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

RF,

APR 29 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: PP#3F2788 - Pendimethalin (Prowl®) on/in Barley
and Wheat.
Review of the September 26, 1991 American Cyanamid
Letter.
(No MRID No.) [CBTS Nos. 8859 and 8860]
{HED Project No. 2-0382} (Bar Code D170619)

FROM: Francis D. Griffith, Jr., Chemist
Chemistry Branch I - Tolerance Support
Health Effects Division (H7509C)

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

and

Toxicology Branch II - Herbicide, Fungicide,
Antimicrobial Support
Health Effects Division (H7509C)

THRU: Debra F. Edwards, Ph.D., Acting Chief
Chemistry Branch I - Tolerance Support
Health Effects Division (H7509C)

American Cyanamid Company has submitted a letter dated September 26, 1991, signed by Barbara Gingher requesting CBTS reverse its deficiency on ruminant metabolism and find the metabolism study acceptable. RD requested CBTS comments on this letter. The specific deficiency identified in our March 5, 1991, review by F.D. Griffith, Jr. is repeated below, followed by the petitioner's rationale for reversal of our conclusion, then CBTS comments. Our revised conclusion (3b) and recommendation follow. Since this September 26, 1991, letter only addressed one of several deficiencies, the other deficiencies noted in the CBTS review are reiterated and incorporated into this review by reference. They remain unresolved and continue outstanding.

EXECUTIVE SUMMARY OF CHEMISTRY DEFICIENCIES

- Plant metabolism studies required.
- Poultry metabolism studies are necessary.
- Ruminant metabolism study characterization of residues is required.
- Confirmatory analytical method needed.
- Multiresidue method data are needed.
- Livestock feeding studies may be required.
- Wheat processing study is necessary.

CONCLUSIONS

- 3b. The petitioner has conducted and reported on a lactating caprine ¹³C- and ¹⁴C-ring labeled pendimethalin metabolism study. Measurable/ detectable total residues were found in caprine liver ranging from 0.08 ppm to 0.17 ppm (n = 3) from a 6.5 ppm dose. Trace amounts of pendimethalin equivalents were detected in kidney (about 0.02 ppm) and in milk (< 0.01 ppm). Fractionation of various liver extracts revealed numerous free, unbound ¹⁴C-pendimethalin equivalents. Chromatographic evidence suggests, but does not confirm this residue probably includes pendimethalin and its alcohol, possibly at the 0.025 ppm level. There is also no spectrophotometric evidence presented to identify any of the radiodetected peaks. CBTS reiterates that the nature of the residue in ruminants is not adequately identified.
- 3c. Although the petitioner did fractionate the radioactivity from the liver, insufficient data were presented to confirm the identity of the major peaks. CBTS suggests the petitioner repeat the HPLC separation step and use MS as the detector. The HPLC/MS interface is to be the thermospray probe and/or particle beam. Alternatively, additional confirmation of known pendimethalin rat metabolites can be carried out in the ruminant tissue using other HPLC detectors, or from the use of other chromatographic techniques that can elucidate organic structure. If the petitioner does not choose to identify the residues by spectroscopic techniques, clearly labeled chromatograms should be provided for authentic standards (at a minimum the parent and the dinitrobenzyl alcohol metabolite) and the liver extracts using the same chromatographic conditions.
- 3d. The petitioner has the option of repeating the ¹⁴C-pendimethalin ruminant metabolism study at the level suggested in the July 1989 guidance memorandum; i.e., 10 ppm or higher. CBTS notes that no data were presented from the 0.1 ppm (or 0.096 ppm) liver. We also feel that

if there is a reserve portion of the liver at the 0.17 ppm level available, then that liver sample should be fractionated and characterized. CBTS reiterates "complete" characterization of the caprine radiolabeled residues is essential for CBTS to ascertain the need for a ruminant feeding study.

