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

005968

JUN 29 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: A Teratology Study in Rabbits with MON 097 (Acetochlor) - WIL Project No. 50009; Monsanto Study No. R.d. 713; EPA Identification No. 382966/524-GUI; Caswell No. 3B; Toxicology Branch Project No. 7-0721.

FROM: Alan C. Levy, Ph.D.
Toxicologist, Review Section V
Toxicology Branch/HED (TS-769C)
Alan C. Levy 6/24/87

TO: Taylor/V K Walters (PM 25)
Registration Division (TS-767C)

THRU: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head, Review Section V
Quang Q. Bui 6/24/87

and

Theodore M. Farber, Ph.D., D.A.B.T.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: Monsanto Agricultural Company

Action Requested: Review a teratology study in rabbits with MON 097 (Acetochlor) - This is a replacement study for IRDC #401-104 which was classified as Supplemental Data.

Recommendations: The Maternal Toxicity No Observed Effect Level (NOEL) is 50 mg/kg/day. The Maternal Toxicity Lowest Observed Effect Level (LOEL) is 190 mg/kg/day. There was a group mean body weight loss during the period of dosing (days 7 through 19 of gestation) in the 190 mg/kg/day rabbits. From days 19-29, the mean body weight gain for this group was greater than for the control and two lower-dose groups. There were no apparent group differences regarding any other parameters.

The Developmental Toxicity No Observed Effect Level (NOEL) is 190 mg/kg/day (Highest Dose Tested). The Developmental Toxicity Lowest Observed Effect Level (LOEL) is >190 mg/kg/day (HDT). There were no apparent compound related differences regarding any Developmental Toxicity parameters in any dose group.

The study is acceptable and is considered to be Core Minimum.

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Primary Reviewer: Alan C. Levy, Ph.D.
Review Section V/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head
Review Section V/HED (TS-769C)

I. Study Type: Teratology
(Guideline § 83-3)

Study Title: A Teratology Study in Rabbits with MON 097 (Acetochlor)

EPA Identification Numbers:

EPA Identification: 382966/524-GUI
EPA Accession: 40134101
EPA Record: 195384/195382
Shaughnessy:
Caswell: 3B
Tox. Branch Project: 7-0721
Document:

Sponsor: Monsanto Agricultural Company
800 North Lindberg Boulevard
St. Louis, MO 63167

Testing Laboratory: WIL Research Laboratories, Inc.
A Subsidiary of Great Lakes Chemical Corporation
Ashland, OH 44805-9281

Study Number: Monsanto - R.d. 713
WIL Research Laboratories, Inc. - Project No. 50009; Study No. WI-86-4

Study Date: September 5, 1986

Study Author: Gabriela Adam, Ph.D.

Test Material:

Name: MON 097 (Acetochlor)
Lot No.: XLF - 349
Description: Red Viscous Liquid
Purity: 94.2%

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Vehicle:

Name: Mazola® 100% Pure Corn Oil
Lot Nos.: V062-A Nov 06 86
V057-D Aug 30 86
Description: Yellow, Viscous Liquid

Test Animal: New Zealand White sexually mature virgin female rabbits from Hazleton-Dutchland, Inc., Denver, PA. Pregnancy by artificial insemination (semen collected from 11 resident males of the same strain and obtained from the same supplier).

II. Material and Methods: Four groups of 20 artificially inseminated female New Zealand White rabbits were administered MON 097 via gastric intubation, on gestation days 7 through 19, in 0.5 ml/kg of corn oil at concentrations of 0, 15, 50 and 190 mg/kg/day. A copy of the Materials and Methods section from the laboratory's report (WIL Research Laboratories, Inc.) is appended.

Statistical methodology was described in detail.

A Quality Assurance statement was included.

The following comments are noted:

The investigators indicated that, "diluted semen from one male was used to inseminate an equal number of females in each group". However, there are no data to substantiate this statement. Insemination data must be appended with future submissions to the Agency.

Historical data are provided, but the period of collection is unknown.

Page 4 of Table 10, "Individual Body Weights (Grams) During Gestation" for Group 4, 190 mg/kg/day (page 42 as numbered by Monsanto), was missing from the report.

III. Results

A. Gross maternal observations: No mortality or spontaneous abortions were observed in any of the groups. There was a statistically significant mean body weight loss during the dosing period (days 7 through 19 of gestation) in the group receiving the highest dose (190 mg/kg/day). In addition, this group of 19 pregnant females had 14 animals which lost weight compared with 5/19, 5/18 and 4/19 in the other groups. The high-dose group compensated for this

weight loss by gaining a mean of 231 gm from days 19-29 (post compound administration) as compared to a mean gain of 129, 30 and 134 gm for the control, low- and mid-dose groups, respectively.

