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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

FEB 29 1984

MEMORANDUM

TO: Robert Taylor, PM#25
Registration Division (TS-769)

FROM: Amal Mahfouz, Toxicologist
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Lasso (Alachlor), EPA Reg.#524-316; Review of the Rat Metabolism Study; Monsanto's Special Report MSL-319, RD-493, October 14, 1983. Accession Nos.: 251543 and 251544.
CASWELL#11

Action Requested:

Monsanto Company submitted for review the following rat metabolism study to support the registration of Alachlor, Reg. #524-316, and its formulated products: Lasso, Reg.#524-314; Lasso EC, Reg.#524-285; Lasso II, Reg.#524-296; and Lasso ME, 524-344. This metabolism study included the following two parts:

°Treatment of animals with single oral dosages (low and high) of radiolabeled Alachlor and the fate of this compound after 48 and 10 days of the initial exposure. Accession#251543

°Identification, characterization and quantification of the above radiolabeled metabolites. Accession#251544

Recommendation:

Study Classification: Core-Minimum

1. Alachlor was rapidly metabolized in rats and equally eliminated in urine and feces as conjugates of mercapturic acid, glucuronic acid, and sulfate. Approximately 89% of the initial dosages (7 mg/kg and 700 mg/kg for the low and high dosage groups respectively) were eliminated within 10 days of the initial exposure; most of this elimination occured within the first 48 hours of exposure. Elimination through CO_2 was minimal (0.02% of the dosage within 48 hours). The rate of elimination through urine and feces was biphasic: an initial rapid phase with a half life of 0.2 to 10.6 hours followed by a slower phase with a half life of 5 to 16 days.

2. After 10 days of an initial exposure to the above mentioned low and high dosage levels, 1.3% to 2.2% residual alachlor/metabolites were detected in blood; 0.66 to 1.27% in carcass; and a total of 0.24 to 0.32% in organ/tissues.

3. Levels of residual alachlor in spleen, liver, kidney and heart were relatively high. However, the radioactivity measured in these organs may be largely due to the presence of blood in these tissues.

4. Although the detected radioactivity in tissues/organs was dose-related, it appears that the eyes and brain in both sexes, the stomach in males (and to a much lesser extent in females), and the ovaries were target organs for a higher accumulation of alachlor/metabolites. Since most of these organs were the sites of specific lesions in the 2-year rat feeding study (BD-77-421, 11/13/81 by Bio/dynamics Inc.), the Agency is interested in any additional studies or data in the possession of the registrant at the present time or in the future that may be helpful in the identification of the alachlor residues in these target organs.

REVIEW

Study Type: Rat Metabolism Study
Part I: General Metabolism-Metabolic Fate
Part II: Identification and Quantification of Metabolites

Accession Nos.: 251543 (Part I) and 251544 (Part II)

Testing Laboratory: Monsanto Agricultural Products Company
800 North Lindberg Boulevard
St. Louis, MO 63167

Report No. & Date: MSL-3198, R.D. 493, 10/14/83 (report compiled by Adrienne J. Zahner).
Part I: Job/Project #810060/ML-81-139, 9/26/83 (Report #MSL-3098)
Part II: Job/Project #7824; June, 1983 (Report #MSL-3016)

Study Performed By: Alan G.E. Wilson (author); Dietrich, M.W. (Group Leader); Part I
and
Moran S.J. and Grabiak M.C. (authors); Malik, J.M. and Purdum, W.R. (Group Leaders); Part II

Date Submitted: 10/21/83

Test Substance: Chemical purity 98-99.9% a.i.
C-14 Alachlor radiochemical purity 98%, and
C-13 Alachlor was enriched at a 90% level.
C-14 specific activity = 8.9 mCi/mmole.

The test material was supplied by the sponsor in batches of isotopic mixture of alachlor containing labeled C-14 alachlor, enriched C-13 alachlor, and unlabeled alachlor. The C-14 alachlor was uniformly labeled in the phenyl moiety, and the C-13 enriched alachlor contained C-13 in the C-2 position in the chloroacetamide moiety. The composition of the alachlor isotopic mixture designated for each experimental animal group is described below in table (#1):

Table 1

Animal Group	Isotopic composition of Alachlor Samples				
	C-14 labelled (mg)	+	C-13 enriched (mg)	+	C-12 unlabelled (mg)
1	23.89	+	777.80	+	598.31
2	15.40	+	10.90	+	00
3*	15.30	+	1204.20	+	1381.80
4	14.02	+	10.88	+	00

According to the registrant, the C-2 position of the C^{13}-label in the alachlor molecule was chosen because "it was expected that the C-2 carbon would be a prime target for metabolic modification". Also, C-13 would provide a better spectra than C-12 alone for identification of metabolites with mass spectroscopy (MS) and nuclear magnetic resonnance (NMR).

Table #2 below reflects the percentage of C-14, C-13 and C-12 in each experimental group (as calculated by this reviewer from table #1 above) and the specific activities of the alachlor samples used in each treatment group (expressed as disintegrations per minute per microgram or per micromole):

Table 2

Groups	Specific Activities of Alachlor Mixture dpm/ug	dpm/umole	Percentage of C_{14}/C_{13}/C_{12} in each mixtures C_{14}	C_{13}	C_{12}
1	1.226×10^3	3.308×10^5	1.07	55.56	42.74
2	4.246×10^4	1.146×10^7	58.56	41.44	0.00
3	4.254×10^2	1.148×10^5	0.59	46.29	53.12
4	4.089×10^4	1.103×10^7	56.31	43.69	0.00

Vehicle: Corn oil, laboratory grade; Fisher Scientific Co., St. Louis, Mo.

