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

006013

JUL 20 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Alachlor Metabolism Study in Monkeys submitted by Monsanto Company November 10, 1986
Accession Number 400009-01

Tox. Chem. No.: 11

FROM: Judith W. Hauswirth, Ph.D
Section Head, Section VI
Toxicology Branch/HED (TS-769C)

Judith W. Hauswirth 7/20/87

TO: David Giamporcaro, PM #79
Special Review Branch
Registration Division (TS-767C)

7/22/87

THRU: Theodore M. Farber, Ph.D., Chief
Toxicology Branch/HED (TS-769C)

Action Requested: Review Study entitled "The Metabolism of Alachlor in Rhesus Monkeys Part II Identification, Characterization and Quantification of Alachlor and It's Metabolites after Intravenous Administration to Monkeys."

Background: A preliminary report of this study was submitted to the agency and reviewed in a Toxicology Branch memorandum signed 2/14/86 (Appendix I). The conclusions based upon this review were as follows:

1. Five metabolites of alachlor were identified in the urine of monkeys injected intravenously with 0.7 or 7.0 mg/kg alachlor. They consisted of a secondary and tertiary mercapturate conjugate and a cysteine, thioacetic acid and glucuronide conjugate of alachlor. The different doses of alachlor administered appeared to quantitatively but not qualitatively alter the metabolic profile.

2. The following metabolic differences between the rat and monkey can be noted:

   - number of identifiable urinary metabolites; five in the monkey and 14 in the rat
   - the ratio of urinary to fecal radioactivity recovered: rat 1:1 and monkey 9-10:1
   - only two urinary metabolites were common to both the rat and monkey, namely the secondary and tertiary mercapturic acid conjugates
   - sulfate conjugation and side chain hydroxylation metabolites were found in the urine of the rat but not the monkey.

3. The results obtained in this study and in previously conducted intramuscular and topical metabolism studies do not support Monsanto's contention that the metabolites of alachlor "formed do not change as a function of the route of administration". This contention is not supported

   - because the metabolites of alachlor as reported for the intramuscular and topical studies appear to differ quantitatively as well qualitatively (number of metabolites found) and
   - because the limited nature of the intramuscular and topical studies in the monkey make it difficult to extrapolate the results obtained in those studies to the intravenous metabolism study.

4. The results of this study do not support Monsanto's argument that the monkey is a better model than the rat for assessing the effects of alachlor in man. No side chain hydroxylated metabolites of alachlor were identified in the urine of monkeys administered alachlor by the intravenous, intramuscular or topical routes, however, these metabolites have been identified in the urine of rats given alachlor orally and in man administered alachlor topically.

   Only that portion of this study not previously reviewed will be discussed in this memorandum.

Conclusions:

1. The only identified fecal metobolite in the monkey was a cysteine conjugate which was also identified in urine.

2. Neutral metabolites found in urine comprise approximately 5% of the administered dose.

3. A mutagenic metabolite of alachlor was identified in the urine of the monkey namely N-[2-ethyl-6-(1-hydroxyethyl)-phenyl]-2-(methylsulfonyl)-acetamide. This metabolite was also reported to be found in rat and mouse urine, is mutagenic in the Ames Salmonella assay (Strain TA 100) and is a HEEA metabolite not previously identified in the monkey.

Core Grade: Acceptable

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REVIEW

Study Type: monkey metabolism

Study Title: The Metabolism of Alachlor in Rhesus Monkeys Part II. Identification, Characterization, and Quantification of Alachlor and Its Metabolites After Intravenous Administration to Monkeys.

Accession No: 400009-01

Animal Phase: International Research and Development Corp. Mattawan, Michigan 49071

Metabolite Identification and Quantitation: Monsanto Agricultural Products Company Chesterfield, Missouri

Project No.: 7824

Report No.: MSL-5727

Report Dated: July, 1986

Authors: R.K. Howe, K.H. Carr, R.C. Chott

Test Animal: Rhesus monkey

No. Animals/Group: 3/sex/group

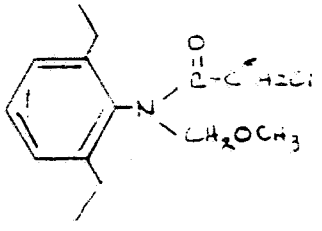
Dosages: 0.7 (group II monkeys) and 7.0 mg/kg (group I monkeys), once on initiation of study

Route of Administration: intravenous (I.V.)

