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

21 APR 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#7E3495. Methomyl on Imported Hops. Amendment of March 12, 1987. No Accession Numbers. RCB Numbers 2057 & [redacted].

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., responded on March 12, 1987 to several deficiencies listed in RCB's memo of subject petition (S. Malak, 2/17/87) and submitted a revised Section F and sample chromtograms. In our discussion to follow, each deficiency is listed first followed by the petitioner's response and our comments.

Deficiencies 2(a) & 2(b)

The metabolism of methomyl in ruminants is presently not adequately understood. Until our deferrals to TOX are addressed, this deficiency remains outstanding. 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.

Petitioner's Response

John Moore, Assistant Administrator (OPTS) decided in the meeting of 4/1/87 (see Attachment 1) that this deficiency will be addressed during the FRSTR review.

This deficiency is resolved for this import tolerance request.

Deficiency 2(c)

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

No response.

RCB's Comments

John Moore, Assistant Administrator (OPTS) decided in the meeting of 4/1/87 (see Attachment 1) that this deficiency will be addressed during the FRSTR review.

This deficiency is resolved for this import tolerance request.

Deficiency 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.

Petitioner's Response

No response.

RCB's Comments

John Moore, Assistant Administrator (OPTS) decided in the meeting of 4/1/87 (see Attachment 1) that this deficiency will be addressed during the FRSTR review.

This deficiency is resolved for this import tolerance request.

Deficiency 3(c)

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

Petitioner's Response

The petitioner resubmitted the proposed analytical method (Exhibit #1) and provided detailed description of the extraction techniques in hops samples. It is apparent that dry hops samples are extracted in ethyl acetate. Water is used later to transfer the residues from the organic phase. The aqueous extract is then acidified and partitioned into hexane.

The petitioner provided information on sample storage prior to analyses. It was apparent that samples were dried immediately following harvest of fresh hops. Drying was accomplished by the use of a mechanical dryer for a period of 3 to 5 hours at 60 °C until the moisture content was reduced to about 12%. Samples were then frozen at -20 to -25 °C.

Samples were shipped from Germany to the duPont Laboratory in Delaware until analyzed, i.e., after storing for a maximum period of 120 days. Methomyl is expected to be stable within this storage interval (see Methomyl Registration Standard, 5/29/81).

Adequate sample chromatograms of standard, fortified, and treated samples were provided.

RCB's Comments

Extraction in organic solvent without the use of water may not be efficient. The use of water either alone or in

combination with an organic solvent, in the first step of extraction may show higher efficiency than the use of organic solvent alone. The proposed extraction technique may result in lower residues than what actually reported by the petitioner (please refer to Section 212.13 in PAM I). However, we are not raising questions on this issue since only 2 dry samples were included in the residue data and our assessment on the proposed tolerance is based largely on data from fresh samples.

Deficiency 3(c) is resolved.

Deficiency 3(d)

The petitioner is requested to clarify the source of contamination in the untreated hops samples.

Petitioner's Response

The petitioner cited two sources that might have contributed to sample contamination of untreated hops samples. These are: drift during application and by mechanical means during harvesting.

RCB's response

The petitioner's response is reflective of an uncontrolled experimental design. RCB does not normally accept these reasoning, however, we are not raising questions on this matter since field testing in Germany could have been done by non trained personnel.

Deficiency 3(d) is resolved.

Deficiency 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.

Petitioner's Response

The petitioner responded by submitting confidential statements of formulas for both Lannate 25 WP and Lannate 20 L (Exhibits 4 & 5). [redacted]

RCB's Comments

The petitioner submitted the necessary information cited in deficiency 4. A detailed description of the formulation is included in Attachment 2 (CBI, one page). The Registration Division should be satisfied that the inerts in both Lannate 25 WP and Lannate 20 L formulation are cleared under 40CFR§180.1001.

Deficiency 4 is resolved.

