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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

MEMORANDUM

SUBJECT: Review of rat dominant lethal assay; Record no. 233009/223010/223017/223015; EPA ID no. 3F2966/6G3345/524-GUI/524-EUP-AT; MRID No. 403893-01; Proj. No. 8-0777; Caswell No. 3B

TO: Robert Taylor/V.K. Walters (PM 25)
Registration Division (TS-769C)

FROM: James N. Rowe, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Branch (TS-769C)
James N. Rowe 6/27/88

THRU: Quang Q. Bui, Ph.D.
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Section Head
Section V, Toxicology Branch
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Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)
6/30/88

ACTION: Expedited review of a rat dominant lethal study; Record no.233009/223010/223017/223015; EPA ID no.3F2966/6G3345/524-GUI/524-EUP-AT; Accession No. 40389301; Proj. No. 8-0777; Caswell No. 3B

RECOMMENDATIONS:

Unacceptably low pregnancy rates among control and low dose animals associated with low mating activities in control males limit the sensitivity of this study to adequately evaluate the potential dominant lethality/reproductive toxicity of MON 097.

This study is designated unacceptable data and cannot be upgraded. A new study is requested.

Reviewed By: James N. Rowe, Ph.D.
Section V, Toxicology Branch (TS-769C)
Secondary Reviewer: Kerry Dearfield, Ph.D.
Section V, Toxicology Branch (TS-769C)

James N. Rowe 6/27/88

Kerry Dearfield 6.27.88

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DATA EVALUATION REPORT

Study type: Dominant Lethal
Test system: Rats, Sprague-Dawley
Guideline: 84-2

Study Title: DOMINANT LETHAL/FERTILITY STUDY OF MON 097 IN SPRAGUE-DAWLEY RATS

EPA ID NOS.: EPA ID NO. 3F2966/6G3345/524-GUI/524-EUP-AT
EPA MRID No. 403893-01
Caswell No. 3B
Project No. 8-0777

Sponsor: Monsanto Company
St. Louis, MO 63110

Testing Laboratory: Monsanto Environmental Health Laboratory
645 S. Newstead
St. Louis, MO 63110

Laboratory Project No.: EHL-86008

Final Report Date: 10/11/87

Date of Study Completion: 8/11/87

Study Author: M.W. Naylor, B.S., Study director

Quality Assurance: A statement of Quality Assurance is signed by Arthur F. Uelner, Manager, Quality Assurance at EHL

Compound: MON-097, ID code T860008, Lot No. XLF-396, purity 94.3% from Monsanto Agricultural Co., Date received 2/12/86, purple liquid; chemical name is acetochlor.

CONCLUSIONS - EXECUTIVE SUMMARY:

Unacceptably low pregnancy rates among control and low dose animals associated with low mating activities in control males limit the sensitivity of this study to adequately evaluate the potential dominant lethality/reproductive toxicity of MON 097.

Recommendation: This study is unacceptable.

Methods:

A photocopy of the experimental methods is attached (see Attachment 1).

The test compound was administered in the diet (0, 100, 1000, 2000 ppm) for approximately 9 weeks to 4 groups of 30 male CD (SD) BR rats each. At the end of the exposure period, each male was co-housed with a single untreated virgin female for up to 5 days. After a recovery period of 2-6 days, the males were again co-housed with a second untreated virgin female. A concurrent positive control group of males (30) received a single intraperitoneal injection (0.3 mg/kg) of triethylenemelamine (TEM) 3 days before mating.

All animals were checked for mortality and morbidity twice daily. Detailed clinical observations for males were performed weekly in males until mating and in females immediately prior to mating. Body weights were measured weekly in males until mating, once again at the end of mating and prior to terminal sacrifice while females were weighed prior to mating. Food consumption was determined weekly in males only prior to mating. Evidence of copulation was determined by the presence of a copulatory plug or by vaginal smear.

At the scheduled sacrifice time, males were examined externally and internally by gross necropsy; female reproductive organs were examined for pregnancy status, number and state of nidations, early resorption sites and corpora lutea counts.

Vehicle: Dietary feed: Ralston Purina RODENT CHOW No. 5002

Statistical analysis:
1) Dunnett's Multiple Comparison Test for body weights and food consumption, 2) Mann-Whitney U test for preimplantation losses, viable and non-viable implants expressed as both per pregnant female and per corporea lutea/pregnant female, dead implants/ total implants and corporea lutea/pregnant female, 3) Chi-square test for fertile males, number pregnant/number co-housed and the number of females with >1 and >2 dead implants.

Results:

Analysis of test compound

Test compound purity and stablity and dietary test mixture homogeneity and stability were within acceptable limits. The stability of the test substance compared with an analytical standard was acceptable during the exposure period (97% of standard concentration and 93% of standard concentration during a three-month period). Analysis for homogeneity of acetochlor in dietary mix indicated an acceptable level of homogeneity for the

low and high dose groups (0-15% variation from nominal with average variation of 4.3%). The dietary test mixture was stable up to 14 days at room temperature (within 10% of day 0 concentration) and when stored in the refrigerator for 36 days (90-110% of day 0 value). Analysis of dietary concentration of MON 097 weekly during the test period indicated that the concentration in all dose groups was within acceptable limits of the target value (85-100% of target).

Mortality/morbidity

There were no mortalities reported in this study and no apparent treatment-related clinical signs of toxicity.

Body weights

At the 2000 ppm dose level (HDT) there was a statistically significant depression in mean male body weights (gm) by the end of one week of treatment as compared with the control group and which was evident throughout the exposure period, i.e.,:

	Week 1	Week 5	Week 9
Controls	443.0	528.5	588.9
HDT	419.1**	493.0**	544.0**

** Dunnett's Test (two-tailed), $p<.01$)

Food consumption

There was a statistically significant depression ($p<.01$) in the mean food consumption (gm/kg/day) during week one of test substance administration (control, 61.4 gm; 1000 ppm, 54.8 gm; 2000 ppm, 48.8 gm). No statistically significant difference in any dose-group was observed thereafter for mean food consumption. Mean food efficiency (% food consumed converted to body weight) was sporadic but generally lower in the high dose group as compared to controls.

Fertility Data

A copy of the summary fertility data from the study report (Table 4) is attached (Attachment 2).

Meaningful analysis of the effects of acetochlor upon fertility/ dominant lethality is limited by the low pregnancy rate observed in the control females (30/60, 50%) as well as in the low dose group (28/60, 47%). A low fertility index in these males (21 males/30 pregnancies, 70%) was also noted in both dose groups. Further, mating activity was quite low in the mated control group (34/60 females co-housed, 57%). This suggests some difficulty in animal husbandry. As indicated by the study author (p. 11 of report) the pregnancy rate (# pregnant/# co-housed) in the negative controls was below the historical mean for this strain of rat in their laboratory. The 50% pregnancy rate in the

control group is not significantly different from the positive control. It is questionable whether meaningful dose-related data can be determined from the study. Also, it is uncertain that other factors may have compromised this study, e.g., to alter the control pregnancy rate. Therefore, the reviewer will not attempt to discuss the additional parameters presented. It is noted that the positive control did produce statistically significant effects for pregnancy rate, depressed number of corpora lutea, increased resorptions, etc. This indicates that the rat strain utilized is reponsive to the positive control, TEM.

Gross necropsy

No compound-related gross pathological effects were noted.