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

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MAY - 7 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: **ACETOCHLOR:** Review of database in support of registration request for use of ACETOCHLOR EC on field corn, silage corn and popcorn and of an acute oral toxicity study with the PJ2 metabolite of acetochlor. EPA DP Barcode: D187730, D187732, D187734; EPA Submission No. S434797-9; MRID # 425499-01; EPA Pesticide Chemical Code 121601, Caswell No. 003B.

TO: Robert Taylor/Vickie Walters, PM 25
Herbicide-Fungicide Branch
Registration Division (H7505C)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/4/93
Senior Pharmacologist
Review Section I, TB II/HED (H7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. J M Ioannou 5/4/93
Section Head, Review Section I
and
Marcia van Gemert, Ph.D.
Chief, Toxicology Branch II
Health Effects Division (H7509C) M van Gemert 5/6/93

Registrant: Acetochlor Registration Partnership - ZENECA

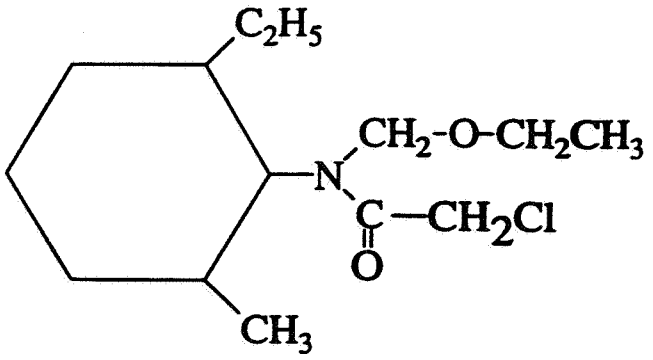
Action Requested: Evaluate database in support of registration request for use of ACETOCHLOR EC on field corn, silage corn and popcorn; review an acute oral toxicity study with the PJ2 metabolite of acetochlor.

Recommendations: TB II has determined that the toxicology database supports the request for use of ACETOCHLOR EC on field corn, silage corn and popcorn. No new tolerances have been requested with this action. The following are the conclusions of the review of *PJ2 Acetochlor Metabolite: Acute Oral Toxicity to the Rat* (ICI Central Testing Laboratory, Study No. AR5345, 2/6/92, MRID# 425499-01):

Under the conditions of this study, the acute oral LD50 of the PJ2 metabolite of acetochlor was > 2000 mg/kg in male and female rats. The Toxicity Category is III and the study is classified as Core-Minimum Data and satisfies the Guideline requirement (§81-1) for an acute oral toxicity study in rats.

NOTE: This chemical is classified as a Group B2 carcinogen (see page 4).

DISCUSSION:



ACETOCHLOR

I. Background

A. General Information

i. From the registrant's request:

The Acetochlor Registration Partnership was formed by ICI Americas and Monsanto Company for the purpose of pursuing joint registration of acetochlor and for obtaining tolerances for acetochlor on certain agricultural commodities. All data owned by ICI Americas and Monsanto Company and previously submitted to the Environmental Protection Agency that is required to support these registration actions has now been transferred to the ARP.

Pesticide Petitions previously submitted by ICI Americas and Monsanto Company requesting establishment of tolerances for acetochlor on corn commodities have also been transferred to the ARP. Therefore, no new tolerance ~~items~~ are being submitted with this application.

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II. Toxicology Profile for Acetochlor (CFR 180.xxx)

Technical: Acetochlor
Use Pattern: food, terrestrial nonfood
Action Type: database evaluation for registration

This compound is a registered active ingredient. The following data are required for technical acetochlor.

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes
§82-1(a)90 day feeding study - rat	Yes	Yes
§82-1(b)90 day feeding study - nonrodent	Yes	No[1]
§82-2 21 day dermal - rabbit	Yes	Yes
§82-3 90 day dermal	No	
§82-4 Subchronic inhalation	No	
§82-4 Subchronic neurotoxicity	No	
§83-1(a)2-year feeding - rodent	Yes	Yes
§83-1(b)1-year feeding - nonrodent	Yes	Yes
§83-2(a)Carcinogenicity - rat	Yes	Yes
§83-2(b)Carcinogenicity - mouse	Yes	Yes
§83-3(a)Teratology - rat	Yes	Yes
§83-3(b)Teratology - rabbit	Yes	Yes
§83-4 Multigeneration reproduction-rat	Yes	Yes
§83-5 Carcinogenicity/Chronic Toxicity - rat	Yes	Yes
§84-2(a)Mutagenicity - Gene Mutation	Yes	Yes
§84-2(b)Muta - Struct. Chromosome Aberr.	Yes	Yes
§84-4 Muta - Other Genotoxic Effects	Yes	Yes
§85-1 General metabolism - rat	Yes	Yes
§85-2 Domestic Animal Safety	No	
§85-2 Dermal Penetration	Yes	Yes

[1] = This requirement is satisfied by a chronic feeding study in dogs.

Formulation: Acetochlor EC

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

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II. Data Gaps

There are no data gaps at this time in the technical or in the formulation, Acetochlor EC database.