Dosage: The following single oral dosages of labeled alachlor were used in this study:

Table 3

Group No.	Mean Dosage ± S.E.M. Single Oral Dosage (mg/kg)		Number of Animals Tested		Mean b.w. (g)	
	Male	Female	M	F	M	F
1 (high-dose)	804.3 ± 14.5	811.3 ± 12.6	3 + 3		159	144
2 (low-dose)	7.11 ± 0.05	7.13 ± 0.05	5 + 5		233	185
3 (high-dose)	701.8 ± 4.1	694 ± 15.7	5 + 5		205	170
4 (multiple low-dose)	5.75 ± 0.21	5.97 ± 0.13	5 + 5		323	211

The above dosages of alachlor were administered orally by gavage to the animals in a 0.2 ml of corn oil per 100 g body weight.

In the high dose groups (#4 & #3), unlabeled alachlor was added to the mixture of C^{14} and C^{13} labeled alachlor samples in order to reduce the level of radioactivity in the administered dosages; the ratio of C_{13}/C_{12} was 1.

In group #4, the rats were dosed daily with unlabeled alachlor at a low dose level of 7 mg/kg b.w./day for 2 weeks prior to the administration of a final dose of 6 mg/kg radioactive alachlor (the radioactive dose was administered within 24 hours of the previous unlabeled dose). The unlabeled alachlor was delivered in the vehicle at a rate of 0.1 ml corn oil per 100 g body weight.

The purpose of each dosage group in this study was explained as follows:

°Group #1 (high dose) was intended to evaluate the amount of labeled CO_2 exhaled, and to determine whether a closed cage system, capable of trapping "volatiles and expired air" should be used in the three other experimental groups". This group was also treated with a high dosage of labelled alachlor in order to obtain excrement with high level of radioactive metabolites for the development of analytical methods to determine the evaluation of metabolites in the remaining groups.

°Groups #2 (low-dose) and #3 (high-dose) were used to determine alachlor metabolism as a function of dose.

°Group #4 (low-dose) was used to determine the metabolism of alachlor as affected by previous exposure (2 weeks of consecutive daily exposure) to low levels of alachlor.

Test Animals: Sprague-Dawley rats, Crl:CD(SD)BR rats of both sexes were used in this study (Supplier: Charles River Laboratories, Wilmington, Ma.) The animals weighed 125 to 250 gram and were six to eight weeks old.

All rats were quarantined for at least 6 days before testing. The animals were ear tagged for identificaiton and divided in four groups as discussed in the above section. The average body weight for each group at the initiation of testing is listed in table 3 on the previous page. This reviewer notes that these body weight data appear to indicate that the animals in group 1 were the youngest and in group 4 they were the oldest. Hence, differences in the rate of metabolim of the test compound should be expected, especially between group 1 and the other groups.

Procedure:

1. Group #1 Rats (3 males and 3 females) were housed in glass Roth-type metabolism units for determination of radioactivity in the expired CO_2. These animals were placed in these units 3 days prior to the administration of a single oral dose of 800 mg/kg b.w. labeled alachlor and for 48 hours afterward.

The airflow in these units was maintained at 400-500 ml/min. The effluent air from the Roth metabolism units was collected in two consecutive traps of 5 methanolamine in methoxyethanol (100 ml in the 1st trap and 50 ml in the second trap) at the following intervals after dosing: 6, 12, 24 and 48 hours for the first trap; and 12, 24, and 48 hours for the second trap. Urine and feces were also collected at 24 and 48 hours after dosing. The urine was separated from feces by a glass separator attached to the Roth unit and directly collected into tubes held at 4°C. At each collection interval urine and feces were weighed, and stored in tared vials until analysis.

At the end of the experiment each cage was rinsed with water then acetone in order to determine the residual radioactivity.

2. Groups 2, 3 and 4 (5 male and 5 female rats per group) were housed in standard stainless steel suspension metabolism cages. The animals were maintained at 12 hour light and dark cycle; food and water were available ad libitum. The animals in each group were dosed according to the specific dosing regimen described in the section on dosage (p. 3).

Urine and feces were collected after 12 and 24 hours and daily thereafter for 10 days of the initial exposure; an additional urine sample was also collected after the first 6 hours of exposure in group 4 . After each urine and feces collection, the stainless steel separator and urine collection beakers were rinsed with water and the water rinses were added to the urine samples. All samples were stored until analysis.

At the end of the study period (240 hours) blood samples (1-3 ml) were collected in 500 units of sodium heparin from the abdominal aorta at the time of sacrifice. The collected blood samples were stored at 4°C and 1 to 2 ml from each sample were centrifuged at 2000 rpm for 5 minutes. The plasma layer, the blood cell fraction, and the remaining whole blood samples where then stored at -20°C until further analysis.