Test Substance: ^{12}C-alachlor (>99% pure)
^{13}C-alachlor 90% enriched at the C-2 carbon (>98% pure)

^{14}C-alachlor uniformally labelled in the phenyl ring (>98% pure)

Structure: * position of ^{13}C



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Vehicle: 1,2-propylene glycol

Composition of High Dose: Specific activity - 3.090×10^9 dpm/g soln. or 3.257×10^9 dpm/mL; conc. of alachlor - 38.99mg/mL soln.; $^{12}C/^{13}C = 0.88$

Composition of Low Dose: specific actvity - 3.64×10^3 dpm/mL soln. or 3.48×10^8 dpm/g soln.; conc. of alachlor-3.90 mg/mL soln; $^{12}C/^{13}C$=0.87

Length of Study: 5 days

Dose Selection: 0.7 mg/kg - highest dose used in a previous rhesus monkey metabolism study
7.0 mg/kg - lowest dose used in rat studies

Material and Methods: see attached Materials and Methods Section from the report - Appendix II (additional methods not used in first review - appendix)

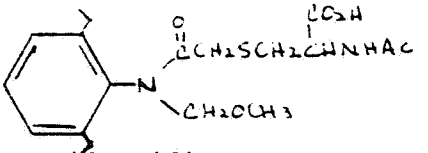
Protocol: Protocol for this study was submitted and reviewed by Toxicology Branch in a memorandum dated 11/30/85. It was found acceptable.

Collection of Samples: fecal and urine samples were collected at 0-4, 4-8, 8-12 and every 12 hours thereafter up to 120 hours. Samples were collected at 0-4°C and were then frozen. Pooled urine samples were used for metabolite identification.

Results:

1. Characterization of Fecal Metabolites

Only one metabolite was identified in the feces. By comparison with retention time to a known standard it was identified as a mercapturic acid conjugate with the following structure.



No other metabolites were identified. The HPLC/RAD metabolic profiles contained no well-resolved peaks and since the level of radioactivity in the feces was low, no further attempt was made to separate and identify other metabolites.

2. Further Characterization of Urinary Metabolites

a. Urinary metabolites were separated into neutral and acid metabolites by ethyl acetate extraction of urine samples adjusted to pH 8.0. Extractions were done on the 0-96 hour urine of each of the twelve monkeys studied. The following data was extracted from Table 30 of the report.

Distribution of ^{14}C-Radioactvity in Monkey Urine Between Aqueous Solution and Ethyl Acetate at pH 8 as Percent of Distribution and Percent of Administered Dose

	% of Distribution		% of Administered Dose	
	Aqueous Fraction	Ethyl Acetate Fraction	Aqueous Fraction	Etnyl Acetate Fraction
Group I:				
Group I Male Avg.	93.97	6.21	76.40	5.09
Group I Male Std. Dev.	1.27	1.27	2.21	1.23
Group I Male Avg.	93.80	6.20	75.33	5.01
Group I Male Std. Dev.	0.27	0.27	12.11	0.94
Group II:				
Group II Male	93.46	6.54	75.60	5.26
Group II Female	1.78	1.78	3.59	1.36
Group II Female Avg.	93.66	6.34	75.70	5.11
Group II Female Std. Dev.	0.58	0.58	7.18	0.41

The ethyl acetate extract which contained 5% of the administered dose should contain the neutral metabolites.

The ethyl acetate fractions were profiled using HPLC/RAD. The major component of these fractions was identified by HPLC retention time to be N-[2-ethyl-6-(1-hydroxyethyl)-phenyl]-2-(methylsulfonyl)-acetamide one of the mutagenic (Ames Salmonella TA 100) metabolites of alachlor identified in the urine of Sprague-Dawley rats and reportedly (Monsanto in rebuttal to the Agency's PD-1, final reports of studies never received) in Long-Evans rats and CD-1 mice This metabolite comprised only 1.3 and 1.2% of the dose for Groups I and II, respectively.

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b. In addition to HPLC/RAD profiling, pooled urine samples (0-96 hours from 4 animals, 1/sex/group) were also subjected to electrophoresis (high voltage paper) experiments to determine the ratio of acidic to neutral metabolites. Electrophoresis was run at pH 5.9 and pH 9.0. The results of these experiments can be found in the following table taken from the report (Table 31).

