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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration # 524-316. Feeding of radiolabelled alachlor metabolites to lactating goats. Accession No. 252793.

FROM: Nancy Dodd, Chemist
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

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

TO: Robert Taylor, PM #25
Herbicide-Fungicide Branch
Registration Division (TS-767)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

Monsanto submitted a study in which synthetic $^{13}C/^{14}C$ - radiolabeled plant metabolites of alachlor (2-chloro-2',6'diethyl-N-(methoxymethyl)acetanilide) were fed to lactating goats. The distribution of radioactivity in milk, tissues, and excreta was examined. Due to low levels of residues in tissues and milk these were not identified. A summary of this study was reviewed previously (N. Dodd, memo of 4/10/84). This study is being submitted in lieu of conventional feeding studies which are apparently in progress in an effort to get EPA to use residue levels lower than the tolerance for risk assessment.

Tolerances are established for the herbicide alachlor [2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide] and its metablites (calculated as alachlor) in meat, fat, and meat by-products of cattle, goats, hogs, horses, poultry, and sheep and in milk and eggs at 0.02 ppm. The sensitivity of the analytical method accepted

for enforcement (Method II, Pesticide Analytical Manual, Vol. II) ranges from 0.01-0.02 ppm for meat, milk, and eggs.

A goat metabolism study was conducted using $^{13}C/^{14}C$ labeled alachlor plant metabolites to determine residue levels in goat milk, tissues, blood and excreta. A mixture of five plant metabolites was administered by oral dose to 3 lactating goats for 5 days. The metabolites were labeled with ^{14}C in the phenyl ring and with ^{13}C at the C-2 carbon of the acetamide moiety. The five metabolites are listed below:

I (29.2%)	N-[[2-ethyl-6-(1-hydroxyethyl)]-phenyl]-N-methoxymethyl-2-(methylsulfonyl)acetamide
II (17.7%)	N-[(2,6-diethyl)phenyl]-N-methoxymethyl-2-(hydroxy)acetamide
III (17.7%)	2',6'-diethyl-N-(methoxymethyl) oxanilic acid, sodium salt
IV (17.7%)	N-[(2,6-diethyl)phenyl]-N-methoxymethyl-2-amino-2-oxoethanesulfonic acid, sodium salt
V (17.7%)	3-[[N-(2,6-diethyl)phenyl-N-methoxymethyl]-2-amino-2-oxoethanesulfinyl]-2-hydroxypropanoic acid, sodium salt

Monsanto has not provided an explanation of why these particular metabolites were chosen. However, the composition of the mixture is consistent with the fact that as much as 40-50% of soybean residue consists of metabolites convertible to 2-ethylaniline upon strong acid hydrolysis.

The daily dose was a total of 9.7 mg/day calculated as alachlor equivalents or 11.3 mg/day calculated as component weight. Since the average daily diet intake is 1.8 kg of feed/day, a level of 5.4 ppm alachlor equivalents was fed in the diet for 5 days. No plateau in milk residues was observed. Two goats and a control were killed approximately 24 hours after the final dose. The third goat was depurated for 5 days before being killed. The ^{14}C activity in blood rose rapidly after the first dose and plateaued during the dosing period. The ^{14}C in plasma and milk decreased rapidly during the first day of depuration. The ^{14}C recoveries (including excreta, milk, tissues, GI tract, and blood) were 78.5-87% for the 3 goats as a percentage of the dose, including 36-46% for urine, 32-42% for feces, and less than 0.5% each for milk, liver, muscle, kidney, and fat. Residues in goats for a 5.4 ppm feeding level are below:

	Values (ppb) from Complete Data Submission*	Values (ppb) from Report Summary Previously Reviewed on 4/10/84
Milk	$\frac{89 \text{ dpm/g}^{**}}{1.8 \times 10^4 \text{ dpm/ug}} = 4.9$	5.4
Liver	$\frac{250 \text{ dpm/g}^{***}}{1.8 \times 10^4 \text{ dpm/ug}} = 14$	15
Kidney	$\frac{205 \text{ dpm/g}^{***}}{1.8 \times 10^4 \text{ dpm/ug}} = 11.4$	12
Muscle	$\frac{<63 \text{ dpm/g}}{1.8 \times 10^4 \text{ dpm/ug}} = <3.5$	<3.7
Fat	$\frac{<70 \text{ dpm/g}}{1.8 \times 10^4 \text{ dpm/ug}} = <3.9$	<4.1

* The nonweighted average value for milk from the data tables was 94 dpm/g. The highest values for milk were 186.763 dpm/g (goat #30), 154.113 dpm/g (goat #29), and 161.882 dpm/g (goat #26).