After 10 days of the initial exposure, the animals in groups #2, #3 and #4 were necropsied and the following tissues/organs were removed, weighed and frozen: eyes, brain, kidney, liver, gonads, heart, spleen, fat samples (taken from the abdominal and testicular/ovarian* pad regions), muscle tissues (removed from the abdominal wall and shoulder), and gastrointestinal tract (stomach, small intestine, large intestine and gastrointestinal contents). All these tissues, also bone samples from the sternum and femur, and the carcass were stored at 4°C until further preparation for radioactivity determinations using a liquid scintillation counter (LSC).

*NOTE: The ovary sample from one female in group #3 (03F01) was lost; and another ovary from animal #02F02 in group #2 was also reported to not have valid data due to the malfunction of the oxidizer.

The levels of radioactivity in the biological samples obtained from the above 4 experimental groups were determined using a liquid scintillation counter (LSC).

The recovered radioactive metabolites in the animal excrements were further analyzed using derivatization and miscellaneous analytical methods, i.e., gas chromatography (GC) with a flame ionization detector; high pressure liquid chromatography (HPLC); polyacrylamide gel electrophorysis (PAGE); and high voltage electrophrorysis (HVE). The separated metabolites were also identified using MS and NMR analysis.

Statistical analyses of the collected data were performed using the student's t-test.

NOTE: For group #4 where multiple dosing with unlabeled alachlor was performed before a final low dose of labeled alachlor was administered, the determined levels of radioactivity in the collected samples were only related to the last radioactive dose. However, it is anticipated by this reviewer that some dilution of the radioactivity is expected to occur in the animal body specially in tissues where unlabeled alachlor would accumulate.

Results:

1. Less than 0.02% of the initial radioactivity was recovered in the expired air when animals in group 1 were exposed to a large dose of alachlor and monitored for 48 hours afterward. Consequently elimination via this route was considered minor and CO_2 elimination was not measured in groups 2, 3 and 4.

2. Alachlor was rapidly metabolized and eliminated in both urine and feces within the first 4 days of the initial oral treatment in groups 2, 3 and 4 animals. Approximately 89% of the dosage was eliminated in this period in these groups; i.e., 37.6 to 45.0% in urine and 47.7 to 51.5% in feces in males, and 42.5 to 53.2% in urine and 37.0 to 49.3% in feces in females. Only 1 to 2% of the eliminated radioactivity in feces were unchanged alachlor; none was detected in urine. The rate of alachlor elimination through these two routes was biphasic: an initial rapid phase with a half-life of 8.2 to 10.6 hours followed by a slower phase with a half-life of 5 to 16 days.

3. According to the authors, "Alachlor was degraded to more than 30 metabolites in the rat, many of which were at levels too low to permit identification".

However, 14 metabolites were identified in urine (Compounds #II to #XV) and 13 metablites were identified in feces (Compounds #XIII to #XX to #XXX); three of these 13 metabolites were also found in urine (Compounds #XIII, #XIV and #XV), see figure 61 on pages 179 and 180 of Volume II. Figure 61 (copy attached) reflected the following findings:

° The mercapturic acid pathway played a major role in the detoxification of alachlor as demonstrated by the number of identified mercapturic acid conjugates and their breakdown products (i.e., compounds IX, XIV, XV).

°The glucuronidation pathway was also important in the detoxification of alachlor (see compounds #VI & #XIII). Glucuronic acid conjugation occurred after hydroxylation occurred. Apparently the C-1 position of the ethyl side chain of the phenyl ring was a prime target for this hydroxylation step (only one metabolite was noted with hydroxylation on C-2, i.e., metabolite #XVIII). The hydroxlation step was also reported (by the authors) to occur in the plant metabolism studies.

°Sulfate conjugation was also one of the detoxification pathways in this study (see compounds #II & #XXIX).

A small amount of the administered alachlor was recovered unchanged in the feces (1% in females 2% in males) of the high dose group. No alachlor was detected in urine.

4. The residual radioactivity in blood as measured after 10 days of the initial exposure in groups 2, 3 and 4 was 1.3 to 2.2% of the administered dose in both sexes. As detected in groups 3 and 4 most of the radioactivity was in the blood cellular fraction (see the attached tables 12 and 13 of Vol. I. The recovered radioactivity in blood appeared to be dose-related.

5. The total residual radioactivity for all organ/tissues (excluding fat and muscles) was relatively very small; i.e. an average of 0.32, 0.27 and 0.24 percent of the dosage in groups 2, 3 and 4 respectively. The highest alachlor/metabolite(s) percentage recovery was obtained from the liver followed by the kidney or spleen, small intestine, stomach, colon, heart and brain. Much lower recovery levels were obtained from the eyes and gonads, see individual animal data in Volume I (EHL's pages 262-3, 285-6, 423-4, 447-8, 592-3, 617-8).

For organs like liver, kidneys, heart and spleen, the authors indicated that the radioactivity measured in these organs may be largely due to the presence of blood in these tissues. However, this reviewer notes that accumulation in the liver and kidney may essentially be associated with the function of these organs, i.e. they are target organs for the detoxification of the chemical. Also, this reviewer notes that in organs like the eye and the ovary, although the percentage of residual alachlor is small, the concentration in terms of ppm in these organs is very high specially in the high dose group. In this group, the levels of residues in eyes and ovaries were almost comparable to the levels in liver, see the attached copies of tables 11, 12 and 13 of Vol. I.

9

6. The residual radioactivity in the carcass for males and females was 0.66 to 1.08 and 0.65 to 1.27% of the dosage in groups 2, 3 and 4 respectively.