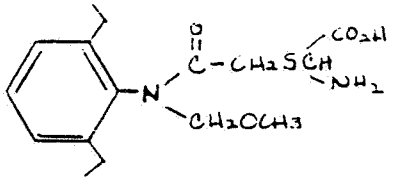
% of Administered Dose

	% Acid pH 5.9	%Neutral pH 5.9	% Acid pH 9.0	%Neutral pH 9.0	Z*
Group I Male	61.46	20.03	77.10	4.38	15.65
Group I Female	57.41	22.93	75.87	4.47	18.46
Group II Male	69.41	11.46	75.75	5.12	6.34
Group II Female	66.86	13.95	74.84	5.97	7.38

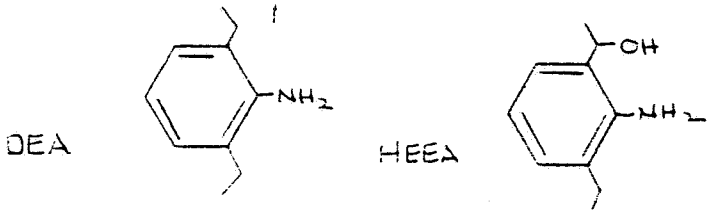
* Zwitterionic species are those that migrate toward the anode (behave as acids) at pH 9 but not at pH 5.9.

The amount of neutral metabolites found at pH 9.0 corresponds well to that found using ethyl acetate extraction (see 2.a. above).

In the report the zwitterionic components were attributed to the cysteine conjugate. The report states on page 7, 14 and 15 that this is metabolite 8, however, metabolite 8 as shown in the figure on pg 55 of the report is a glucuronide conjugate. Metabolite 7 is the cysteine conjugate.



c. The amount of benzylic hydroxylation was determined by acid pressure hydrolysis/acelytation on pocled urine (0-96 hrs/monkey/sex/group); the major hydrolysis product was 2, 6-diethyl-aniline (DEA). The ratio of hydroxylated (HEEA) to non-hydroxylated (DEA) metabolites was determined to be an average of 0.33 for Group I animals and 0.25 for Group II animals.



Appendix I

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Michael McDavit, PM #61
Special Review Branch
Registration Division (TS-767C)

FROM: Judith W. Hauswirth, Toxicologist Judith W. Hauswirth 2/14/86
Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Theodore M. Farber, Chief Theodore M. Farber 2/14/86
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Reto Engler, Chief
Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

SUBJECT: Lasso (Alachlor), EPA Reg. # 524-285, 524-286, 524-314, 524-329, 524-341, 524-344; Review of Monkey Metabolism Study; Monsanto's Special Report MSL-5117, RD 641, October 30, 1985. Accession No. 260258.

Caswell #11

Action Requested:

Monsanto Company submitted for review a study entitled, "The Metabolism of Alachlor in Rhesus Monkeys. Part II. Identification, Characterization and Quantification of Alachlor and Its Metabolites After Intravenous Administration to Monkeys." In the Overview section of the report Monsanto states that this is an interim report as the analytical portion of the study has not been completed.

Conclusions:

Study Classification: Supplementary, pending submission of the final report.

1. Five metabolites of alachlor were identified in the urine of monkeys injected intravenously with 0.7 or 7.0 mg/kg

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alachlor. The structures of these metabolites are given in the Results and Discussion section of the Review portion of this memorandum. They consisted of a secondary and tertiary mercapturate conjugate and a cysteine, thioacetic acid and glucuronide conjugate of alachlor. The different doses of alachlor administered appeared to quantitatively but not qualitatively alter the metabolic profile.

2. The following metabolic differences between the rat and monkey can be noted:

   - o number of identifiable urinary metabolites; five in the monkey and 14 in the rat
   - o the ratio of urinary to fecal radioactivity recovered: rat 1:1 and monkey 9-10:1
   - o only two urinary metabolites were common to both the rat and monkey, namely the secondary and tertiary mercapturic acid conjugates
   - o sulfate conjugation and side chain hydroxylation metabolites were found in the urine of the rat but not the monkey.

