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

APR 6 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Amitraz. ID No. 106201. List A Reregistration Case No. 0234. MRID No. 421335-01. CBRS No. 9371. DP Barcode No. D173972.

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TO: Mario Fiol (PM-74)
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Nor-Am has submitted a waiver request for dermal metabolism studies in cattle (ruminant) and swine. The 12/18/91 submission provides rationale for the request, and a study entitled "Dermal Absorption of Amitraz in the Rat" (MRID No. 421335-01), to provide additional support for the rationale.

Conclusion and Recommendation

The dermal treatment of hogs appears to be an expanding use for this chemical, and therefore it is imperative that the registrant submit a dermal metabolism study for swine. CBRS will reserve the requirement for the cattle dermal metabolism study pending the outcome of the swine study. Provided the registrant commits to conduct the swine dermal metabolism study, CBRS sees no reason for delaying the issuance of the RED.

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DETAILED CONSIDERATIONS

The 7/6/90 update to the amitraz Registration Standard (10/15/84) concluded that ruminant dermal metabolism studies submitted to the Agency in 1970 and 1972 do not meet current acceptance criteria because animals were not sacrificed within 24 hours of the final dose, and because ^{14}C-activity in milk and tissues was not characterized. Metabolism studies in which cattle and swine receive direct dermal application of ring-labeled [^{14}C]amitraz remain outstanding.

In the current submission, the registrant cites numerous studies regarding the fate of [^{14}C]amitraz following oral and/or dermal treatment in mice (oral); dogs (oral and dermal); rats (oral and dermal); cats (oral); laying hens (oral); cattle (oral); baboon (oral); and pigs (dermal). An additional study depicting dermal absorption of amitraz in the rat (MRID No. 421335-01) is submitted to CBRS in support of the waiver request and also to TOX for formal review. The rationale provided by the registrant in support of the subject data waiver request is summarized briefly:

1. Dermal and oral exposure studies reveal qualitatively similar metabolism results in two species [dog and rat].

2. Metabolism studies in numerous species have indicated that the major route of excretion is urine; furthermore, metabolism in all species examined is qualitatively similar.

3. Metabolism studies have led CBRS to conclude that the nature of the residue (following oral treatment) in poultry and ruminants is adequately understood.

4. Metabolism in plants and soil is well understood, and does not differ significantly from the metabolism of amitraz in animals.

5. An ample database of residue studies is available to support current and pending tolerances in animal commodities.

The registrant does not believe that dermal metabolism studies in ruminant and swine are necessary, and that the sacrifice of additional animals to confirm the already established metabolism picture is unwarranted.

CBRS Response

CBRS has examined the list of references submitted by the registrant, and found the following to provide limited information regarding the metabolic fate of amitraz via oral and dermal routes of application:

(1) "The Absorption, Metabolism and Excretion of MITIBAN (U36,059) [amitraz] in the

Dog from Oral and Dermal Exposure," R.E. Hornish and Nappier, J.M. NOR-AM Report Reference M-72, MRID No. 161006.

(2) "Fate of ^{14}C-BTS 27419 [amitraz] Applied to Rats as a Single Dermal Dose," D.K. Lewis. NOR-AM Report Reference M-41, MRID Nos. 28670, 41493, and 55721.

(3) "Dermal Absorption of ^{14}C Amitraz in EC Formulation by Male and Female Pigs Given a Single Topical Application of 18 mg a.i.," J.K Campbell and Needham, D. NOR-AM Report Reference M-69, MRID No. 161007.

CBRS was unable to locate TOX Branch conclusions in the TOX One-Liner data base for MRID Nos. 161006 and 161007. According to the data base, MRID Nos. 38670, 41493, and 55721 (one study) meet core grade minimum requirements for a rat dermal metabolism study. The results of these studies are as follows:

(1) MRID Nos. 38670, 41493, and 55721: 2 rats were treated dermally with ^{14}C amitraz in acetone, and killed after 24 hrs. Approximately 50% of the radioactivity was absorbed through the skin, and was excreted in the urine and feces. Less than 1% of the dose was recovered from the liver and kidneys. The remaining 50% of the radioactivity was found on the skin and wrapping materials. The radioactive residues found in the excreta and tissues were quantitated, but not characterized.

