ATTACHMENT J

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

FEB 3 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 524-EUP-56: Renewal of temporary tolerances and an Experimental Use Permit (EUP) for Harness® Herbicide (Acetochlor). Caswell #3B. Accession # - . Tox. Proj. #7-0206

TO: Robert Taylor (12)
Registration Division (TS-767C)

FROM: Winnie Teeters. Ph.D. Winnie Teeters 1-29-87
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THRU: Quang Bui, Ph.D. Quang Bui 2-3-87
Acting Section Head, Section V
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2/3/87

and

Theodore M. Farber, Ph.D.
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CHEMICAL: Acetochlor (2-chloro-N-[ethoxymethyl]-N-[2-ethyl-6-methyl phenyl] acetamide), MON 097, CP 55097. Harness® is an EC formulation containing 86.4 - 86.5% A.I.

ACTION REQUESTED: Review requests for renewal of temporary tolerances and an EUP for Harness® Herbicide. No additional data were submitted.

The EUP Program: An amended experimental program is being proposed, with only 2200 pounds being requested for use under the renewed program. This amount will be applied over a two-year program in 13 states to 1100 acres.

Requested Renewal of the following Temporary Tolerances:

Corn (grain)	0.1 ppm
Corn (forage and fodder)	0.5 ppm
Eggs	0.02 ppm
Milk	0.02 ppm
Beef tissue	0.02 ppm
Hog tissue	0.02 ppm
Chicken tissue	0.02 ppm

History: On March 20, 1980, the Agency approved a crop destruct EUP for acetochlor (now Harness® Herbicide) for use on corn, soybeans, peanuts and

grain sorghum. On Feb. 10, 1982, temporary tolerances for acetochlor on corn(all grain 0.1 ppm) and soybean grain (0.4 ppm) were granted. The EUP and temporary tolerances were allowed to lapse on March 20, 1985. A petition (3F2966 & 524-GUI) for permanent tolerances and data submitted with an EUP and Petition (524-EUP-65/2G2797 and 3G2791) for temporary tolerances were reviewed earlier (memo of Teeters to Taylor, Aug., 5, 1985) and it was recommended that the permanent tolerances were not supported by the available data; furthermore, acetochlor was found to be an oncogen in both the rat and mouse.

Recommendations: Studies for acetochlor in our files are adequate to support the requested renewal of the EUP and temporary tolerances, except for an acute inhalation study with the formulation, a subchronic, or longer term, feeding study in a non-rodent (the 119-day dog feeding study [Pharmocopathics Res. Labs. #7920, 10-10-80] did not establish a NOEL and the 1-year dog feeding study [Pharmocopathics Res. Labs. #PR-80-008, 10-14-81] was classified as Supplementary Data) and a mutagenicity study for chromosome aberration (Hazleton Labs. America #83-006, 5-14-83 was Unacceptable).

However, the following information should be considered when decisions are made regarding these requests:

Acetochlor had been found in chronic studies to be oncongenic in both mice and rats, and chronic systemic toxicity has not been adequately defined. A new study is necessary to establish a NOEL for chronic toxicity. See memo of Teeters to Taylor, 8-5-85.

A risk assessment (memo of Lacayo to Teeters, 5-4-86) based on the findings in these oncogenic studies estimates a worst case potency of Q_1^* (mg/kg/day) to be 10^{-2} for humans; for mice and rats the corresponding values are 10^{-3} and 10^{-4}, respectively.

In an informal note from Lacayo using tolerances the same as the ones requested in this action, except that 0.02 ppm each in goat, horse and sheep tissues were included, the dietary risk to humans was estimated to be 3.3×10^{-6} (see memo of Teeters to Taylor, 5-15-86), indicating there appears to be only a minor risk from dietary exposure at requested tolerance levels (including the extra tissues). But the risks to applicators have not been assessed.

Furthermore, acetochlor is one of a series of closely related analogs having oncogenic activities (memo of Teeters to Engler, 8-23-85). In a draft "Peer review of Acetochlor" (Jan. 21, 1987) it was concluded that there is evidence that acetochlor meets the criteria for Group B2- Probable Human Carcinogen.

Summary of data in our files to support these requests:

Memo of Teeters to Taylor, 8-5-85. (Petition 3F2966 & 524-GUI and 524-EUP-56/2G2797 and 3G2791.) Studies with acetochlor (MON 097, CP 55097).

1. Subchronic 21-day dermal, IRDC Study #IR 80-356, 12-11-81.

   LOEL for systemic effects (mortality and decreased weight gain): 1200 mg/kg (HDT).
   NOEL for systemic effects: 400 mg/kg

LOEL for dermal irritaton· 100 mg/kg (LDT)
NOEl for dermal irritation· not established

Core minimum.

