are submitted to the Agency (See memo of 11/8/88, K. C. Swentzel, PP#7F3526). However, according to a previous decision, the Assistant Administrator (OPTS) decided that this data gap would be addressed during the FRSTR review. The Guidance Document was released April 1989; the due date for this data is October 1990.

Hops are only used in the production of beer. Processing data show methomyl residues <0.02 ppm in the final "sud" product and <0.04 ppm in the only animal feed item spent hops. Therefore, at this present time, since 1) due to the limited use and very low levels of possible methomyl (and metabolite acetonitrile) residues in dry hops and processed commodities, 2) the decision of the Assistant Administrator to address these issues in the FRSTR, the the only residue of concern for the proposed use in/on dry hops would be the parent methomyl. However, additional methomyl metabolic studies in animals could result in the need for the inclusion of other metabolites, in the tolerance expression for the proposed use in/on dry hops.

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Analytical Methods:

Analytical methodology (GLC/sulfur microcoulometric detection, MRID#00009009) for methomyl residues is available in PAM II, Method I. This method has undergone a successful FDA method tryout. In this method methomyl is converted to its hydrolysis product methomyl oxime. The limit of detection of the oxime is 0.02 ppm and recovery ranged from 75 to 115% for plant and animal samples fortified with methomyl residues at 0.02-2.0 ppm. In addition, a modification of the detector to a flame photometric equipped with a sulfur filter is also an adequate method (MRID#00008837). The limit of detection is 0.05 ppm and recoveries ranged from 81-85% for approximately 90 crop samples fortified with methomyl at 0.07-10 ppm. The hops residue data for methomyl residues submitted in PP#7E3495 were evaluated by this method. The data submitted in this petition, FAP#9H5584, used a different GLC method. The method involved homogenation of hops (green or dry) in methanol/water (65:35), acidification of the extract, then liquid-liquid partition with methylene chloride. The organic layer was evaporated and the residuum hydrolyzed with 1M sodium hydroxide at 95°C for 30 minutes, cooled and acidified (pH 2-3) and extracted with methylene chloride. The organic layer was applied to an alumina column and eluted with methylene chloride/hexane, then by methylene chloride/ethanol. The methylene chloride was evaporated and the remaining ethanol solution, which contained the analyte methomyl oxime, was analyzed with a GLC method equipped with a mass spectrometer as the detector; the mass spectrometer was set to register peaks at m/e 105 and 88. The limits of detection were 0.04 ppm for green hops, 0.1 ppm for dry hops, 0.02 ppm for "sud", and 0.04 ppm for spent hops. The average recoveries were 84%, 99%, 95%, and 57%, respectively, for four to eight methomyl-fortified (0.02 to 51 ppm) samples of each r.a.c. or processed product.

In the previous petition, PP#7E3495, residue data for methomyl residues in/on dry hops were collected by the PAM II method. (Plant samples were spiked with 0.05 to 20 ppm's of methomyl, 71 to 120% recoveries.) In this petition, FAP#9H5584, the GLC/MS method above gave good recoveries of fortified samples (0.04 to 51 ppm, 75 to 116% recoveries). In addition, methomyl residue are adequately recovered (>80%) by the FDA's multiresidue Protocol III (PAM I, Sec. 232.4) According to Agency guidelines, data must be submitted for the other multiresidue protocols I, II, and IV. However, based upon the limited use on the minor crop of dry hops, additional data for the other multiresidue protocols will not be needed before the establishment of any tolerances for dry hops only.

Storage stability data:

Adequate storage stability data have been submitted previously for beets and beet tops (-10°C for ca. 1 year), snap beans

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(-18°C for 30 months), and several other raw agricultural commodities. The data were collected using the PAM II enforcement method for methomyl residues. In PP#7E3495, samples were frozen immediately after harvesting (and following a 3-5 hour drying period) at -20 to -25°C for 120 days before analyzed (See memo of 4/21/87, S. Malak). Data were collected by the PAM II method (except the florosil clean-up column for plant oils before GLC analysis were not needed for hops). In this petition, FAP#9H5584, residue data are submitted for samples apparently stored for up to 12 months ('87 crop) before shipment to the lab for analysis of residues. In addition, a different analytical methodology was applied for data collection.