7. A relatively higher accumulation of radioactivity was noted in some organs of the high dose group 3, i.e., eyes, brain, stomach and ovaries, as compared to those of the low dose group 2. However a relatively lower level of radioactivity was reported in the liver and small intestine in group 3, see the attached table 14 of Volume I.

8. Comparisons between the low dose group 2 and the multiple low dose group 4 reflected a higher concentration in the blood plasma and brain. However a lower level of radioactivity was recovered from the eyes, ovaries, bones, carcass, and female whole blood of group 4 rats as compared to group 2, see the attached table 15 of Volume I.

Discussions:

Comparisons between the low dose group 2 and the high dose group 3 indicated that although the reported radioactivy levels in tissues/organs were dose-related, it appears that the eyes and brain, the stomach in males (and to a lesser extent in females), and ovaries were target organs for a higher accumulation of alachlor/metabolite(s). For example, a 6x increase in the level of radioactivity was noted in the eyes of the high-dose animals as compared to the eyes of the low-dose rats. Similar trends (but with a lower level of increased bioaccumulation) were noted in the brain, stomach and ovaries, see attached table 14.

Also of interest to this reviewer in group 4, the relative decrease in the radioactivity recovered in bones, eyes, liver, carcass and fat of both sexes, and in female whole blood, liver kidney and ovary as compared to group 2, see the attached table 15. A possible explanation for this decrease may be the previous accumulation of the daily unlabeled dosage in these organs/tissues, which led to the dilution of the radioactivity measured in these organ/tissues.

Finally this reviewer notes that some of the relatively higher affinity of alachlor/metabolites to the following target organs: eye, ovary, stomach and brain as demonstrated in this metabolism study, may partially explain the chronic toxic effects of this chemical (i.e. uveal degeneration syndrome in eyes, malignant tumors in stomach) which were previously noted in the submitted 2-year chronic feeding/oncogenicity study in rats (Bio-dynamics Inc., BD-77-421, 11/13/81).

Thus, the Agency is interested in any additional studies or data in the possession of the registrant at the present time or in the future that may be helpful in the identification of the alachlor metabolites in the above mentioned target organs.

The individual animal data for urine and feces in group #1 were inconsistent and appeared to be unreliable, see data in Vol. I, pages 98 to 101 for males and pages 115 to 118 for females. Hence, data from this group were only valid for the CO_2 recovery.

Approximately 8 replicates were used in the determination of the residual alachlor in the eyes of each rat in group #4 instead of the usual duplicates used in the other groups. One possible explanation may be the noted variability in the results obtained from duplicates. However, this variability may indicate a possible progressive dilution of the radioactivity from one sample to another due to the previous accumulation of unlabeled alachlor residues in the ocular tissues (see individual animal data in Vol. I, pages 462, 471, 479, 487, 495, 503, 511, 519, 527, 535). Thus, data from this group should be considered with reservations.

Conclusions:

1. Alachlor was rapidly metabolized in rats and equally eliminated in urine and feces as conjugates of mercapturic acid, glucuronic acid and sulfate; approximately 89% of the dosages (7 mg/kg and 700 mg/kg for the low and high dosage groups respectively) were eliminated during the 10-day study period. Most of this elimination occured within the first 48 hours of exposure and followed a biphasic elimination model: an initial rapid phase with a half-life of 0.2 to 10.6 hours followed by a slower phase with a half-life of 5 to 16 days. Elimination as CO_2 was minimal (0.02% of the dosage within the first 48 hours of exposure).

2. After 10 days of the initial exposure to the above mentioned low and high dosage levels, 1.3 to 2.2% residual alachlor/metabolites were detected in blood; 0.66 to 1.27% in carcass; and a total of 0.24 to 0.32% in organ/tissues.

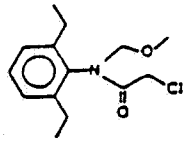
3. The levels of residual alachlor in spleen, liver, kidney and heart were relatively high. However, , the radioactivity measured in these organs may be largely due to the presence of blood in these tissues; and due to the fact the liver and kidney are the target organs for the detoxification process of the chemical in the animal body.

4. Although the detected radioactivity in tissues/organs was dose-related, it appears that the eyes and brain in both sexes, the stomach in males (and to a lesser extent in females), and the ovaries were target organs for a higher accumulation of alachlor residues. Hence, the Agency is interested in any additional studies or data in the possession of the registrant at the present time or in the future that may be helpful in the identification of the alachlor residues in these organs which were also identified as target organs in the chronic feeding study in rats by Bio/dynamics Inc., BD-77-421, 11/13/81.

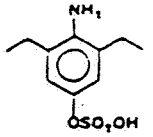
Classification: Core-Minimum

Figure 61. Structures of Metabolites and Other Compounds Referenced in this Report.