(2) MRID No. 161006: Dogs were treated both orally and dermally with radiolabeled amitraz in a xylene-based formulation, as well as with a non-radiolabeled registered formulation (Mitaban), and residues were characterized in blood plasma, urine, and feces using TLC and HPLC. For radiolabeled studies, oral metabolism showed rapid absorption and elimination (peak output of radioactivity was within 24 hrs) via the urine, whereas dermal studies showed much slower absorption and elimination (peak output of radioactivity was between 1 and 3 days). In addition, the studies showed that elimination of radioactivity following dermal treatment was extended over a longer period of time (80% eliminated by day 6) than was seen following oral dosing (80% eliminated within 24 hours). The results of these studies are questionable, since the same four dogs were used for oral and dermal dosing (oral occurred first). The nonradiolabeled studies confirmed the radiolabeled results, indicating that dermal absorption is much slower than oral absorption. Residues in tissues were not examined (it appears that the animals were not sacrificed).

(3) MRID No. 161007: 4 weanling pigs were treated with one dermal application of radiolabeled amitraz in an EC formulation typically applied to pears (the study attempted to simulate worker skin exposure to the formulation applied to pears). The dose area was washed after 12 hrs, removing 57 - 81% of the radioactivity. Pigs were sacrificed 60 hrs after treatment; at this time, a total of 6.7 $\pm$ 2.7% of the original dose was recovered from the excreta, while 2.8 - 10.5% of the radioactivity remained on the treated area. Skin samples collected from the loin, a remote location from the dosing

site, contained the highest residues, but these were considered to have come from contamination with urine. Residues in all other tissues except the eye were lower than the 0.05 ppm detection limit.

The current submission contains an additional rat metabolism study, in which 10 rats were treated with a dermal application of radiolabeled amitraz in a 50WP formulation. The skin area to which the dose had been applied was cleaned with soapy water 10 hours following treatment. Five of the rats were sacrificed 24 hours after treatment, while the remaining 5 were sacrificed 5 days after treatment. Radioactive residues in urine, feces, gastrointestinal tracts, and carcasses were examined using TLC. Rats killed within 24 hours had absorbed 0.55 - 4.49% of the applied radioactivity, while rats killed after 5 days had absorbed 1.37 - 7.75%. The registrant concluded that amitraz (in the 50WP formulation) has a low potential for dermal penetration in the rat.

These studies afford us with information regarding the rate of dermal penetration, and in a limited sense, with information regarding metabolism via the dermal route, but they do not lead CBRS to conclude that the dermal and oral metabolism are qualitatively similar. None of the studies have resulted in characterization of radioactive residues in tissues (i.e. liver, kidney, fat, and muscle), only in feces, urine, and blood. Although residues in tissues in the weanling pigs were considered to be below the method limit of detection, CBRS is not certain that a significant amount of radioactivity was absorbed, since a registered [^{14}C]amitraz-spiked dermal-use formulation was not used and since pigs were washed 12 hours after treatment. The dog study indicated that amitraz is absorbed slowly through the skin, and is eliminated over a longer period of time than is seen for oral dosage and absorption. Since it is unlikely that cattle and swine will be washed following treatment, the chemical will remain on the skin, and continue to be absorbed.

Although the nature of the residue in ruminants and poultry following oral dosing is adequately understood, the dog study has revealed different rates of absorption and elimination following oral and dermal dosing; since the residues in dog tissues were not characterized, CBRS can make no conclusions regarding the nature of the residue. Differences in absorption rate, and theoretically even metabolic processes, could result in significant levels of one or more residues in livestock following dermal exposure when the same residues were absent or insignificant following oral exposure, thus escaping detection and/or regulation. Radioactivity was washed off the skin of rats and pigs treated dermally, so it is possible that low residues in tissues were due to inadequate uptake of radioactivity through the skin. The objective of the pig study was to determine possible effects of worker exposure, so the radiolabeled amitraz was applied in a formulation typically used to control mites on pears. There are no data for <u>any animal</u> depicting radioactive residues of amitraz in tissues following dermal treatment with representative formulations registered for such direct-animal treatment.