Deficiency 5

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

Petitioner's Response

The petitioner stated that both Lannate 25 WP and Lannate 20 L have been registered for use on hops in West Germany. A letter formally notifying the EPA of this registration, dated March 12, 1987, is included in Exhibit 6.

RCB's Response

The petitioner complied with the deficiency #5.

Deficiency 5 is resolved.

Deficiency 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.

Petitioner's Response

The petitioner stated that only dried hops will be imported. Accordingly, a revised Section F was included in Exhibit 7 requesting the following:

"It is proposed that a tolerance be established for residues of methomyl in or on dried hops as 4.0 ppm."

RCB's response

The available residue data previously submitted and reviewed by S. Malak, 2/17/87, reflect six fresh and

two dried hops samples. Data from 6 fresh hops samples at 10-day PHI, showed methomyl residues in the range of 0.37 to 1.7 ppm, averaging 0.94 ppm reflecting the proposed use of 5 applications beginning with 0.53 and graduating to 1.61 lb act/A, equal to 1X of the lower dose and slightly below the 1X of the higher proposed rate of 1.77 lb act/A/application.

For the two dried hops samples, Lannate 25 WP was applied to one test and Lannate 20 L was applied to a second test, each 5 times at 3, 4.8, 4.8, 4.8, and 6 kg/ha, equal to 0.54-1.07 lb act/A of Lannate 20 L and 0.67-1.34 lb act/A of Lannate 25 WP. This rate is equivalent to 1X of the lower range, however, no data were submitted in which the higher range of the proposed use, 1.77 lb act/A, was used (refer to RCB's comments for discussion on the proposed rates under deficiencies 7 & 8). Methomyl residues were reported at three PHI's as follow: 13 and 21 ppm reflecting 0-day PHI; 0.45 and 1.2 ppm at the proposed PHI of 10 days; and 0.03 and 0.11 ppm at 21-day PHI. Control dry samples had methomyl residues quantitated at 0.22 and 0.2 ppm reflecting 0- and 14-day PHI, respectively (no data at 10-day PHI). Considering this situation of the control samples, the fact that no processing study was submitted, and only two treated dry samples are available, a meaningful assessment on the proposed tolerance would be scientifically unsound. Furthermore, the extraction technique may not be efficient [see RCB's Comments under deficiency 3(c)].

The petitioner should submit additional residue data on the raw agricultural commodity reflective of the proposed use at the maximum rate/number of applications and minimum PHI and a processing study to determine the concentration of methomyl residues in dry hops, or if only dried hops will be imported, then additional residue data on dried hops reflective of the proposed use on the raw agricultural commodity at the maximum rate/number of applications and minimum PHI are needed. Data should represent adequate geographical coverage from the major hop growing areas of the Federal Republic of Germany. Furthermore, samples of dried hops should be extracted using aqueous solution as described in Section 212.13 of the Pesticide Analytical Manual, Volume I. The petitioner should assure himself that the optimum aqueous solvent is used to extract the maximum residues from the dried samples.

A revised Section F should accompany the requested data in which an appropriate level for residues of methomyl should be proposed as a food additive tolerance in or on dried hops as follows:

"§193.--- Methomyl.
A tolerance is proposed for residues of the insecticide methomyl (S-methyl N-[(methylcarbamoyl)oxy] thioacetimidate) when present as a result of its application as a pesticide chemical to the growing crop as follows:

xxx parts per million in or on dried hops."

While the petitioner is gathering the necessary residue data to support this tolerance request and as discussed with the Assistant Administrator of OPTS during the meeting of April 1, 1987 (see Attachment 1), a tolerance of 7 ppm in or on dried hops, based on a theoretical concentration factor of 4X and the maximum residues reported in green hops (1.7 ppm), could be used. This tolerance may be higher than necessary and can be adjusted downward after the additional residue data is submitted and evaluated.

