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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Reg. No. 3125-280. Methamidophos (Monitor®)on tobacco. Accession Number 252991.

FROM: Richard Loranger, Chemist R. Loranger
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

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

TO: William Miller, PM-16,
Insecticide/Rodenticide Branch
Registration Division (TS-767)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

Mobay Chemical Corporation has requested that the label of Monitor 4 Liquid Insecticide (active ingredient methamidophos or 0,S-dimethyl phosphoramidothioate) be amended to allow use on tobacco.

Tolerances of 0.02-1.0 ppm exist for residues of methamidophos on various vegetables, melons and cottonseed (40 CFR 180.315). Monitor® is also the major metabolite of the insecticide acephate and is regulated under several tolerances for that active ingredient (40 CFR 180.108).

The proposed use is ground application of 1-2 pints product (0.5-1.0 lb active) per acre in sufficient water for thorough coverage (max. 40 gallons spray/A). The maximum dose per season is 3 lb ai/A. Treatment should not occur within 21 days of harvest.

Nature of Residue

The metabolism of methamidophos on tomato plants, cabbage and tobacco plants involves the same hydrolytic pathways (W. Boodee, 4/8/71, PP# OF0956). The major metabolite is 0,S-dimethyl phosphorothioate formed by hydrolysis of the P-N bond. Further hydrolysis yields methyl mercaptan and methyl dihydrogen phosphate. TOX Branch does not consider the metabolites significant. Therefore, the residue of concern on food crops and tobacco is the parent compound. The radiolabeled studies also showed that Monitor is systemic and absorbed by both roots and leaves.

To examine the total residue on tobacco and the nature of pyrolysis products the registrant used Monitor labeled with ^{14}C in the S-methyl group (Report 86242). A solution of labeled Monitor was sprayed onto the leaves of 6 white burley tobacco plants at a rate equivalent to the proposed 1 lb ai/A (assuming 16 leaves/plant and 6800 plants/A for field grown tobacco). The plants were maintained in a closed plastic chamber during the treatment period (4 applications at weekly intervals). Leaves were sampled 0,7,21 and 35 days after the final application. Discs were removed for radioanalysis and portions also kept for determination of Monitor residues by the GC method discussed below (Report 45439). The remainder of the leaves were cured for ca 14-days in a lab fume hood. Cured leaves were also analyzed for total activity and Monitor residues before shredding for production of cigarettes (ca 1g).

For comparison purposes field grown tobacco was treated with unlabeled Monitor at the same rate and schedule described above for ^{14}C-methamidophos. The same PHI's (0,7,21,35 days) were observed before curing. Residues of Monitor per se were determined by GC for both the fresh and cured leaves.

Due to the storage stability problem (see Residue Data) the registrant should provide the storage conditions (temperature, duration) for the fresh and cured leaves in this study (Report 86242), especially for the field treated samples. If these samples were analyzed a short time after harvest and curing, we may be able to use the data for estimating Monitor residues in cigarettes. The field studies under Residue Data are questionable due to the long storage intervals prior to analysis.

The Monitor per se residues from the above field study (unlabeled methamidophos) are summarized below. The ppm Monitor represent averages of 3 replicates.

Ppm Monitor

	0 day	7 days	21 days	35 days
fresh tobacco	92	34	6	3
cured leaves	107	34	11	6

The results of the radiolabel work (closed plastic chamber) are presented below for Monitor per se and total radioactivity.

Ppm Monitor

	0 day	7 days	21 days	35 days
fresh tobacco	137	319	180	71
cured leaves	434	659	327	142

Total ^{14}C

fresh tobacco	158	426	192	91
cured leaves	1235	904	985	485

As expected, residues of Monitor were much higher in the chamber grown tobacco than in the field grown crop. The first three points of the field crop give a straight line (log residue versus time) with a resulting half life of 5.5 days. The registrant reports a half life of 15 days for the chamber study, but we question the validity of drawing a straight line through the widely scattered points. It can be seen from the table that the 7 day Monitor residues are much higher (<2x) than the 0 day values and the latter are even less than the 21 day residues.

In most of the samples a significant increase (ca 2x) in Monitor residues occurred upon curing. However, there is apparently also degradation of the insecticide during the process as the ^{14}C- total/Monitor per se ratio increased from 1.1-1.3 in fresh leaves to 1.4-3.4 in cured leaves. In other words, Monitor comprised 75-90% of the fresh tobacco residue, but as little as about 25% of the residue in cured leaves.