The petitioner must clarify the conditions for the submitted storage stability data, e.g., the length of storage in months and dates of analyses should be submitted for all samples. Similar data must be provided for the two processed commodities of "sud" or spent hops. (Based upon the previous data for other crops, methomyl residues in/on hops should be stable under the storage conditions reported, but DEB needs this data to properly assess the validity of the sample storage and the residual analyses.)

Residue Data:

In the previous petition, PP#7E3495, residue data were submitted in support of the proposed use. However, the data were insufficient and additional data were required (See also Federal Register Vol 52, p35730, September 23, 1987).

In this petition, FAP#9H5584, residue data are provided for six hops varieties, data for both green (or fresh) and dry hops, from three locations in West Germany: Ravensburg, Rudelzhausen-Pumpenudl, and Kressbronn-Betznau for the '87 and '88 crops. LANNATE®20 L (200g a.i./l) was applied at two rates: 1.4 to 1.6 kg a.i./ha or 2.4 to 3.1 kg a.i./ha. The petitioner refers to these as 1X and 2X rates, respectively. The label only defines a 0.15% (150ml/100 liters) spray application with a "waiting period" of 10 days. We are asking the petitioner to define "waiting period" as stated in the Proposed Use Section above. The label does not define the maximum gallonage/ha/ application.

The following data are submitted for the proposed use of insecticide methomyl on hops:

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Methomyl in/on hops			
Rate ^a	PHI ^b	Residue, ppm	
		fresh	dry
1.4 (1.6)	19	0.23	0.63
1.6 (1.8)	10	1.1	2.8
1.6 (1.8)	10	0.12	0.41
1.5 (1.7)	10	1.8, 1.8	5.5
1.5 (1.7)	10	3.7	8.3
2.9 (3.2)	0	18, 16, 21	26, 52
2.9 (3.2)	10	0.94, 1.2	2.7
3.1 (3.4)	0	5.1	49
3.1 (3.4)	10	0.98	3.4, 2.3
3.1 (3.4)	0	11	61, 73
3.1 (3.4)	10	2.3	5.8, 5.3
2.9 (3.1)	0	18	64
2.9 (3.1)	10	<0.02	<0.04
2.4 (2.7)	0	14	84
2.4 (2.7)	10	1.3	8.6
control ^c	0	<0.04 - 0.32	<0.1 - 1.2
control ^d	10	<0.04	<0.1

a LANNATE[®] 20 L formulation; kg a.i./ha (lb a.i./A)

b preharvest interval in days

c 8 control samples for fresh hops; 8 control samples for dry hops

d 6 control samples for fresh hops; 6 control samples for dry hops

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Samples of fresh hops were spiked with methomyl from 0.04 to 5 ppm, while dry hops were spiked with methomyl from 0.1 to 51 ppm. Recoveries ranged from 75 to 116%.

Assuming the "waiting period" expressed in the proposed use refers to the PHI, the above data shows that the proposed 12 ppm tolerance for dry hops (fresh hops will not be import into the US) is adequate using a 10 day PHI for the LANNATE®20 L formulation. The LANNATE®25 WP formulation was not applied in any of the field trials submitted in this petition, FAP#9H5584. Data using the LANNATE®25 WP formulation were submitted in the previous petition, PP#7E3495. The residue data for the LANNATE®25 WP formulation showed slightly higher methomyl residues in hops than crops treated with the LANNATE®20 L formulation because of a different application rate. Therefore, the proposed 12 ppm methomyl tolerance would be adequate to cover any methomyl residues in/on dry hops from either formulation at the proposed rate and 10-day PHI.