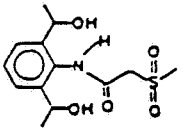
Alachlor



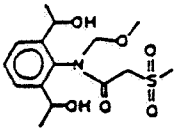
I



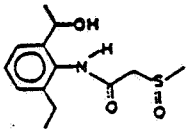
II



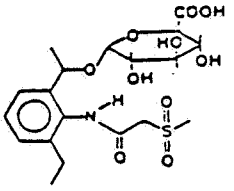
III



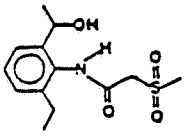
IV



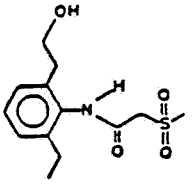
V



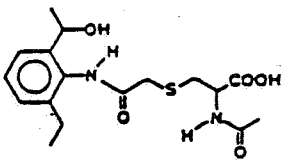
VI



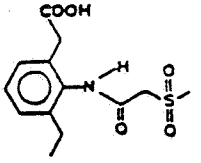
VII



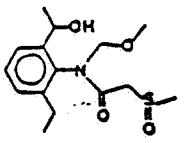
VIII



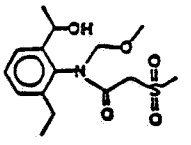
IX



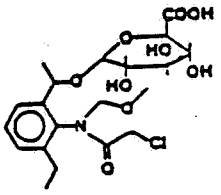
X



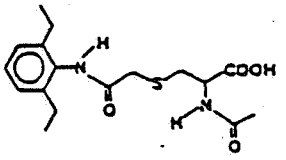
XI



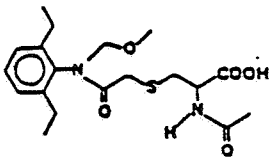
XII



XIII

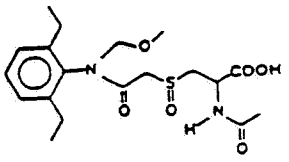


XIV

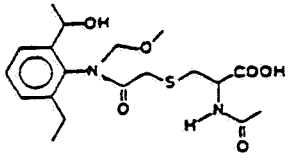


XV

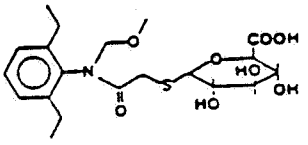
Figure 61 (Continued)



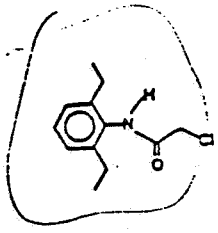
XVI



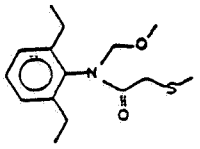
XVII



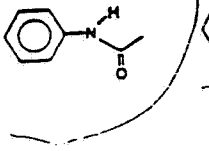
XVIII



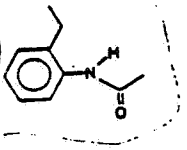
XIX



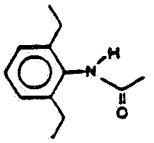
XX



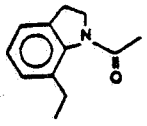
XXI



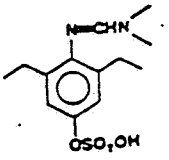
XXII



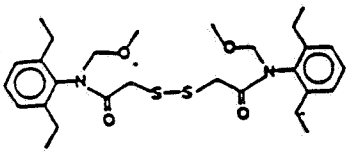
XXIII



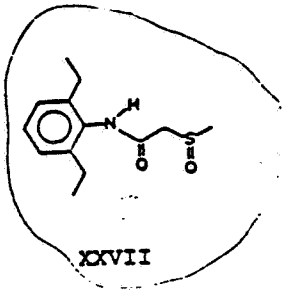
XXIV



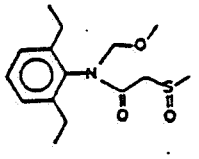
XXV



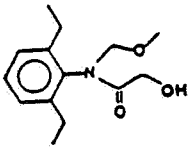
XXVI



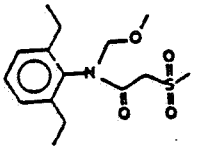
XXVII



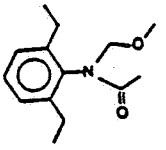
XXVIII



XXIX

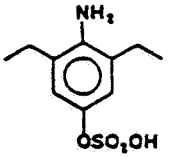
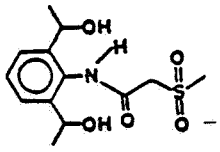
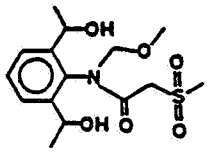
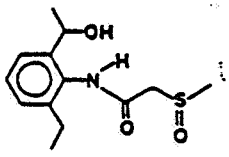
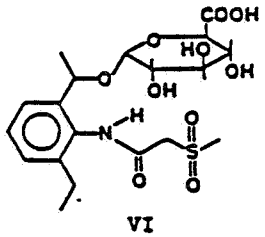


XXX

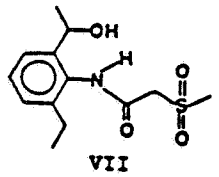
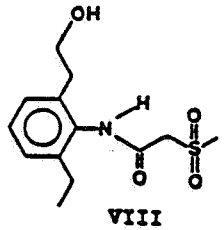
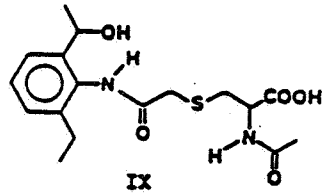
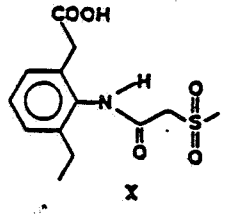
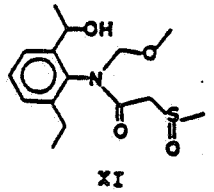


