AUG 5 1985

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

004586

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

AUG 5 1985

MEMORANDUM

SUBJECT: Petition (3F2966 & 524-GUI) for Permanent Tolerances (Acc#071962-72) and Review of Data Previously Submitted with an EUP and Petition (524-EUP-56/2G2797 and 3G2791) for Temporary Tolerances (Acc#248618-20) for Harness® (Acetochlor)

Caswell #3B

TO: Robert Taylor (25)
Registration Division (TS-767C)

FROM: Winnie Teeters, Ph.D. W. Teeters 9-5-85
Pharmacologist, Section V
Tox/HED (TS-769C)

THRU: Laurence D. Chitlik, D.A.B.T. LDC 8/5/85
Head, Section V
Tox/HED (TS-769C)
and
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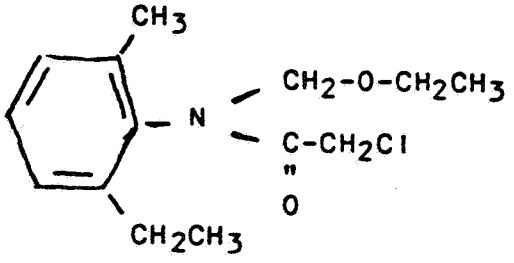
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

CHEMICAL: 2 Chloro-N-Ethoxymethyl-N-(2 Ethyl-6-Methylphenyl) Acetamide



Synonyms: Acetochlor, MON 097, CP-55097
Harness® (an emulsifiable concentrate containing 86.5% a.i. [CP-55097])

ACTION REQUESTED: Review studies submitted previously with a denied EUP and petition for temporary tolerances and recently submitted studies to support Monsanto Chemical Company's request for registration

and establishment of permanent tolerances for Harness® in/on the following raw agricultural commodities:

Corn (grain)	0.1 ppm
(forage & fodder)	0.8 ppm
Soybeans (grain)	0.4 ppm
(forage & hay)	5.0 ppm
Grain Sorghum (grain)	0.2 ppm
(forage & fodder)	3.0 ppm
Peanuts (nuts)	0.4 ppm
(hulls)	2.5 ppm
Eggs and chicken tissue	0.02ppm
Milk and beef tissue	0.02ppm
Hog tissue	0.02ppm

Recommendations:

At this time Toxicology Branch does not find the requested permanent tolerances supported by the available data. Further, Acetochlor has been found to be a carcinogen in both the rat and mouse. A risk assessment must be performed based on these findings; this has been tentatively scheduled for the week of August 29, 1985 by the Mission Support Staff.

Additionally, it is recommended that the recently submitted Pharmacopathics Research Laboratories' studies in the mouse, rat and dog (Report Nos. PR-80-007, PR-80-006, PR-80-008, respectively) be audited. The chromosome aberration assay performed by Hazleton Laboratories America is also a candidate study for an audit (Study #HL-83-006)

Summary of Reviewed Data

The following is a summary of data reviewed in this action submitted with the EUP and petition for temporary tolerances (Acc#248618-20; 524-EUP-56/2G2797 and 3G2791) and the petition for permanent tolerances (Acc#071962-72; 3F2966 and 524- GUI)

1. Subchronic 21-day dermal toxicity study in rabbits. Acc. #248620, International Research and Development Corp., Study #IR-80-356, 12-11-1981.

   The LOEL for systemic effects (mortality and decreased body weight) was 1200 mg/kg (HDT); the NOEL for systemic effects was 400 mg/kg. The LOEL for dermal irritation was 100 mg/kg (LDT) and a NOEL for dermal irritation was not established. The study is classified as Core-Minimum.

2. Dermal sensitization study in guinea pigs with MON 097 Technical. Acc. #071970, Bio-dynamics Incorp., Study # BD-82-204, 4-13-83.

Technical MON 097 was a positive dermal sensitizer.

3. Dermal sensitization study in guinea pigs with MON 097 8 lbs/gal. E.C. Acc. #071970, Bio-dynamics Incorp., Study # BD-82-205, 4-13-83.

The E.C. formulation of MON 097 was a positive dermal sensitizer.

4. In Vivo bone marrow chromosome study in rats with Acetochlor (MON 097). Acc. #071970, Hazleton Laboratories America, Inc., Study #HL83-006, 5-24-83.

Under conditions of the study, MON 097 gave no evidence that it induced chromosomal abnormalities, but the study is Unacceptable because of several deficiencies. This study is a candidate for audit. For details see pages 1 and 2 of review.

5. Rat hepatocyte primary culture/DNA repair test. Acc. #071970, Pharmacon Research International, Inc., Study #PK-52-151, 2-17-1983.