Since dermal treatment of swine is an expanding use for amitraz (memo, C.B. Swartz, 12/31/91), it is essential to understand the nature of the residue following dermal treatment of swine with a representative dermally-applied formulation (spiked with [^{14}C]). While CBRS

would prefer to have both ruminant and swine dermal metabolism results, submission of the swine dermal metabolism study may satisfy the requirement for reregistration. CBRS will reserve the requirement for the cattle dermal metabolism study pending the outcome of the swine study. Provided the registrant commits to conduct the study, CBRS sees no reason for a delay in the issuance of the forthcoming RED.

cc: CSwartz; Amitraz Reg. Std. File; SF; RF; Circulate; C. Furlow (PIB/FOD)
H7509C:CSwartz:CM#2:Rm 800D:703 305 5877:3/20/92
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AMITRAZ (LIST A REREGISTRATION CASE NO. 0234/SHAUGHNESSY CODE NO. 819393) RESIDUE CHEMISTRY DATA SUMMARY THROUGH 4/1/92[1]

REASSESSMENT OF U.S. TOLERANCES AND POTENTIAL FOR HARMONIZATION WITH CODEX[2]

Guideline Number and Topic[3]	Phase V data requirements satisfied?	MRID(s)[4]
171-3 Directions for use		
171-4(a) Plant Metabolism	Y	
171-4(b) Animal Metabolism	N[5]	42133501
171-4(c) Residue Analytical Methods - Plants	Y	
171-4(d) Residue Analytical Methods - Animals	Y	
171-4(e) Storage Stability	Y	
171-4(k) Crop Field Trials		
171-4(k) Pome Fruits Group		
Apples [see 171-4(l)]	Y[6]	
Pears	Y	
171-4(l) Processed Food/Feed		
Apples	Y[7]	
171-4(j) Meat/Milk/Poultry/Eggs	Reserved[8]	
171-4(f) Potable Water	N/A	
171-4(g) Fish	N/A	
171-4(h) Irrigated Crops	N/A	
171-4(i) Food Handling Establishments	N/A	
171-5 Reduction of Residues	N/A	

[1] Registration Standard issued 10/11/84, Guidance Document 10/87. Reregistration Standard Update issued 7/6/90.

[2] There are no Canadian or Mexican tolerances for amitraz residues. Although the proposed CODEX tolerance expression is somewhat different than the U.S. tolerance expression, it appears that the same residues of concern will be regulated. There are proposed CODEX tolerances in the following commodities for which there are no U.S. tolerances: cherries (0.5 ppm); cottonseed (0.5); cottonseed oil (0.05); cucumber (0.5); oranges, sweet and sour (0.5); peach (0.5); and tomato (0.5). For tolerances which the U.S. and CODEX have in common, CODEX tolerances are somewhat lower than U.S. tolerances. Specifically, the tolerance in meat by-products of cattle and pigs is 0.3 ppm in the U.S., and 0.2 ppm under the CODEX system; the milk tolerance is separated into milk (0.03 ppm) and milk fat (0.3 ppm), while the CODEX tolerance for all "milks" is 0.01 ppm. There are no U.S. food/feed additive tolerances.

[3]N/A = Guideline requirement not applicable.

[4]MRIDs that were reviewed in the current submission are designated in shaded type.

[5] Nor-Am submitted a waiver request for cattle and swine dermal metabolism studies. Due to the lack of studies depicting the nature of the residue in any animals following treatment with registered dermal formulations (spiked with [^{14}C]amitraz), and due to the expanding use of amitraz on hogs, CBRS