These data indicate that the administration of MON 097 at 190 mg/kg/day from days 7 through 19 of gestation causes a mean group body weight loss as well as an increased number of dams which lost weight during this period. In addition, there was a compensatory weight gain in this group during days 19-29 (post dosing).

Mean Body Weight Changes of Dams During Dosing (Gestation Days 7 Through 19) and Post Dosing (Gestation Days 19 to 29)

mg/kg/day	0	15	50	190
DURING DOSING				
Mean gm weight change	+81	+112	+93	-146[a]
Standard Deviation	±127	±164	±125	±225
Number of dams that lost weight/total number of pregnant dams	5/19	5/18	4/19	14/19
POST DOSING				
Mean gm weight change	+129	+30	+134	+231
Standard Deviation	±252	±184	±113	±152

a = Significantly different from control group at 0.01 level using a two-tailed Dunnett's Test.

Data extracted from WIL Report 50009 (WI-86-4), Tables 4 (p. 33) and 11 (p. 43-46).

B. Fertility Index: There was essentially no difference in the fertility index between groups (95%, 90%, 95% and 95% for control, low, mid and high doses, respectively).

C. Cesarean section observations: There did not appear to be any compound related effect on the incidences of viable fetuses, early or late resorptions, postimplantation loss, implantation sites or corpora lutea.

Table 5, reproduced from the WIL Report, appears on p. 5 of this review and presents fetal data at scheduled necropsy of pregnant rabbits.

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____ Description of the product manufacturing process.

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____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

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D. External, visceral and skeletal malformations/variations: There did not appear to be any compound related effects on the incidence of external, visceral or skeletal malformations/ variations observed in fetuses.

Pages 7 and 8 of this review are a summary of the above fetal data as extracted from WIL Report Tables 6 and 7 for malformations and Tables 8 and 9 for variations.

E. Analysis of dosing preparations: WIL Research Laboratories validated a method for measuring MON 097 in the corn oil vehicle. A low concentration of 7.5 mg/ml averaged 102.1% and a high concentration of 380 mg/ml averaged 100.6% of expected values. Aliquots were taken from the top, middle and bottom of each of the dosing preparations to show homogeneity, and values ranged from 99.0 to 106.8%. Stability of MON 097 in corn oil was ascertained after seven days and three weeks, with values ranging from 98.2 to 107.4%. Analyses made on the eleventh day of dosing on preparations to be used on the last five days, yielded values ranging from 93.5 to 100.7%.

These data indicate that the preparations of MON 097 in corn oil were homogenous, stable for three weeks and contained the required amount of compound to assure that the rabbits received the doses indicated.

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Number and Percent of Fetuses and Litters with Malformations

	Fetuses				Litters			
Dose Group (mg/kg/day)	0	15	50	190	0	15	50	190
Number examined	149	124	135	130	19	17	19	19
EXTERNAL								
Carpal and/or tarsal flexure	1[a] 0.7	0	0	0	1 5.3	0	0	0
Omphalocele	1 0.7	0	0	0	1 5.3	0	0	0
Spina bifida	0	0	0	1 0.8	0	0	0	1 5.3
Nare(s) closed	1 0.7	0	0	0	1 5.3	0	0	0
VISCERAL								
Kidney and ureter absent	0	0	1 0.7	0	0	0	1 5.3	0
Iris bombe	0	3 2.4	1 0.7	0	0	3 17.6	1 5.3	0
Hydrocephaly	0	0	1 0.7	0	0	0	1 5.3	0
SKELETAL								
Extra site of ossification anterior to sternebra #1	0	0	0	1 0.8	0	0	0	1 5.3
Rib anomaly	2 1.3	0	2 1.5	3 2.3	2 10.5	0	2 10.5	2 10.5
Vertebral anomaly with or without associated rib anomaly	2 1.3	0	1 0.7	2 1.5	2 10.5	0	1 5.3	2 10.5
Costal cartilage anomaly	1 0.7	0	0	0	1 5.3	0	0	0
Vertebral centra anomaly	0	0	1 0.7	0	0	0	1 5.3	0
Skull anomaly	0	1 0.8	0	0	0	1 5.9	0	0
Caudal vertebrae anomaly	0	0	1 0.7	0	0	0	1 5.3	0
TOTAL MALFORMATIONS								
External	1 0.7	0	0	1 0.8	1 5.3	0	0	1 5.3
Soft Tissue	0	3 2.4	3 2.2	0	0	3 17.6	3 15.8	0
Skeletal	5 3.4	1 0.8	5 3.7	6 4.6	5 26.3	1 5.9	5 26.3	5 26.3
Total with malformations: #	6	4	8	7	5	3	7	6
Total with malformations: %	4.0	3.2	5.9	5.4	26.3	17.6	36.8	31.6

a = Whole number is number and decimal is percent malformations.
None significantly different from control (number of fetuses or litters) at 0.05 level using Fisher's Exact Test.
Data extracted from WIL report (Tables 6 and 7).