XXXI

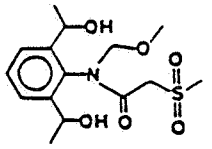
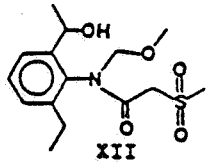
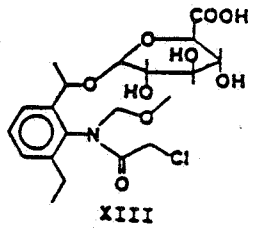
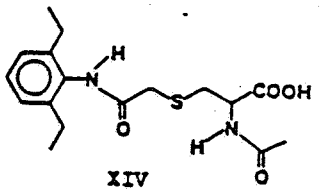
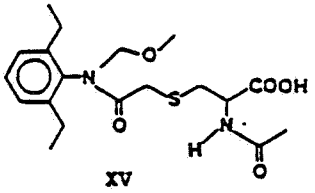
Metabolites of Alachlor Identified in Rat Urine

Metabolite Structure	Name
 II	4-amino-3,5-diethylphenyl-sulfate
 III	N-[2,6-bis(1-hydroxyethyl)-phenyl]-2-(methylsulfonyl)-acetamide
 IV	N-[2,6-bis(1-hydroxyethyl)-phenyl]-N-(methoxymethyl)-2-(methylsulfonyl)acetamide
 V	N-[2-ethyl-6-(1-hydroxyethyl)-phenyl]-2-(methylsulfinyl)-acetamide
 VI	N-[2-ethyl-6-(1-0-glucuronyl)-phenyl]-2-(methylsulfonyl)-acetamide

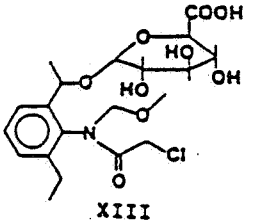
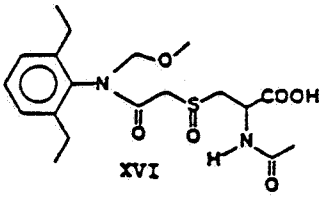
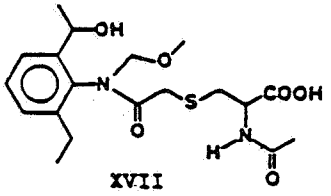
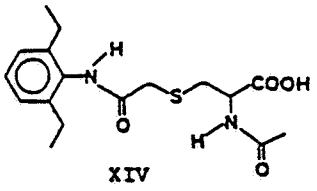
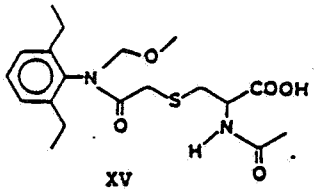
Metabolites of Alachlor Identified in Rat Urine

Metabolite Structure	Name
 VII	N-[2-ethyl-6-(1-hydroxyethyl)-phenyl]-2-(methylsulfonyl)-acetamide
 VIII	N-[2-ethyl-6-(2-hydroxyethyl)-phenyl]-2-(methylsulfonyl)-acetamide
 IX	3-{(2-{[2-ethyl-6-(1-hydroxy-ethyl)phenyl]amino}-2-oxoethyl)-thio}-2-(acetylamino)propanoic acid
 X	3-ethyl-2-[(methylsulfonyl)-acetyl]aminobenzeneacetic acid
 XI	N-[2-ethyl-6-(1-hydroxyethyl)-phenyl]-N-(methoxymethyl)-2-(methylsulfinyl)acetamide

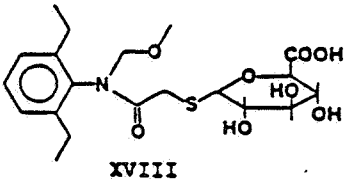
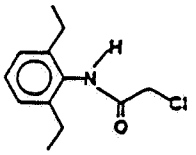
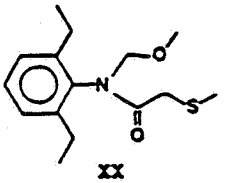
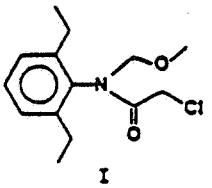
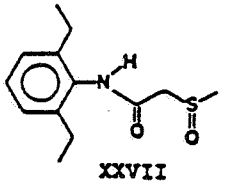
Metabolites of Alachlor Identified in Rat Urine

Metabolite Structure	Name
 IV	N-[2,6-bis(1-hydroxyethyl)-phenyl]-N-(methoxymethyl)-2-(methylsulfonyl)acetamide
 XII	N-[2-ethyl-6-(1-hydroxyethyl)-phenyl]-N-(methoxymethyl)-2-(methylsulfonyl)acetamide
 XIII	2-chloro-N-[2-ethyl-6-(1-O-glucuronyl)phenyl]-N-(methoxy-methyl)acetamide
 XIV	3-{(2-[(2,6-diethylphenyl)-amino]-2-oxoethyl)thio}-2-(acetylamino)propanoic acid
 XV	3-{(2-[(2,6-diethylphenyl)-N-(methoxymethyl)amino]-2-oxoethyl)thio}-2-(acetylamino)-propanoic acid