3. The results obtained in this study and in previously conducted intramuscular and topical metabolism studies do not support Monsanto's contention that the metabolites of alachlor "formed do not change as a function of the route of administration". This contention is not supported

   - o because the metabolites of alachlor as reported for the intramuscular and topical studies appear to differ quantitatively as well as qualitatively (number of metabolites found) and
   - o because the limited nature of the intramuscular and topical studies in the monkey make it difficult to extrapolate the results obtained in those studies to the intravenous metabolism study discussed in the attached Review.

4. The results of this study do not support Monsanto's argument that the monkey is a better model than the rat for assessing the effects of alachlor in man. No side chain hydroxylated metabolites of alachlor were identified in the urine of monkeys administered alachlor by the intravenous, intramuscular or topical routes, however, these metabolites have been identified in the urine of rats given alachlor orally and in man administered alachlor topically.

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REVIEW

Study Type: monkey metabolism

Study Title: The Metabolism of Alachlor in Rhesus Monkeys Part II. Identification, Characterization, and Quantification of Alachlor and Its Metabolites After Intravenous Administration to Monkeys.

Accession No: 260258

Animal Phase: International Research and Development Corp. Mattawan, Michigan 49071

Metabolite Identification and Quantitation: Monsanto Agricultural Products Company Chesterfield, Missouri

Report No. and Date: MSL-5117, RD 641, October 30, 1985. Compiled by S. R. Muench Job/Project No.: 7842, MSL-4939

Test Animal: Rhesus monkey

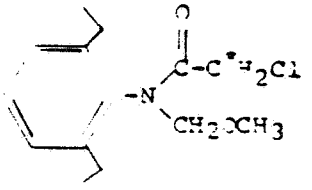
No. Animals/Group: 3/sex/group

Dosages: 0.7 and 7.0 mg/kg, once on initiation of study

Route of Administration: intravenous (I.V.)

Test Substance: ^{12}C-alachlor (>99% pure)
^{13}C-alachlor 90% enriched at the C-2 carbon (>98% pure)
^{14}C-alachlor uniformally labelled in the phenyl ring (>98% pure)

Structure:



* position of ^{13}C

Vehicle: 1,2-propylene glycol

Composition of High Dose: specific activity - 3.090 x 10^9 dpm/g soln. or 3.257 x 10^9 dpm/mL; conc. of alachlor - 38.99 mg/mL soln.; $^{12}C/^{13}C$ = 0.88

Compositon of Low Dose: specific activity - 3.64 x 10^8 dpm/mL soln. or 3.48 x 10^8 dpm/g soln.; conc. of alachlor-3.90 mg/mL soln; $^{12}C/^{13}C$=0.87

Length of Study: 5 days

Dose Selection: 0.7 mg/kg - highest dose used in a previous rhesus monkey metabolism study
7.0 mg/kg - lowest dose used in rat studies

Materials and Methods: see attached Materials and Methods Section from the report

Protocol: protocol for this study was submitted and reviewed by Toxicology Branch in a memorandum dated 11/30/85. It was found acceptable.

Collection of Samples: fecal and urine samples were collected at 0-4, 4-8, 8-12 and every 12 hours thereafter up to 120 hours. Samples were collected at 0-4°C and were then frozen. Pooled urine samples were used for metabolite identification.

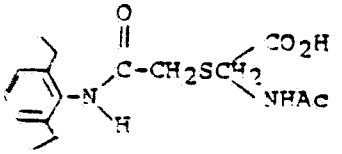
Metabolite Characterization and Quantification:
1. HPLC
2. liquid scintillation counting
3. mass spectral analysis.

Results and Discussion:

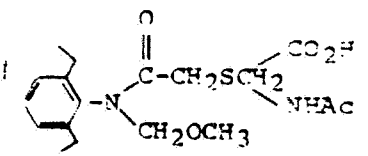
The average dose given Group I monkeys was 6.840 mg/kg (6.67-7.12) and Group II monkeys 0.653 mg/kg (0.536-0.693). The total excretion of radioactivity as percent of dose over 5 days was 81.12% in the urine and 9.640% in the feces of Group I monkeys and 81.075% in the urine and 8.662% in the feces of Group II monkeys. Total recovered radioactivity including rinses (of syringes, etc.) was 98.393% for Group I and 96.372% for Group II.