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Number and Percent of Fetuses and Litters with Variations

Dose Group (mg/kg/day)	Fetuses				Litters			
	0	15	50	190	0	15	50	190
Number Examined	149	124	135	130	19	17	19	19
EXTERNAL								
Findings	0	0	0	0	0	0	0	0
VISCERAL								
Renal papilla(e) not developed and/or distended ureter(s)	1[a] 0.7	0	0	1 0.8	1 5.3	0	0	1 5.3
Major blood vessel variation	2 1.3	6 4.8	3 2.2	3 2.3	2 10.5	5 29.4	3 15.8	2 10.5
Retrocaval ureter	1 0.7	3 2.4	6 4.4	2 1.5	1 5.3	2 11.8	4 21.1	2 10.5
Gallbladder absent or small	1 0.7	0	1 0.7	0	1 5.3	0	1 5.3	0
Hemorrhagic ring around the iris	0	0	0	1 0.8	0	0	0	1 5.3
Dense white region in eye	1 0.7	0	0	0	1 5.3	0	0	0
SKELETAL								
13th rudimentary rib(s)	27 18.1	28 22.6	20 14.8	24 18.5	14 73.7	13 76.5	12 63.2	14 73.7
Hyoid arch(es) bent	10 6.7	2 1.6	9 6.7	8 6.2	7 36.8	2 11.8	5 26.3	6 31.6
Sternebra(e) #5 and/or #6 unossified	21 14.1	26 21.0	21 15.6	19 14.6	11 57.9	10 58.8	9 47.4	7 36.8
13th full rib(s)	45 30.2	39 31.5	51 37.8	49 37.7	15 78.9	12 70.6	13 68.4	16 84.2
Accessory skull bone(s)	1 0.7	1 0.8	1 0.7	0	1 5.3	1 5.9	1 5.3	0
Sternebrae with thread-like attachment	1 0.7	5 4.0	0	3 2.3	1 5.3	3 17.6	0	1 5.3
27 presacral vertebrae	17 11.4	10 8.1	28 20.7	22 16.9	8 42.1	6 35.3	10 52.6	9 47.4
7th sternebra	1 0.7	0	0	0	1 5.3	0	0	0
Hyoid body and/or arches unossified	3 2.0	4 3.2	1 0.7	1 0.8	2 10.5	1 5.9	1 5.3	1 5.3
Sternebra(e) malaligned (slight or moderate)	4 2.7	3 2.4	9 6.7	5 3.8	3 15.8	2 11.8	7 36.8	4 21.1
14th rudimentary rib(s)	0	1 0.8	0	0	0	1 5.9	0	0
25 presacral vertebrae	0	0	0	1 0.8	0	0	0	1 5.3

a = Whole number is number and decimal is percent variations.
None significantly different from control (number of fetuses or litters) at 0.05 level using Fisher's Exact Test.
Data extracted from WIL report (Tables 8 and 9).

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IV. CONCLUSIONS

The Maternal Toxicity No Observed Effect Level (NOEL) is 50 mg/kg/day. The Maternal Toxicity Lowest Effect Level (LOEL) is 190 mg/kg/day. There was a group mean body weight loss during the period of dosing (days 7 through 19 of gestation) in the 190 mg/kg/day rabbits. From days 19-29, the mean body weight gain for this group was greater than for the control and two lower-dose groups. There were no apparent group differences regarding any other parameters.

The Developmental Toxicity NOEL is 190 mg/kg/day (Highest Dose Tested). The Developmental Toxicity LOEL is >190 mg/kg/day. There were no apparent compound related differences regarding any Developmental Toxicity parameters.

V. CORE CLASSIFICATION: Core Minimum.

Maternal Toxicity NOEL = 50 mg/kg/day
Maternal Toxicity LOEL = 190 mg/kg/day (HDT)
Developmental Toxicity NOEL = 190 mg/kg/day (HDT)
Developmental Toxicity LOEL = >190 mg/kg/day (HDT)

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