Processing Data:

The field-treated hops were processed similarly to the industrial brewing process in the laboratory. The "sud" fraction is the aqueous filtrate after the hops have been filtered before the yeast addition or fermentation process begins. This solid from the filtrate is the spent hops. Only dry hops treated with the LANNATE®20 L formulation were processed.

Methomyl in/on processed hops			
Rate ^a	PHI ^b	Residue, ppm	
		"sud"	spent
3.1 (3.4)	0	<0.02	<0.04
2.9 (3.2)	0	<0.02	<0.04
control ^c	0	<0.02	<0.04

a LANNATE®20 L formulation; kg a.i./ha (lb a.i./A)

b preharvest interval in days

c 2 control samples for "sud"; 2 control samples for spent hops

Based upon the methomyl residues measured in these two fractions it appears that residues of methomyl will not be of concern in human consumption of any final fermented product or in the spent hops which are used as livestock feed. The proposed 12 ppm tolerance for dry hops should cover any methomyl residues which might be present in these processed commodities.

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Milk, meat, eggs, and poultry:

The only possible animal feed would be the spent hops. At the most this might be 5% of the total livestock diet. Based upon the expected methomyl residues after processing of the dry hops, secondary residues in milk and meat would be negligible. Since spent hops are not a poultry feed item, then secondary residues of methomyl in eggs and poultry meat, fat, and by-products, would not be a problem.

In the previous petition, PP#7E3495, the possible presence of both acetamide and acetonitrile in milk and meat might cause additional data needs, i.e., additional analytical methodology for each, and additional residue data for each compound in the hops. Since the Agency, as previously discussed in this memo, has determined that the ubiquitous nature of acetamide precludes the submission of any data for acetamide. However, according to the TOX recommendation, i.e., the inclusion of acetonitrile in the tolerance expression until adequate toxicological data are available to the Agency, data for acetonitrile might be needed. Also, based upon the previous decision of the Assistant Administrator (OPTS), the problems with acetonitrile will be addressed in the Methomyl FRSTR. The Guidance Document was released April 1989. The methomyl FRSTR calls for the data March 1989, and states that the data have been submitted and under review. The present submission (DEB#5319) does not contain data for acetonitrile.

Other Considerations:

A Codex limit of 2 ppm is established on dry hops for the sum of the parent methomyl and its metabolite methomyl oxime. No Canadian or Mexican limits are currently established. Comparability is not possible since this petition proposes a 12 ppm tolerance in/on dry hops and the supporting residue data show the methomyl residues to exceed the 2.0 ppm Codex tolerance. Perhaps the use pattern is different.

Attachment 1: CODEX

cc with Attachment 1: J. Stokes (DEB); FAP#9H5584; PP#7E3495; Methomyl S.F.; E. Eldredge (PMSD/ISB); R.F.; Circulation (7)
RDI: PERRICO:9/13/89: JGarbus:9/18/89: RLoranger:9/19/89
H7509C:DEB:JStokes:js:Rm 805:CM#2:9/19/89

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INTERNATIONAL RESIDUE LIMIT STATUS

F. Ives
8/2/89

CHEMICAL Methomyl

CODEX NO. 94

CODEX STATUS:

No Codex Proposal
Step 6 or above

PROPOSED U.S. TOLERANCES:

Petition No. FAP#9H5584

RCB Reviewer J. Stokes

Residue(if Step 8): sum of
methomyl and methyl hydroxythio-
acetimidate (methomyl oxime)
expressed as methomyl

Residue: methomyl

Crop(s) Limit
 (mq/kg)

Crop(s) Limit
 (mq/kg)

hops, dry 2

hops, dry 12

CANADIAN LIMITS:

No Canadian limit (on hops)

Residue: _____

MEXICAN LIMITS:

No Mexican limit (on hops)

Residue: _____

Crop(s) Limit
 (mq/kg)

Crop(s) Limit
 (mq/kg)

NOTES:

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