The ratios of urine/fecal elimination were 9.4±1.5 and 10.3±1.8 for Groups I and II, respectively. A half life of approximately five hours was calculated from previous studies in monkeys. Ninety-two to 94% of total radioactivity in the urine was excreted during the first 24 hours and 91-94% of the radioactivity in the feces was excreted during the first 48 hours.

Identified Urinary Metabolites



secondary mercapturate (4)



tertiary mercapturate (5)

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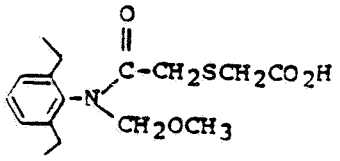
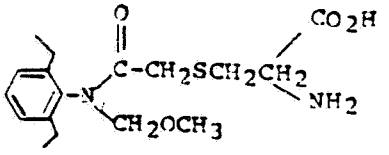
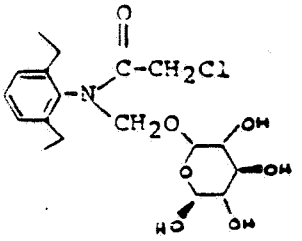


thioacetic acid conjugate (6)



cysteine conjugate (7)



glucuronide conjugate (8)

These metabolites accounted for 51-52% of the recovered urinary radioactivity for both treatment groups.

Distribution of Metabolites in Pooled Monkey Urine as % of Administered Dose

	Met. 4	Met. 5	Met. 6	Met. 7	Met. 8
Group I			Percent		
males	6.30±2.70	15.37±2.57	5.90±1.01	9.54±2.83	4.41±1.63
females	6.10±1.34	13.34±2.02	3.86±0.97	12.46±5.82	6.34±3.23
both	6.45±1.94	14.36±2.35	4.88±1.43	11.00±4.39	5.37±2.52
Group II					
males	8.35±1.75	19.79±1.45	7.06±0.28	2.63±1.34	3.90±1.81
females	10.91±0.98	16.42±2.94	10.08±2.77	3.31±2.81	2.05±0.77
both	9.63±1.89	18.10±2.77	8.57±2.42	2.72±1.98	2.97±1.61

At the lower dose (Group II) the major metabolites were #'s 4, 5 and 6. At the higher dose (Group I) the major metabolites were #'s 5 and 7. The dosage of alachlor administered appears to quantitatively alter the metabolic profile.

Fecal samples were not analyzed for individual metabolite identification and quantification. Apparently this is being done since the registrant states that the analytical portion of this study has not been completed and that this is an interim report (see Overview of Special Report MSL-5117).

The registrant concludes from the data obtained in this study

that alachlor is metabolized differently in rat and monkey. The rat metabolism study referred to is a study submitted by Monsanto in 1983 entitled "Rat Metabolism Study". MSL-3198, RD 493. Part I and II and reviewed by Toxicology Branch in a memorandum dated 2/29/84. In this study alachlor was administered by gavage to rats (Sprague-Dawley). Fourteen metabolites of alachlor were identified in urine and 13 in feces. Only three metabolites were common to both urine and feces. Approximately 89% of the radioacativity was eliminated within the first four days after dosing. The ratio of radioactivity found in urine versus feces was about 1:1. The rate of alachlor elimination was biphasic with the half-life of the first phase being 8.2 to 10.6 hours and of the second phase 5 to 16 days. Mercapturic acid, glucuronic acid, sulfate conjugation and side chain hydroxylation were important metabolic pathways for alachlor metabolism in the rat.

Notable differences in the metabolism of alachlor in the rat and the monkey:

1. number of identifiable urinary metabolites; five in the monkey versus 14 in the rat
2. ratio of urinary to fecal recovered radioactivity: rat 1:1, monkey 9-10:1. The registrant claims that this difference is due to the different molecular weight thresholds for biliary excretion in rats and monkeys (325±50 versus 475±50, respectively)
3. only two metabolites were common to both rat and monkey urine (#4 and 5 as shown above)
4. sulfate conjugation and side chain hydroxylation were not metabolic pathways identified for alachlor in the monkey (urine only).