Metabolites of Alachlor Identified in Rat Feces

Metabolite Structure	Name
 XIII	2-chloro-N-[2-ethyl-6-(1-O-glucuronyl)phenyl]-N-(methoxymethyl)acetamide
 XVI	3-{(2-[(2,6-diethylphenyl)-N-(methoxymethyl)amino]-2-oxoethyl)sulfinyl}-2-(acetylamino)propanoic acid
 XVII	3-{(2-[(2-ethyl-6-[1-hydroxyethyl]phenyl)-N-(methoxymethyl)-amino]-2-oxoethyl)thio}-2-(acetylamino)propanoic acid
 XIV	3-{(2-[(2,6-diethylphenyl)amino]-2-oxoethyl)thio}-2-(acetylamino)propanoic acid
 XV	3-{(2-[(2,6-diethylphenyl)-N-(methoxymethyl)amino]-2-oxoethyl)thio}-2-(acetylamino)-propanoic acid

Metabolites of Alachlor Identified in Rat Feces

Metabolite Structure	Name
 XVIII	2-[(2,6-diethylphenyl)-(methoxymethyl)amino]-2-oxoethyl-1-thio-β-D-glucopyranosiduronic acid
 XIX	N-[2,6-diethylphenyl]-2-chloroacetamide
 XX	N-(2,6-diethylphenyl)-N-(methoxymethyl)-2-(methylthio)acetamide
 I	2-chloro-N-(2,6-diethylphenyl)-N-(methoxymethyl)-acetamide
 XXVII	N-(2,6-diethylphenyl)-2-(methylsulfinyl)acetamide

Metabolites of Alachlor Identified in Rat Feces

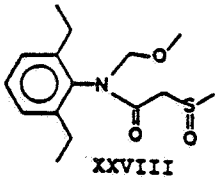
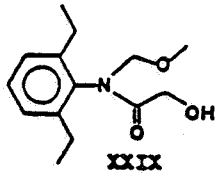
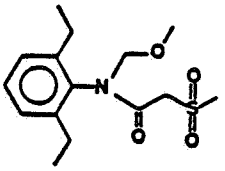
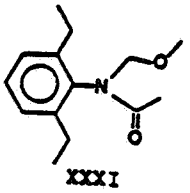
Metabolite Structure	Name
 XXVIII	N-(2,6-diethylphenyl)-N-(methoxymethyl)-2-(methylsulfinyl)acetamide
 XXIX	N-(2,6-diethylphenyl)-2-hydroxy-N-(methoxymethyl)-acetamide
 XXX	N-(2,6-diethylphenyl)-N-(methoxymethyl)-2-(methylsulfonyl)acetamide
 XXXI	N-(2,6-diethylphenyl)-N-(methoxymethyl)acetamide

Table 11

Distribution of Radioactivity in Tissues and Organs of Rats in Group 2

	(Mean ppm + SEM)(b)	
	Male	Female
Whole Blood	1.654 ± 0.135	2.369 ± 0.116(a)
*Spleen	0.331 ± 0.037	0.489 ± 0.034(a)
*Kidney	0.234 ± 0.044	0.357 ± 0.047
Residual Carcass	0.247 ± 0.016	0.288 ± 0.026
*Heart	0.175 ± 0.031	0.176 ± 0.026
*Liver	0.225 ± 0.028	0.259 ± 0.020
*Ovaries	-	0.139 ± 0.012
Femur	0.101 ± 0.012	0.134 ± 0.017
*Stomach	0.061 ± 0.004	0.101 ± 0.011(a)
Sternum	0.100 ± 0.013	0.151 ± 0.013(a)
Abdominal Muscle	0.061 ± 0.009	0.078 ± 0.006
Abdominal Fat	0.068 ± 0.028	0.031 ± 0.003
*Brain	0.033 ± 0.003	0.039 ± 0.003
*Small Intestine	0.067 ± 0.002	0.069 ± 0.007
*Colon	0.045 ± 0.004	0.049 ± 0.005
Shoulder Muscle	0.026 ± 0.002	0.034 ± 0.001(a)
Testicular/Ovarian Fat	0.116 ± 0.031	0.083 ± 0.023
*Testes	0.020 ± 0.001	-
*Eye	0.017 ± 0.002	0.020 ± 0.002
Blood Plasma	0.016 ± 0.002	0.022 ± 0.002

(a) Statistically different from male (Student's t-test for unpaired data; $p \leq 0.05$).

(b) The organs marked * accounted for a total of 0.31 and 0.32 percent of the dose for males and females, respectively.