Cigarettes prepared from the cured radiolabeled leaves were smoked in a closed chamber (4x5 second puffs per minute) with both mainstream and sidestream smokes pulled consecutively through traps of deionized water (for polar and water solubles), 4N HCL with saturated cuprous chloride (for carbon monoxide - see Merck Index), isooctane (for highly volatiles), and 1N sodium hydroxide (for carbon dioxide). The unburned portions of the cigarettes were radioassayed as were aliquots of each trap. The CO_2 was also measured by addition of barium to the final trap (precipitating barium carbonate). The isooctane trap was further analyzed by GC and HPLC. Workup of the water trap

was more complicated. The sample was extracted with 1:2 acetone -methylene chloride, the water layer taken to dryness, and the organic layer reduced using gylcerin as a keeper. The organic layer was then transferred to the dried water flask and concentrated further prior to GC, HPLC and TLC analyses. Retention times and R_F values for radioactive peaks/spots were then compared to standards for identification.

The distribution of the radiolabel in the 4 cigarettes (0,7,21,35 day PHI's) was 77-86% in the smoke (main- + sidestreams), 8-16% in the ash plus butt, and 0-15% lost during the experiment. By comparison, a cigarette fortified with ^{14}C- Monitor had 90% of the label in the smoke and 7% in the ash/butt. Therefore, at least the proportion of total residue going into the smoke is not significantly reduced upon aging. The distribution of activity between mainstream (69-82%) and sidestream (18-31%) was similar in all cases.

The above study succeeded in identifying 96-98% of the activity in the 4 smoke samples. The major component by far in all cases was carbon monoxide (40-47% of total ^{14}C in smoke). Carbon dioxide from the NaOH trap comprised 10-13% of the smoke residue. The other eleven identified smoke contaminants were all found in the deionized water trap (although some dimethyldisulfide and thioanisole also in the isooctane trap). The following table summarizes the distribution of the smoke radioactivity. The percentages represent the sum of the mainstream and sidestream. All components were found in both streams.

Component	% Total smoke activity
carbon monoxide	40-47
carbon dioxide	10-13
dimethylsulfide	7-13
methanethiol	3-10
dimethyldisulfide	5- 9
dimethyl sulfone	2- 4
dimethylsulfoxide	1- 2
thioanisole	$\leq$ 1
methamidophos (Monitor®)	1- 5
N-methyl methamidophos	4-12
acephate (0,S-dimethyl acetylphosphoramidothioate)	1- 5
"amidate" (0,S-dimethyl phosphoramidothiaoate	2
N-methyl "amidate"	1- 2
unknown	2- 4

The first eight components represent products formed by cleavage of the P-S bond and further reaction of the CH_3S moiety with oxygen and other substrates. The other 5 identified smoke components still have the organophosphate moiety with at least 2 insecticides (the parent Monitor and acephate = N - acetyl

derivative of Monitor) in that group. The "amidate" apparently comes from the migration of the methyl group in Monitor from sulfur to oxygen.

The autoradiograph (TLC) and gas chromatogram for the water trap show 10 spots and 11 peaks, respectively. Since methanethiol and thioanisole have the same R_f value on the TLC plate, both techniques are consistent with the presence of the 11 metabolites listed above (excluding CO and CO_2).

The above radiolabel study is adequate for characterization of the pyrolysis products of aged residues of methamidophos on tobacco. However, the registrant should provide the storage information for at least the field treated leaves as discussed above so that we can determine whether the data are acceptable for estimating the quantity of Monitor residues in cured tobacco. The radiolabel work provides an excellent description of the qualitative nature of the smoke residue but is not useful for quantitative purposes due to the growth in a closed plastic chamber.

Analytical Method

To determine levels of methamidophos in tobacco Mobay used the "Gas Chromatographic Method for the Determination of Residues of MONITOR® in Peanut Meat and Hay, Sorghum Grain, and Rapeseed" (Report 45439, 12/22/75). In this method samples are refluxed with chloroform/methanol (in some cases prior blending with those solvents is needed), filtered, concentrated, and partitioned between acetonitrile and hexane (peanut hay, sorghum grain) or between benzene and water (rapeseed, peanut meat). In the latter case the Monitor is partitioned from the water layer into chloroform-acetone. Samples are further purified by silica gel columns prior to GC determination with a thermionic detector. In most cases it is not indicated which extraction solvent and partitioning were used for tobacco. However, in Report 68591 (recovery study) it is specified that the prior blending with chloroform/methanol and partitioning with acetonitrile/hexane were employed.

Control values for cured tobacco leaves were <0.01 ppm with one exception (0.02 ppm). Recoveries ranged from 77 to 108% for 0.05, 0.1, and 0.5 ppm fortifications in cured leaves. Submitted chromatograms indicate peaks on the order of 0.02 ppm or less are measurable.

Two different GC column polarities (Poly A-101, Carbowax 20M) create the equivalent of a confirmatory method. Recovery data were obtained with each column.