- 3e. If the caprine pendimethalin metabolism differs significantly from that in rats, then a ¹⁴C-ring labeled pendimethalin porcine metabolism study may also be necessary.
- 3f. If the petitioner can establish that all peaks represent <0.005 ppm pendimethalin equivalents, further characterization and identification will not be required.

RECOMMENDATION

CBTS cannot, at this time, recommend the requested pendimethalin tolerance of 0.1 ppm on wheat grain, wheat forage, barley grain, and barley forage; and the 0.3 ppm tolerance on wheat and barley straw for the reasons cited in our Executive Summary of Deficiencies and detailed in our Conclusions 2 through 8 of our March 5, 1991, memorandum and Conclusion 3 above.

For further consideration of this petition, the petitioner needs to be advised to resolve these deficiencies. CBTS and CBRS scientists are willing to meet and discuss our position on this subject.

DETAILED CONSIDERATIONS

Nature of the Residue - Livestock

Deficiency

- 3b. The petitioner has conducted and reported on a lactating caprine ¹³C- and ¹⁴C-ring-labeled pendimethalin metabolism study. Measurable/ detectable residues were found only in caprine liver ranging from 0.08 ppm to 0.17 ppm (n = 3) from a 6.5 ppm dose. Trace amounts were detected in kidney (about 0.02 ppm) and in milk (< 0.01 ppm). Fractionation of various liver extracts revealed numerous free, unbound ¹⁴C-components in the 0.005 ppm to 0.025 ppm range that were not characterized. CBTS concludes that the petitioner has not adequately identified the nature of the residue in ruminants. CBTS suggests that the petitioner repeat the HPLC identification steps for all

fractions above 0.005 ppm, characterizing major peaks and using detectors that can elucidate organic structures such as but not limited to MS, FTIR, FTUV, and NMR. The petitioner needs to confirm the presence of or absence of all metabolites identified in the rat metabolism study. Complete characterization of caprine radiolabeled residues is essential for CBTS to ascertain the need for a ruminant feeding study. If caprine metabolism differs significantly from that in rats, then a ^{14}C -ring labeled pendimethalin porcine metabolism study may also be necessary. The deficiency is not resolved and continues outstanding.

Petitioner's Response

The petitioner's September 26, 1991, letter disagrees with the March 5, 1991, memorandum conclusions on ruminant metabolism and requests CBTS reconsider its conclusion, and if we do not overturn our original decision, then RD is to overrule the Branch and find this ruminant metabolism study acceptable. American Cyanamid challenges CBTS on four specific points.

CBTS Comments

CBTS has reconsidered its decision on the nature of the pendimethalin residue in ruminants. Senior scientists in CBTS have consulted with senior scientists in CBRS on this topic, and this memorandum reflects current thinking of both Branches. CBTS notes the same study with the same MRID number was recently submitted to CBRS for review.

CBTS reiterates that the ruminant metabolism study does not define the nature of the residue. After reconsideration, CBTS still concludes this study does not follow the guidance offered in the July 25, 1989, memorandum. That memorandum states that following FAO's lead we suggest 10 ppm in the diet as the dosing level, not slightly more than one-half that level as the appropriate dose. Reviewing again the chromatograms presented as figures 5, 6, and 7 (pages 141, 142, and 143), we agree there are a number of peaks that show radioactive components. CBTS reiterates further work is required on the major components in these chromatograms (3 to 7 peaks depending on the chromatogram). CBTS points out that since the petitioner chose to use about one-half the suggested dose, we have used one-half the suggested ppm for each cut point where fractionation followed by characterization are required. The same analytical answers can be obtained using 1992 state of the art analytical instruments and techniques.