The registrant also claims that the profiles of alachlor metabolites in the monkey are similar whether alachlor is administered by the intravenous, intramuscular or topical route. The intramuscular and topical (#MA-81-261, November 28, 1981; Monsanto Special Report MSL-4609, RD 596, March 30, 1985; Accession No. 257283 and 258393) studies were reviewed in a Toxicology Branch memorandum of June 5, 1985 and according to that reviewer "the registrant recently submitted a study determining the nature of alachlor metabolites in monkeys and identified three major metabolites; conjugates of two DEA derivatives and a conjugate of thioacetic acid. This reviewer questions these data because (1) not all the urine samples were tested, (2) the urine tested was 2 to 3 years old (urine stored from the old monkey study #MA-81-261)." The registrant states that they only used urine samples that had high levels of radioactivity, that if these samples "had been combined with the urine samples which contained lower levels of metabolites, the chances of being able to identify the metabolites would have been greatly diminished".

The pattern of metabolites as well as the percentage of each

found in the urine for the three routes of administration is summarized below.

% of Metabolite Found in Monkey Urine[a]

Met. No.	Route of Administration			
	I.V.[b] low dose	I.V.[b] high dose	I.M.[c]	Topical[d]
4	11.91±2.24	7.94±2.13	31.16±5.49	32.98±5.70
5	22.36±3.03	17.88±3.23	14.00±3.45	12.07±5.70
6	10.54±2.44	6.13±1.90	24.71±3.31	16.65±3.34
7	3.40±2.53	13.33±4.12	-	-
8	3.64±1.88	6.57±2.61	-	-

[a]For the I.V. route this percentage represents the percent of urine containing radioactivity. For the I.M. and topical exposures the report did not state if the percentage was percent of total dose administered or percent of urine containing radioactivity.

[b]pooled urine 0-96 hours
[c]pooled urine 0-4 hours
[d]pooled urine 24-48 hours

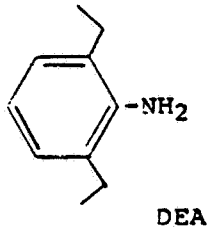
The major metabolite found in the I.M. and topical studies was metabolite #4 while the major metabolite in the I.V. studies was #5. The metabolites as reported for the I.M. and topical studies appear to differ quantitatively as well as qualitatively (number of metabolites identified) from the metabolites reported for the I.V. study. Furthermore, due to the limited nature of the I.M. and topical metabolism studies in the monkey it is difficult to extrapolate the data obtained in those studies to the I.V. study reviewed here and, therefore, it is not possible to conclude that the metabolites of alachlor "formed do not change as a function of route of administration" as stated by the registrant in this submission (see Overview of Special Report MSL-5117).

The registrant further argues that "rats are not an appropriate model for assessing the effects of alachlor in man" (Overview,

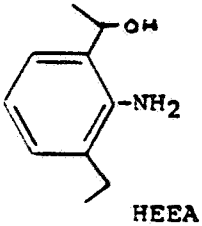
Special Report MSL-5117) and that "the rhesus monkey is considered a much better simulator of humans in regard to metabolism (Summary p. 2. of Special Report MSL-5117). In a reference given by Monsanto, Calabrese (Drug Metabolism Reviews 15(3) 505-523, 1984) concludes "monkeys are the best simulators of humans with regard to plasma protein binding, a number of metabolic patterns (especially certain amino acid conjugation patterns for arylacetic acids), and susceptibility to teratogenic agents". Although the threshold molecular weight for biliary excretion in man has not been adequately determined it is estimated to be approximately 500 which is closer to the monkey (475) than the rat (325) (J. R. Gillette, in Drug Metabolism from Microbe to Man. D. V. Parke and R. L. Smith, eds. Taylor and Francis Ltd. London, 1977. p. 149). It should be noted, however, in man that 15% of a given dose of indomethacin (molecular weight = 358), 15% of a given dose of diazepam (molecular weight = 285) and 23-40% of a given dose of practolol (molecular weight = 264) were excreted in the bile (Douglas E. Rollins in Pharmacokinitic Basis for Drug Treatment. edited by L. Z. Benet, et. al. Raven Press, N. Y. 1984, pp. 77-78). Molecular weight plays a role in biliary excretion but other factors also influence it. It should also be noted that although the Rhesus monkey is a good metabolic model for man, for a series of arylacetic acids, amphetamine and isoniazid for example, the rat is a bettex model for man for oxisuran and 2-acetamidofluorene and as good as the Rhesus monkey for hydratropic acid and diphenylacetic acid (R. L. Smith and J. Caldwell in Drug Metabolism from Microbe to Man. D. V. Parke and R. Smith, eds. Taylor and Francis Ltd. London, 1977. p. 149). Furthermore, the rates of elimination of drugs are generally lower in man than in experimental animals including the monkey (see D. S. Davies in Drug Metabolism from Microbes to Man. D. V. Parke and R. L. Smith, eds. Taylor and Francis Ltd. London, 1977. pp. 357-368).