The estimated 7 ppm in or on dried hops is a calculated value. The petitioner should be given 18 months from the time of publication in the Federal Register (see PR-Notice 85-5, 8/22/85) to submit the requested residue data from dried hops reflecting two growing seasons. To allow time for the Agency to evaluate the submitted residue data, this calculated tolerance should expire 24 months after publication in the Federal Register. An agreement should be obtained from the petitioner to submit the additional requested data. If the petitioner agrees to submit the additional data discussed above, a revised Section F is needed requesting a 7 ppm food additive tolerance for methomyl to read as follows:

"§193.--- Methomyl.
Tolerance With Expiration Date.
A tolerance is established for residues of the insecticide methomyl (S-methyl N-[(methylcarbamoyl)oxy] thioacetimidate) when present as a result of its application as a pesticide chemical to the growing crop as follows:

7 parts per million in or on dried hops."

This tolerance will expire on --/--/198- (the time period allowed is 24 months from the publication of the FR-Notice).

Deficiency 6 is partially resolved.

Deficiencies 7 & 8

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

Petitioner's Response

In the cover letter by F. O'Neal of du Pont to D. Edwards of the EPA, dated 3/12/87, the petitioner indicated that the maximum number of applications per season is five times at 0.6 to 1.5 kg/ha of Lannate 20 L and 0.9 to 1.98 kg/ha of Lannate 25 WP.

RCB's Comments

The proposed dosage was calculated at 0.54 to 1.77 lb/A. The petitioner, Dr. Fredrick O'Neal of duPont, was contacted on 3/31/87 to clarify if the proposed rates are of the formulated end use products or are expressed on the basis of active ingredient. Dr. O'Neal replied that the rates are expressed on the basis of active ingredients. This clarification was added to Section B.

Deficiencies 7 & 8 are resolved.

Deficiency 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.

Petitioner's Response

The dietary intake estimate for cattle by the Residue Chemistry Branch was clearly a worst case estimate which did not consider the probability of cattle consuming a diet consisting of the components listed at their tolerance concentrations. The time period over which this diet would likely be consumed was also not addressed. Nevertheless, the maximum dietary intake calculated was 28.25 ppm assuming bermuda grass hay (with tolerance of 40 ppm) accounted 70% and small grains (1 ppm tolerance) accounted for 25% of the diet. When one

assumes that spent hops are included at 5% of the diet, there is a 0.2 ppm or 0.71% increase in the theoretical methomyl residues. Even under the worst-case scenerio presented in this example, an incremental increase of this magnitude will neither have a measurable effect on potential meat and milk resiudes nor have an effect on the health of those who consume these products.
The letter stated that the maximum theoretical dietary intake of methomyl residues for dairy cattle was 28.45 ppm. It also pointed out that because this exceeded the maximum dose in the cattle feeding study, 20 ppm, the RCB is unable to conclude on the magnitude of secondary residues in/on livestock commodities. This value is only 8.45 ppm or approximately 42% greater than the level used in the cattle feeding study in which no methomyl residues were detected in milk or meat products. It is not likely that an increase of 8 ppm will result in a different outcome.

RCB's Comments

John Moore, Assistant Administrator (OPTS) decided in the meeting of 4/1/87 (see Attachment 1) that this deficiency will be addressed during the FRSTR review.

This deficiency is resolved for this import tolerance request.

Deficiency 9(b)

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

Petitioner's Response

Methomyl is metabolized to the volatile product, acetonitrile. A goat metabolism study demonstrated this metabolite in milk (approximately 25 to 35% of the radioactivity in milk or 0.5 to 0.7 ppm, maximum in gaots fed a diet that contained 20 ppm methomyl). The TOX Branch was reviewing acetonitrile toxicity several years ago and were to make a determination regarding potential hazards posed by residues in milk. We have not received a response regarding this issue.
In the same goat study, we demonstrated that methomyl was metabolized to basic biochemical components which were reincorporated into lactose, casein and other