We consider the above method adequate for determining residues of methamidophos in cured tobacco.

Residue Data

A limited stability study (2 stored samples) indicates that Monitor® residues are unstable during frozen storage (Report 68556). Cured leaves spiked with 1.0 ppm Monitor apparently had 43% and 64% decomposition of the insecticide after 14 and 97 days, respectively, of storage at 0 to -10°F. At this time we are not convinced that this study represents typical behavior of methamidophos during storage since several of the residue trials report significant residues in samples analyzed 16 months to 3.5 years after havest. For example, in Report 67575 the 28 day leaf sample, which was air cured 60 days and then kept over 3 years prior to analysis, contained 4.43 ppm Monitor. If methamidophos were really disappearing at the rate shown in the storage study, it is unlikely residues of that level would be found after 3 years. In any case the long storage intervals (6 months-- 3.5 years) used in the field trials discussed below render them questionable at this point. A final conclusion concerning Montior residues in tobacco will not be made until the storage conditions for the field study discussed under Nature of Residue have been submitted.

Residue trials described in this submission include six in Kentucky for air-cured (burley) tobacco and four in the Carolinas for flue-cured tobacco.

The Kentucky trials all involved 3 applications of 1.0 lb ai/A (max. requested use) in spray volumes of 18-40 gallons/acre. Leaves were sampled at intervals of 1-56 days after the final treatment (21 day PHI proposed) and air cured at ambient temperatures for 2-3 months in at least three trials. The length of curing was not specified in the other studies. The highest Monitor residue observed was in the only 1 day sample with 14.4 ppm methamidophos on a whole leaf basis (27.4 ppm in the leaf portion and only 1.4 ppm in the midrib). For 7-10 day PHI's residues ranged from 0.19 to 12.8 ppm. Those samples closest to the proposed use contained 0.13-7.88 ppm (21-23 day PHI's). This compares to the 11 ppm found at 21 days in the field portion of the study (Report 86242) discussed under Nature of Residue. At significantly longer intervals (37-56 days) Monitor decreased to <0.01-1.04 ppm.

The flue-cured studies in the Carolinas also reflected the proposed use of 3 x 1 lb ai/A. Leaves were harvested 3-21 days after the third application and flue-cured for 6-7 days with maximum temperatures of 160-180°F. Monitor residues were considerably lower than those in air-cured tobacco. Three day leaves contained up to 5.64 ppm Monitor with 0.96-1.23 ppm on day 14 and 0.74-0.94 ppm on day 21 (requested PHI).

To demonstrate the effect of aging, an air-cured sample with 0.13 ppm Monitor and a flue-cured sample having the 0.74-0.94 ppm leaves were aged ca 1.5 years at ambient temperature. The leaves were then stemmed (mid-ribs removed) and found to contain <0.01 ppm methamidophos. This is not surprising considering the loss observed in the storage stability study.

At this time we are unable to determine maximum Monitor residues expected in flue-cured tobacco due to the long storage intervals in the above trials. We await storage information for the samples in Report 86242 to see if the leaves in that experiment may be used for estimating residues. Once we can determine that level we will provide TOX Branch with the nature and quantity of methamidophos components expected in smoke.

Conclusions

1. The residue of concern on tobacco is methamidophos per se.

2. The registrant should provide the storage conditions (temperature, duration) prior to analysis for the fresh and cured leaves in Report 86242. This is especially important for the field treated leaves which were also cured since they represent likely levels in cigarettes.

3. The pyrolysis products from aged residues of methamidophos on tobacco have been adequately characterized. The major components in smoke are carbon monoxide (40-47%), carbon dioxide (10-13%) and dimethylsulfide (7-13%). For the remainder of the smoke residue see the Nature of Residue section above.

4. Adequate analytical methodology is available to determine residues of methamidophos in tobacco.

5. The long storage intervals (6 months - 3.5 years) employed in the tobacco field trials in conjunction with the storage stability data showing 64% loss after 97 days render the submitted residue data questionable at this time. For a final conclusion concerning Monitor levels in tobacco the registrant should submit the storage information requested in Conclusion 2.

6. The highest methamidophos residues observed in air-cured and flue-cured leaves following the proposed use in the field trials were 7.88 ppm and 0.94 ppm, respectively. These levels are questionable at this time due to storage problems noted in Conclusion 5.

Recommendation

We recommend against the use of Monitor on tobacco at this time for the reasons noted in Conclusions 2 and 5.

cc: R.F. Circu: Reviewer, Methamidophos:S.F. Amend use File
Tobacco
RDI: A. Rathman:8/20/84: RDS: 8/20/84
TS-769:RCB: R.L.:bj: RM-810: CM#2: X557-7377: 8/21/84