Toxicology Branch has already addressed this issue briefly in relation to the results obtained in the I.M. and topical metabolism studies in the monkey. Toxicology Branch concluded "alachlor metabolism in monkeys and man may be different: the identification of metabolites in the urine of monkeys indicated that only metabolites which contained the DEA moiety were present, while in the human biomonitoring studies, metabolites which contained the HEEA moiety were also present in urine at a level that required attention (i.e., DEA: HEEA

was generally 4:1 but in one individual it was 1:2). Hence, the monkey may not be the best model for man and all available data from other animal species should be considered for extrapolation to man". The DEA and HEEA moieties refer to the following structures:



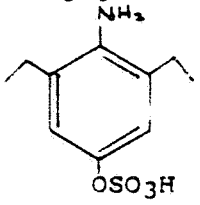
DEA



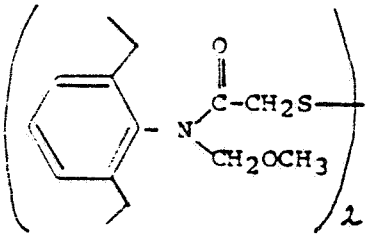
HEEA

The data obtained from the newly submitted metabolism study of alachlor in monkeys (I.V. administration) further supports this conclusion. No HEEA containing metabolites were identified in monkey urine in this study but were found in rat and the human.

On page 1 of this submission the registrant refers to two other metabolism studies which they have apparently conducted and are preparing reports for submission, one in Long-Evans rats (oral administration) and the other in CD-1 mice (oral administration). They claim that alachlor is converted to the same metabolites in Long-Evans rats as in Sprague-Dawley rats with minor quantitative differences. The differences between rats and CD-1 mice were the greater formation of the phenol sulfate, of the alachlor disulfide and of glucuronic acid conjugates in mice.



phenol sulfate



alachlor disulfide

Conclusions:

1. Five metabolites of alachlor were identified in the urine of ~~rats~~ monkeys injected I.V with 0.7 or 7.0 mg/kg alachlor. The structures of these metabolites are given in the Results and Discussion section of this review. They consisted of a secondary and tertiary mercapturate conjugate and a cysteine, thioacetic acid and glucuronide conjugate of alachlor. The different doses of alachlor administered appeared to quantitatively alter the metabolic profile.

2. The following metabolic differences between the rat and monkey can be noted:

   - o number of identifiable urinary metabolites: five in monkey versus 14 in the rat.
   - o the ratio of urinary to fecal radioactivity recovered: rat 1:1 and monkey 9-10:1.
   - o only two urinary metabolites were common to both the rat and monkey, namely the secondary and tertiary mercapturic acid conjugates
   - o sulfate conjugation and side chain hydroxylation metabolites were found in the urine of the rat but not the monkey.

3. The results obtained in this study and in previously conducted I.M. and topical metabolism studies do not support Monsanto's contention that the metabolites of alachlor "formed do not change as a function of the route of administration". This contention is not supported because

   - o the metabolites of alachlor as reported for the I.M. and topical studies appear to differ quantitatively as well as qualitatively (number of metabolites found)
   - o the limited nature of the I.M. and topical studies in the monkey make it difficult to extrapolate the results obtained in those studies to the I.V. metabolism study reviewed herein.

4. The results of this study do not support Monsanto's argument that the monkey is a better model than the rat for assessing the effects of alachlor in man. No side chain hydroxylated metabolites of alachlor were identified in the urine of monkeys administered alachlor by the I.V., I.M. or topical routes; however, these metabolites have been identified in the urine of rats given alachlor orally and in man administered alachlor topically.

Study Classification: Supplementary, pending submission of the final report of this study.

Page_____ is not included in this copy.

Pages 18 through 29 are not included.

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