proteins, and fatty acids. These data strongly suggest that biochemical components that are building blocks common to sugars, proteins, and fats were formed; acetic acid and carbon dioxide are likely to be those methomyl metabolites in ruminants. Concern was raised in earlier discussion with EPA and RCB regarding the unidentified liver metabolites. These metabolites partitioned exclusively in the hexane fraction (as did the triglycerides in the milk samples). Du Pont had previously presented the argument that these unidentified metabolites represent reincorporation of labeled methomyl metabolites into the fatty acid components of liver triglycerides. We still support this view. Further support for this stems from the following: the liver is the primary organ involved in the metabolism of xenobiotics including methomyl; the liver is also the major site for the synthesis of fatty acids and incorporation of these into triglycerides which may be stored in this organ or secreted and transported to other tissues; and acetic acid is converted to acetyl coenzyme A, an obligatory step in fatty acid synthesis, in the liver. Bridging from identification labeled fatty acids in hexane-extract fractions of milk and considering the above information, we still believe that the weight of the scientific evidence suggest that the unidentified liver fraction represents radiolabeled fatty acids.

RCB's Comments

RCB has reviewed all the data cited in the petitioner's response and deferred our findings to the Toxicology Branch. At this writing, RCB has not received any response from TOX. However, John Moore, Assistant Administrator (OPTS) decided in the meeting of April 1, 1987 (see Attachment 1), that this deficiency will be addressed during the FRSTR review.

This deficiency is resolved for this import tolerance request.

Conclusions

Per the instructions of the Assistant Administrator, deficiencies 2(a), 2(b), 2(c), 3(b), 9(a), and 9(b) will be addressed during the FRSTR review. Additional residue data reflective of the maximum proposed use is also required. For more details, please refer to our discussion in the preceding pages and our Recommendations below.

Recommendations

We recommend against the proposed tolerance of 4 ppm for residues of methomyl in/on imported dried hops because of deficiency 6. To address deficiency 6, the petitioner should be informed of the following:

The petitioner should submit additional residue data on the raw agricultural commodity reflective of the proposed use at the maximum rate/number of applications and minimum PHI; and a processing study to determine the concentration of methomyl residues in dry hops, or if only dried hops will be imported, then additional residue data on dried hops reflective of the proposed use on the raw agricultural commodity at the maximum rate/number of applications and minimum PHI are needed. Data should represent adequate geographical coverage from the major hop growing areas of the Federal Republic of Germany. Furthermore, samples of dried hops should be extracted using aqueous solution as described in Section 212.13 of the Pesticide Analytical Manual, Volume I. The petitioner should assure himself that the optimum aqueous solvent is used to extract the maximum residues from the dried samples.

A revised Section F should accompany the requested data in which an appropriate level for residues of methomyl should be proposed as a food additive tolerance in or on dried hops as follows:

> "§193.--- Methomyl.
> A tolerance is proposed for residues of the insecticide methomyl (S-methyl N-[(methylcarbamoyl)oxy] thioacetimidate) when present as a result of its application as a pesticide chemical to the growing crop as follows:
>
> xxx parts per million in or on dried hops."

While the petitioner is gathering the necessary residue data to support this tolerance request and as discussed with the Assistant Administrator of OPTS during the meeting of April 1, 1987, a tolerance of 7 ppm in or on dried hops, based on a theoretical concentration factor of 4X and the maximum residues reported in green hops (1.7 ppm), could be used. This tolerance may be higher than necessary and can be adjusted downward after the additional residue data is submitted and evaluated.

The estimated 7 ppm in or on dried hops is a calculated value. The petitioner should be given 18 months from the time of publication in the Federal Register (see PR-Notice 85-5, 8/22/85) to submit the requested residue data from dried hops reflecting two growing seasons. To allow time for the Agency to evaluate the submitted residue data, this calculated tolerance should expire 24 months after publication in the Federal Register. An agreement should be obtained from the petitioner to submit the additional requested data. If the petitioner agrees to submit the additional data discussed above, a revised Section F is needed requesting a 7 ppm food additive tolerance for methomyl to read as follows:

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"§193.--- Methomyl.
Tolerance With Expiration Date. A tolerance is established for residues of the insecticide methomyl (S-methyl N-[(methylcarbamoyl)oxy] thioacetimidate) when present as a result of its application as a pesticide chemical to the growing crop as follows:

7 parts per million in or on dried hops."