Under the conditions of the study, MON 097 did not appear to induce unscheduled DNA synthesis, but the study is Unacceptable because of multiple deficiencies, See "Conclusion" in the review, page 1.

6. Evaluation of mutagenic potential of MON 097 employing the L5178Y $TK^{+}/-$ mouse lymphoma assay. Acc. #071970, SRI International, Study #SR-81-150, Aug.-1982

MON 097 was a positive mutagen in this assay only in the presence of metabolic activation. The study is Acceptable.

7. CHO/HGPRT gene mutation assay with MON 097. Acc. #071970, Monsanto Environmental Health Lab., Study #ML-82-281, 6-9-1983.

MON 097 was weakly positive at near-toxic doses. However, the vehicle used (alcohol) did not appear to be inert in the assay. The study is Acceptable.

8. Rabbit teratology studies. Acc. #248620; International Research and Development Corp.; Pilot Studies #IR-79-292, Final Report #s 401-103, 401-103a, 401-103b; Primary Study #IR-79-293, 11-24-81.

There were 3 pilot teratology studies and a primary study. Two of the pilot studies (401-103,401-103a) are classified as Invalid Data. The third pilot study is classified Supplementary Data as a dose range-finding study. See

"Recommendation" on page 1 of review for an explanation of these classifications for these pilot studies.

The primary study is also classified as Supplementary Data and a new study is requested. Insufficient numbers of litters were available to fully assess the teratogenic potential so no conclusions were reached. See "Recommendations" on page 1 of the review for requested additional data for this primary study.

9. Two Generation Reproduction Study in Rats. Acc. #071969, International Research and Development Corp., Study # IR-80-053, 12-16-82.

The doses were 500, 1500 and 5000 ppm. A slight decrease (about 20%) in litter size was noted at the high dose in all matings. The high dose also caused decreases in pup body weight gain during lactation for both generations; this effect was also seen in male F_{2b} pups of the mid level.

Chronic nephritis was increased in females of the F_1 generation fed the high level and a slight increase in prostatis in this level may have been related to treatment.

Apparent treatment-related increases in thyroid weights were noted in low and mid dose F_{1b} (male) and F_{2b} (male and female) pups and in mid and high F_1 dams. Liver weights (nonsignificant in males) and ratios were increased in mid(not statistically significant) and high F_1 parents. Pituitary weights were decreased in all doses of F_1 adult males(mean absolute only at low and high doses), and in low and high dose F_{2b} male pups but were increased in low F_{1b} female pups. Decreases were also seen for ovary weights for adult F_1 females fed all levels.

The reproductive NOEL is 500 ppm and the LOEL is 1500 ppm based on decreased body weight gain of F_{2b} pups.

The systemic LOEL is 500 ppm based on absolute and relative organ weight: decreases for ovary weights in F_1 females, decreases for pituitary weights for F_1 and F_{2b} males and increases for thyroid weights in F_{1b} and F_{2b} pups. The systemic Noel was not established.

The study is classified as Core- Supplementary because of inadequate gross and histopathological examinations. See discussion under "Protocol" on page 1 of the review.

10. The Metabolism of Acetochlor in the Laboratory Rat. Acc. # 071971 and 071972, Hazleton Raltech Inc., Report # MSL-2824, June, 1983.

Acetochlor was rapidly excreted (>70% within 48 hours) with the urinary route accounting for about twice the percentage of the fecal route; pulmonary excretion was

insignificant. Elimination was biphasic with a rapid (t 1/2 < 10 hrs) and slow (t 1/2=128-286 hrs) phase.

Acetochlor was extensively metabolized, with less than 1% unchanged compound found in the feces and none detectable in the urine. The early (<24 hour) metabolites were mostly mercapturates and later ones mostly sulfoxides, sulfones and sulfates; 20 metabolites were identified. Early conjugation with glutathione is assumed.

The only tissue retaining significant amounts of labeled Acetochlor (about 2.5%) was the erythrocytes; their turnover rate in the rat correlates well with the slow phase of Acetochlor elimination. The radioactivity was covalently bound to hemoglobin and retention data suggested a possible cumulative effect on erythrocyte function.

Repeated doses of Acetochlor had little effect on excretion kinetics; the single large dose increased the half-lives for the slow and rapid phases about 50%.

There did not appear to be any significant sex differences in the metabolism of Acetochlor.

The study is classified as Core Guideline.

11. A one-year feeding study in dogs with MON 097. Acc. #248618-19, Pharmacopathics Research Laboratories, Study # PR-80-008, 10-14-81.