The highest values for liver were 241.811 dpm/g (goat #30) and 278.180 dpm/g (goat #26). The average value for liver from the tables was 252 dpm/g.

The highest values for kidney were 144.068 dpm/g (goat #30) and 285.750 dpm/g (goat #26). The average value for kidney is 205 dpm/g.

** Average values including AM and PM milkings and reflecting weighted averages.

*** Average values for 2 goats sacrificed approximately 24 hours after last dose.

Calculated residues assuming a 0.2 ppm dietary burden of alachlor and its metabolites and a linear relationship between feeding levels and residue concentration are below:

	Values (ppb) from Complete Data Submission	Values from Report Summary Previously Reviewed on 4/10/84
Milk	0.18	0.20
Liver	0.52	0.55
Kidney	0.42	0.44
Muscle	0.13	0.14
Fat	0.14	0.15

Residues using the highest reported dpm/g values for milk, liver, and kidney of goats are below:

		Residues from a 5.4 ppm Feed Level (ppb)	Calculated Residues for a 0.2 ppm Feed Level (ppb)
Milk			
$\frac{186.763 \text{ dpm/g}}{1.8 \times 10^4 \text{ dpm/ug}}$	=	10.4	0.38
Liver			
$\frac{278.180 \text{ dpm/g}}{1.8 \times 10^4 \text{ dpm/ug}}$	=	15.45	0.57
Kidney			
$\frac{285.750 \text{ dpm/g}}{1.8 \times 10^4 \text{ dpm/ug}}$	=	15.9	0.59

In goat urine, little or none of metabolites I and II were found, which means that compounds I and II are further metabolized by goats. Glucuronide conjugates of I and II are found among the modified metabolites of I and II. Metabolite III is excreted unchanged. In goat feces, major metabolites III and IV and minor metabolite I are excreted unchanged. These three metabolites account for more than 80% of the radioactivity in feces. Residue levels in milk and tissues were too low to allow identification.

Monsanto has indicated that complete results of this study will be submitted in the latter part of 1984.

Conclusions

1. The reliability of the study is questionable since the data reflect only one feeding level, only three goats, and a short (5days) feeding period. (Since no plateau in the milk residue levels was observed the animals should have been kept on the test diet for at least 4 weeks).

2. The calculations of residues resulting from a 0.2 ppm feeding level are based on an assumption that a linear relationship for feeding levels vs residue concentration exists at low feeding levels. This may not be true.

Also the calculations do not consider that a reasonable diet for cattle could consist of 60% peanut hay and 40% corn grain which would result in a dietary intake of 1.9 ppm of alachlor and its metabolites.

3. No validated analytical method exists which would reliably determine alachlor residues below the 0.02 pm level in meat and milk.

In addition, recently reviewed soybean and corn metabolism data indicate that a significant portion of plant residues, particularly in soybeans, consists of metabolites convertible upon acid hydrolysis to 2-ethylaniline. These metabolites would not be detected by the present enforcement methodology.

We requested (M. Kovacs, PP#0F2448, 3F2832, 4/23/84) that Monsanto submit residue data for these metabolites. A reevaluation of the presently established crop tolerances will then be made. This may result in recalculation of livestock's dietary burden.

The submitted study is not an adequate response to the requirement of the registration standard that animal metabolism studies be conducted in order to determine if the residues of concern in animals do indeed contain only the 2,6-diethylaniline moiety; only residues containing this moiety were determined in the previously submitted animal residue studies.

Recommendation

RCB recommends that the established tolerance of 0.02 ppm in meat and milk be used to assess risk.

cc: R.F., Circu., Reviewer, Alachlor S.F., E. Zager, D.Ierley/RD
RDI:EZ:6/28/84:RDS:6/28/84
TS-769:RCB:N.Dodd:gmk:CM#2:RM800:X77484:Date:6/28/84