CBTS points out to the registrant that, on page 3 of our March 5, 1991 CBTS memorandum, line 5 under "b" reads 0.08 ppm. The petitioner claims that 60X is a highly exaggerated dose. We do not feel 6.5 ppm is a highly exaggerated dose when a ruminant livestock feed item is to have a 0.3 ppm tolerance. CBTS reiterates the total radioactive residues in liver ranged from 0.077 ppm (which CBTS rounded to 0.08 ppm) to 0.17 ppm with $n = 3$. The petitioner chose to fractionate for characterization the lowest residues found in liver. CB feels that if the higher residue levels based on radio counts had been used for fractionation followed by characterization, then the results would have been above the level where complete characterization would be required.

Reviewing Figure 8 of Report CY37, we note that 91 percent of the residue in the hexane extract is CL 92,553; thus, 91+ percent of the residue of 0.025 ppm as noted in Figure 4 is probably CL 92,553. However, we have no direct spectrophotometric evidence this is the case. If we were to compare the radio peaks of the standards from figure 3 to the peaks in figures 5 and 7, then there is a presumption that both CL 92,553 and CL 202,347 are present in quantities that can be quantitated. CBTS requests spectrophotometric confirmation, or evidence from use of various chromatographic techniques that these peaks are or are not CL 92,553 and CL 202,347 and if confirmed then the petitioner needs to quantitate these results. CBTS is interested in the major peaks (3 to 7 peaks depending on the chromatogram). We are not interested at this time, for example, in the petitioner identifying the minor peaks between 45 minutes and 70 minutes. Clearly the extractable activity is in the 0.01 to 0.05 ppm range that the July 25, 1989, Schmitt memorandum suggests that partitioning followed by adequate chromatographic analysis is necessary. We reiterate the petitioner needs to compare the chromatographic behavior of the known pendimethalin and its metabolites as determined in the rat metabolism study to this study. Use of HPLC as a separatory technique is adequate. We strongly suggest use of HPLC/MS, not just a radio counting device, as the determinative step for this comparison. We fully recognize that HPLC/MS requires use of a sophisticated interface to separate the analyte from the mobile phase and in this regard the thermospray probe and/or particle beam interfaces are acceptable. CB notes that on page 13 of our discussion in the March 5, 1991 memorandum, we suggested use of HPLC detection systems that could elucidate organic structure. The petitioner still has the option of repeating the ¹⁴C-pendimethalin ruminant metabolism study using 10 ppm or an even higher dose to resolve the issue.

Although the petitioner did fractionate the radioactivity from the liver, insufficient data were

presented to confirm the identity of the major peaks. If the petitioner can establish that all peaks represent <0.005 ppm pendimethalin equivalents, then further identification will not be required.

The petitioner is referred to the third paragraph on page 12 of our March 5, 1991 review. The petitioner reported only results of the 0.077 ppm liver. What were the results of the 0.096 (or 0.1 ppm) liver? Is this liver still available for fractionation and characterization? Are portions of the 0.17 ppm liver still available for fractionation and identification? CBRS and CBTS feel that the petitioner should not have chosen to use the lowest residue liver to characterize the nature of the residue.

The petitioner's two remaining issues cannot be addressed until the issues above are resolved. CBTS reiterates that "complete" characterization as noted above is needed to ascertain the need for a ruminant feeding study. The criteria for needing or not needing a feeding study has been addressed in the CBTS policy memorandum noted above. CBTS continues to state that the presence or absence of the known rat metabolites is to be confirmed in the ruminant metabolism study; and if the ruminant metabolism is different, then a porcine ¹⁴C-pendimethalin metabolism study may be necessary.

cc: R.F., Circ (7), Reviewer(FDG), PP # 3F2788, 3F2844, and 3F3049, CBRS (Perfetti), PIB/FOD (Furlow).

H7509C:CBTS:Reviewer(FDG):CM#2:Rm 812D:305-5826:JOB:
53589:I:C.Disk:KEVRIC:03/30/92:rj:wo:dd:rj:dd/dd:edit:fdg:
4/27/92.

RDI:SecHd:RSQuick:4/27/92:BrSrSci:RALoranger:4/27/92.