Table 12

Distribution of Radioactivity in Tissues and Organs of Rats in Group 3

	(Mean ppm + SEM)(b)	
	Male	Female
Whole Blood	160.06 ± 18.04	235.43 ± 13.53(a)
*Spleen	34.85 ± 5.05	48.66 ± 4.10
*Kidney	18.64 ± 1.86	23.24 ± 2.03
Residual Carcass	21.93 ± 1.36	24.90 ± 2.69
*Heart	13.54 ± 1.55	16.16 ± 0.99
*Liver	12.74 ± 0.80	18.53 ± 1.32(a)
*Ovaries	-	19.36 ± 0.70(c)
Femur	9.18 ± 0.49	10.98 ± 0.56(a)
*Stomach	12.10 ± 1.32	11.77 ± 1.09
Sternum	11.25 ± 0.99	16.68 ± 1.61(a)
Abdominal Muscle	4.35 ± 0.44	4.80 ± 0.21
Abdominal Fat	2.88 ± 0.71	3.36 ± 0.43
*Brain	6.24 ± 0.34	6.93 ± 0.72
*Small Intestine	4.10 ± 0.30	4.18 ± 0.19
*Colon	4.33 ± 0.34	5.03 ± 0.15
Shoulder Muscle	2.60 ± 0.24	3.31 ± 0.39
Testicular/Ovarian Fat	3.93 ± 0.47	4.53 ± 0.49
*Testes	1.64 ± 0.25	-
*Eye	10.06 ± 1.34	10.46 ± 0.72
Blood Plasma	1.55 ± 0.18	1.64 ± 0.07
Blood Cell Fraction	402.61 ± 38.54	529.62 ± 24.69(a)

(a) Statistically different from male (Student's t-test for unpaired data; $p \leq 0.05$).
(b) The organs marked* accounted for a total of 0.25 and 0.29 percent of the dose for males and females, respectively.
(c) Based on four animals.

Table 13

Distribution of Radioactivity in Tissues and Organs of Rats in Group 4

	(Mean ppm + SEM)(b)	
	Male	Female
Whole Blood	1.394 ± 0.080	1.160 ± 0.225
*Spleen	0.269 ± 0.029	0.422 ± 0.060
*Kidney	0.205 ± 0.014	0.175 ± 0.009
Residual Carcass	0.137 ± 0.007	0.148 ± 0.011
*Heart	0.106 ± 0.026	0.148 ± 0.019
*Liver	0.133 ± 0.007	0.152 ± 0.015
*Ovaries	-	0.071 ± 0.008
Femur	0.035 ± 0.005	0.038 ± 0.004
*Stomach	0.057 ± 0.007	0.060 ± 0.003
Sternum	0.041 ± 0.003	0.055 ± 0.007
Abdominal Muscle	0.070 ± 0.013	0.054 ± 0.011
Abdominal Fat	0.027 ± 0.005	0.018 ± 0.003
*Brain	0.048 ± 0.004	0.044 ± 0.005
*Small Intestine	0.070 ± 0.009	0.079 ± 0.011
*Colon	0.058 ± 0.013	0.053 ± 0.008
Shoulder Muscle	0.018 ± 0.001	0.025 ± 0.003
Testicular/Ovarian Fat	0.036 ± 0.006	0.032 ± 0.004
*Testes	0.015 ± 0.002	-
*Eye	0.011 ± 0.002	0.011 ± 0.001
Blood Plasma	0.026 ± 0.003	0.036 ± 0.002(a)
Blood Cell Fraction	3.003 ± 0.102	3.670 ± 0.339

(a) Statistically different from male (Student's t-test for unpaired data; $p \leq 0.05$).

(b) The organs marked * accounted for a total of 0.24 and 0.23 percent of the dose for males and females, respectively.

Table 14

Ratio of Tissue and Organ Levels of Radioactivity
in Group 3 Compared to Group 2.
Data Normalized with Respect to Dose

	Ratio Group 3/Group 2	
	Male	Female
Dose	1.00	1.00
Whole Blood	0.98	1.02
Spleen	1.07	1.02
Kidney	0.81	0.67
Residual Carcass	0.90	0.89
Heart	0.78	0.95
Liver	0.57(a)	0.74(a)
Ovaries	-	1.44(a)
Femur	0.92	0.84
Stomach	2.02(a)	1.20
Sternum	1.14	1.14
Abdominal Muscle	0.72	0.63(a)
Abdominal Fat	0.43	1.11
Brain	1.95(a)	1.82(a)
Small Intestine	0.63(a)	0.63(a)
Colon	0.98	1.06
Shoulder Muscle	1.03	0.99
Testicular/Ovarian Fat	0.34	0.56
Testes	0.85	-
Eye	6.18(a)	5.66(a)
Blood Plasma	1.01	0.75

(a) Statistically significant at $p \leq 0.05$. Calculated from normalized ppm differences between groups.

Table 15

Ratio of Tissue and Organ Levels of Radioactivity
in Group 4 Compared to Group 2.
Data Normalized with Respect to Dose

	Ratio Group 4/Group 2	
	Male	Female
Dose	1.00	1.00
Whole Blood	1.04	0.58(a)
Spleen	1.00	1.03
Kidney	1.09	0.58(a)
Residual Carcass	0.68(a)	0.61(a)
Heart	0.75	1.00
Liver	0.73	0.70(a)
Ovaries	-	0.61(a)
Femur	0.43(a)	0.34(a)
Stomach	1.16	0.71
Sternum	0.51(a)	0.44(a)
Abdominal Muscle	1.42	0.82
Abdominal Fat	0.50	0.70
Brain	1.82(a)	1.33
Small Intestine	1.31	1.37
Colon	1.60	1.31
Shoulder Muscle	0.86	0.89
Testicular/Ovarian Fat	0.38	0.46
Testes	0.97	-
Eye	0.83	0.64(a)
Blood Plasma	2.06(a)	1.94(a)

(a) Statistically significant at $p \leq 0.05$. Calculated from normalized ppm differences between groups.