The dogs at the high dose (40 mg/kg) showed testicular atrophy (6/6) accompanied by decreased absolute and relative (to body weight) testicular weight, decreased body weight gain of males and decreased terminal body weight of females. There is also suggestive evidence at the high level for anemia and hepatotoxicity but a NOEL and LOEL cannot conclusively be determined for these effects at lower dose levels because of the variability of control data during the study and the wide range of normal values for these parameters established at the testing facility. There is also suggestive evidence for effects on adrenal weights.

Additional data are requested and the study has been recommended for audit. See page 1 of the review for the requested information and the conclusions. The study is classified as Supplementary Data.

12. MON 097: Chronic toxicity and oncogenicity study in the rat. Acc. #071962-65, Pharmacopathics Research Laboratories, Inc., Study #PR-80-006, 5-20-1983.

The dose levels were 500, 1500 and 5000 ppm (25, 75 and 250 mg/kg). MON 097 was carcinogenic to the rat; the high level caused an increased incidence of liver carcinomas and thyroid follicular cell adenomas in males.

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There were positive trends for hepatic carcinomas in females and thyroid follicular cell adenomas in males. The high level also caused increased incidences of polyarteritis of the testes and arteries of males and liver necrosis and alveolar histiocytosis in females. It increased mortality in females and decreased food consumption in both sexes. There was a dose-related decrease in body weights of both sexes at the mid and high levels and a decrease in males only at the low level.

Based on organ weight effects and decreased body weight in males, the systemic LOEL is 500 ppm (25 mg/kg, LDT) and a NOEL was not established; one must be established in the rat in a new chronic study. The study is classified as Minimum Data, but it is recommended for audit.

13. MON 097: 24 month oncogenicity study in the mouse. Acc. #071966-68, Pharmacopathics Research Laboratories, Inc., Report # PR-80-007, 5-4-83.

Doses were 500, 1500 and 5000 ppm (75, 225 and 750 mg/kg/day). MON 097 was a carcinogen in mice. There were increased incidences of: liver carcinomas in high level males, total lung tumors in females of all levels, carcinomas of the lungs in low and high level females, uterine histiocytic sarcomas in females of all levels and total benign ovarian tumors in mid level females. There were positive linear trends for: liver carcinomas in both sexes, and pulmonary carcinomas, total lung tumors, ovarian benign tumors and kidney adenomas in females. There was an increase in interstitial nephritis in both sexes of the high level. Treatment decreased body weight and increased mortality of both sexes at the high level. Absolute and relative liver weights were increased in all levels of males and in high level females. Absolute and relative kidney weights were also increased in all levels of males.

Based on increased liver and kidney weights of males, the LOEL for systemic effects is 500 ppm(LDT) and a NOEL was not established. The study is classified as Minimum Data. It is recommended for audit.

Data Gaps

The following studies are presently data gaps:

1. Chronic rat
2. Chronic dog
3. Reproduction
4. Teratology in the rabbit
5. Mutagenicity- structural chromosome aberration
   - other genotoxicity (DNA repair)

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Previously Reviewed Data

Data submitted previously were reviewed by William Dykstra in a memo of 3-24-81 for PP# 1G2454. These data are summarized as follows:

1. Acute oral LD_{50}, Rat, Mon 097, 2953 mg/kg (both sexes), Category II, Minimum Data. Environmental Health Laboratory Report #80-49, 10-15-80.

2. Acute dermal LD_{50}, Rabbit, Mon 097, 3667 mg/kg (both sexes), Category III, Minimum Data. Environmental Health Laboratory Report #80-48, 10-15-80.

3. Primary dermal irritation, Mon 097, P.I.=0.6/8.0, Category IV, Minimum Data. Environmental Health Laboratory Report #80-50, 10-15-80.

4. Primary eye irritation, Mon 097, scores for unwashed= 18.8/110, for washed=1.2/110, Category II, Minimum Data. Environmental Health Laboratory Report #80-51, 10-15-80.

5. 91-Day feeding, Rat, CP-55097, NOEL = 800 ppm
   LOEL = 2000 ppm based on body weight loss and food consumption decrease, Minimum Data. Pharmacopathics Report #7914, 10-10-80.

6. 119-Day feeding, Dog, CP-55097, NOEL <25 mg/kg/day (LDT), dose-related elevated SGPT - Minimum Data. Pharmacopathics Report #7920, 10-10-80.

7. Teratology, Rat, CP-55097, Negative at 400mg/kg/day Fetotoxic NOEL = 200 mg/kg/day, Maternal NOEL = 200 mg/kg/day, Minimum Data. IRDC Report #401-066, 10-15-80.

8. Mutagenicity, Ames Salmonella Assay, CP-55097, Negative for strains TA-98, 100, 1535 and 1537, with and without mouse and rat microsomal preparations, Minimum Data. Monsanto Report # MRC-DA-838, 12-5-78.