This tolerance will expire on --/--/198- (the time period allowed is 24 months from the publication of the FR-Notice)."

Note to PM

The Registration Division should be satisfied that the inerts in both Lannate 25 WP and Lannate 20 L formulation are cleared under 40CFR§180.1001.

Attachment 1: Minutes of HOP Briefing by J. Akerman, 4/1/87 (2 pages).
Attachment 2: Confidential Statement of Formulas for Lannate 25 WP and Lannate 20 L (one page).

cc With Attachments (Including CBI) : RF, SF (methomyl or Lannate®), PP#7E3495, S. Malak, D. Edwards/RD, TOX, and PMSD/ISB.

cc With Attachment 1: Circu, EAB, EEB, FDA, Anne Lindsay/PSPS, Anne Barton/HED, and James Akerman/RD.

RDI: P.V.Errico:4/15/87:R.D.Schmitt:4/15/87
TS-769:RCB/HED:CM#2:RM:814A:S.Malak:X557-4379:3/31/87

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Attachment]

MEMORANDUM

SUBJECT: Minutes of HOP Briefing

FROM: James W. Akerman, Deputy Director
Registration Division

TO: RD
HED
PSPO

OPP briefed Dr. Moore on April 1, 1987 on the status of the five petitions submitted for imported hops. These petitions had been filed in January-February of this year. The Federal Republic of Germany (FRG) encouraged companies to file the petitions. The five petitions are for pesticides the Agency had earlier identified as having good toxicological data bases. The five pesticides are: methomyl, vinclozolin, metalaxyl, triadimefon, and triforine. Attached is a copy of the briefing notes.

OPP sought guidance from Dr. Moore on two issues. The first had to do with the need for meat and milk tolerances for the feeding of brewery wastes (See 1 and 2 below) and the second on metabolites to be included in the tolerance description (See 3 and 4 below).

The following decisions were made:

1) Methomyl - OPP to proceed to finalize the methomyl tolerance for imported hops. The meat and milk issue will be addressed during the FRSTR review along with other feed items (tolerances) for methomyl. Methomyl tolerances are already established for several feed items and at higher levels than needed for brewery waste.

2) Vinclozolin - OPP to require the animal feeding studies prior to establishing the hop tolerances. Currently there are no feed item tolerances for vinclozolin.

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CONCURRENCES

SYMBOL	TS-769						
SURNAME							
DATE	4/9/87						

EPA Form 1320-1 (12-70)

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*U.S. GPO : 1985-467-853

3) Metalaxyl - OPP to proceed to finalize the metalaxyl tolerances for imported hops. RCB will extrapolate from existing data to include metalaxyl metabolites in the tolerance description for hops.

4) Triadimefron - OPP needs to sort out the toxicity of the metabolite Baytan before tolerances are established. RCB will have difficulty with extrapolations from existing data to include the metabolites. It apears that hop analyses using the U.S. method will be needed prior to establishing triadimefon tolerances.

The fifth pesticide is triforine. This pesticide was not discussed with Dr. Moore because OPP only needs to do the appropriate clearance review for one of the inerts in triforine. The inert is already cleared for the current tolerances for triforine.

In summary, decisions were made to move on the proposed tolerances for methmoyl, metalaxyl, and triforine (non-issue). The Agency expects to establish these tolerances before the 1987 FRG hops would be imported to the U.S. (late 1987). Vinclozolin and triadimefon will require significant work before the tolerances can be established. For the latter two pesticides, the Agency is unable at this time to give any projected completion dates.

Attachment

Page 15 is not included in this copy.

Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

X The product confidential statement of formula

___ Information about a pending registration action

___ FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.