2. Dermal sensitization, (MON 097 technical). Bio/Dynamics, Inc. Study #BD-82-204, 4-13-83.
   Positive dermal sensitizer
   Core minimum

3. Dermal sensitization, (MON 097, 8 lbs/gal EC formulation, Harness®). Bio/Dynamics, Inc. Study #BD-82-205, 4-13-83.
   Positive dermal sensitizer
   Core minimum

4. In Vivo bone marrow chromosome study, Hazleton Labs. America, Inc. Study #HL83-006, 5-24-83.
   No evidence of chromosome abnormalities induced, but the study is Unacceptable.

5. Rat hepatocyte primary culture/DNA repair test, Pharmacon Res. Internat'l, Inc. Study #PK-52-151, 2-17-83.
   No evidence of inducement of unscheduled DNA synthesis.
   Study is Acceptable.

6. Mouse lymphoma assay, SRI Internat'l Study #SR-81-150, Aug.-82.
   Positive mutagen only in the presence of metabolic activation.
   Study is Acceptable.

7. CHO/HGPRT gene mutation assay, Monsanto Environmental Health Lab. Study #ML-82-281, 6-9-83.
   Weakly positive at near-toxic doses, but the vehicle used (alcohol) did not appear to be inert in the assay.
   Study is Acceptable.

8. Rabbit teratology studies, IRDC, Pilot Studies #IR-79-292, Primary Study #IR-79-293, 11-24-81.
   Two pilot studies are Invalid Data: the third pilot study is Supplementary Data as a range-finding study.

   The primary study is also Supplementary Data and a new study is requested; insufficient numbers of litters were available to fully assess the teratogenic potential.

9. Two generation reproduction study in rats, IRDC Study #IR-80-053, 12-16-82.
   Reproductive NOEL: 500 ppm
   Reproductive LOEL: 1500 ppm (based on decreased body weight gain of F_{2b} pups)
   Systemic NOEL: <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, increases for thyroid weights in F_{1b} and F_{2b} pups.

   Minimum Data

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10. Metabolism study with rats, Hazleton Raltech, Inc. Study #MSL-2824, June-83.

Little (0.5%) eliminated via lungs: >70% excreted within 48 hrs., preferentially in urine. Elimination is biphasic with a fast half-life of < 10 hrs. and a slow half-life of 128-286 hrs. Early metabolites are mainly mercapturates: later ones were sulfoxides, sulfones, and sulfates; over 20 metabolites were identified. Less than 1% of parent compound is excreted unchanged in feces. There was retention of 2-2.5% of dose in RBC due to covalent binding to hemoglobin.

Core Guideline

11. One year feeding study in dogs, Pharmacopathics Res. Lab. Study #PR-80-008, 10-14-81.
Dogs at 40 mg/kg (HDT) showed testicular atrophy accompanyied 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 this level for anemia and hepatotoxicity but a NOEL and LOEL cannot conclusively be determined for these effects at lower levels because of control data variability and the wide range of normal values for these parameters established at the testing facility.

Supplementary Data

12. Chronic toxicity and oncogenicity study in rats, Pharmacopathics Res. Labs. Study #PR-80-006, 5-20-83.
Oncogenic NOEL: 1500 ppm
Oncogenic LOEL: 5000 ppm -increased incidence of liver carcinomas and thyroid follicular cell adenomas in males.
There were positive trends for hepatic carcinomas in females and thyroid follicular cell adenomas in males.
Systemic LOEL: 500 ppm (LDT) based on organ weight effects and decreased body weight in males.
Systemic NOEL was not established. One must be established in a new study.
The high level (5000 ppm) also increased incidences of polyarteritis of the testes and arteries of males and liver necrosis and alveolar histiocytosis in females. Mortality was increased in females and food consumption was decreased in both sexes.

Minimum Data

13. Oncogenicity study in mice, Pharmacopathics Res. Labs. Study #PR-80-007, 5-4-83.
Oncogenic NOEL: < 500 ppm (LDT). There were increased incidences of: liver carcinomas in high level males, total tumors in females of all levels, carcinomas of the lumgs 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

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benign tumors and kidney adenomas in females.
Non-neoplastic lesions included an increase in interstitial nephritis in both sexes of the high level(5000 ppm).
Systemic LOEL: 500 ppm(LDT) based on increased liver and kidney weights in males.

Minimum Data

Memo of Dykstra to Taylor, dated 3-21-84 for PP# 1G 2454. 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.

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