III. Actions Being Taken to Obtain Additional Information or Clarification

None at this time.

IV. Reference Dose

The RfD is 0.02 mg/kg/day based on the chronic feeding study in the dog with a NOEL of 2.0 mg/kg/day and an uncertainty factor (UF) of 100.

V. Pending Regulatory Actions

None at this time.

VI. Additional Toxicological Information

This chemical has been classified as a Group B2 Carcinogen (Probable Human Carcinogen) by the HED Peer Review Committee (PRC), CRAVE and the Science Advisory Panel (SAP). This is based on the evidence that administration of acetochlor causes increased incidence of benign and malignant tumors at multiple sites in Sprague-Dawley rats (papillary adenomas of the nose/turbinates in both sexes at doses below the MTD; hepatocellular carcinomas in both sexes and thyroid follicular cell adenomas in males at levels exceeding the MTD). Also, increased incidence of benign and malignant tumors at multiple sites in Swiss albino CD-1 mice (hepatocellular carcinoma in both sexes; lung carcinomas in females; uterine histiocytic sarcoma and benign ovarian tumors in females; kidney adenomas in females). There is positive mutagenicity data and structural analogues to Acetochlor that have positive carcinogenicity data.

The unit risk, Q_1^* of acetochlor is $10^{-2}(mg/kg/day)^{-1}$ in human equivalents. This estimate of the Q_1^* is based upon papillary adenomas (of the nose/turbinates) in both male and female Sprague-Dawley rats fed 0, 40, 200, or 1000 ppm in the diet.

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Reviewed by: Timothy F. McMahon, Ph.D.
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 5/3/93
Section I, Toxicology Branch II (H7509C)

Data Evaluation Report

Study type: Acute oral-rats (§81-1) Tox. Chem. No.: 003B
P.C. Code: 121601

MRID number: 425499-01 Submissions: S434797; S434798; S434799

Test material: 2-carboxy-3'-hydroxy-6'-ethyl-acet-o-toluidine

Synonyms: PJ2 Metabolite of Acetochlor

Study number: AR5345

Testing Facility: ICI Central Toxicology Laboratory
Cheshire, UK

Sponsor: Acetochlor Registration Partnership

Title of report: PJ2 Acetochlor Metabolite: Acute Oral Toxicity To The Rat

Author(s): L. Duerden

Study completed: February 6, 1992

Conclusions:
Under the conditions of this study, the acute oral LD_{50} of PJ2 metabolite of Acetochlor was > 2000 mg/kg in male and female rats.

Toxicity Category III

Core Classification: minimum

This study fulfills the guideline requirements (§81-1) for an acute oral toxicity study in rats.

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I. MATERIALS

A. Test Material: PJ2 Acetochlor metabolite, 96% a.i.; description: brown solid; reference # WRC-13021-35.

B. Test Animals: Male and female SPF Wistar-derived albino rats (Crl:(WI)BR strain). Source: Charles River Limited, Margate, Kent, England. Age: young adult; Weight (on day 1 of the study): males: 224-236g; females, 209-222g.

II. METHODS

Five male and 5 female rats per dose group were selected for use in this study. Rats were given a commercially available rodent diet (Porton Combined Diet, SDS Ltd) and tap water *ad libitum*. Rats were housed in groups of up to 5 rats/cage in metal cages with wire mesh floors. Temperature and humidity were in the range of 21±2 °C and 55 ± 15% , respectively. A 12 hour light/dark cycle was used. An acclimation period of six days was allowed prior to dosing.

Prior to the main study, a preliminary study was conducted in which an oral dose of 2000 mg/kg was tested. Based on the results of this preliminary study, 2000 mg/kg was selected as the dose for the main study. Five male and 5 female rats were selected for dosing. The rats were given a single oral dose of the test chemical in corn oil at a dose volume of 10 ml/kg. Each animal was observed for signs of clinical toxicity once within 2 hours of dosing, and again between 4 and 7 hours post-dosing. After day 7, observations were made once daily up to study termination (day 15). Body weights were recorded on study days -1, 1, 3, 6, 8, and 15. At study termination, animals were anesthetized with halothane and were then killed by exsanguination. Post mortem examination was then performed on the animals.

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III. RESULTS

Mortality

There were no animal deaths recorded during the period of this study.

Clinical Toxicity

Some slight signs of toxicity were seen in one female rat on the day of dosing. These signs included salivation and urinary incontinence. However, these were not present past day 1 of the study.

Median Lethal Dose Estimation

The median lethal dose could not be estimated in this study, as only one dose was used. Based on the use of a 2000 mg/kg dose, a Toxicity Category of III can be assigned to this study. This category is equal to that found from administration of technical acetochlor (MRID # 415651-04).

IV. CONCLUSIONS

Under the conditions of this study, the acute oral LD_{50} of PJ2 Metabolite of Acetochlor was > 2000 mg/kg in male and female rats.

Toxicity Category III

V. CORE CLASSIFICATION: minimum

This study fulfills the requirements (§81-1) for an acute oral toxicity study in rats.