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

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APR 28 1993

OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ALACHLOR: Review of 6(a)(2) data - acute oral toxicity with MON5775 (§81-1).
EPA Barcode D139873; EPA Submission No. S438260; EPA MRID No: 427015-00 and -01; EPA Pesticide Chemical Code 090501, Toxicology Chemical No. 011.

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

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 4/23/93
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (H7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y M Ioannou 4/26/93
Section Head, Review Section I
and
Marcia van Gemert, Ph.D. Marcia Gemert 4/27/93
Chief, Toxicology Branch II
Health Effects Division (H7509C)

Registrant: Monsanto Company, 800 N. Lindbergh Blvd. St. Louis, MO 63167

Action Requested: Review 6(a)(2) data - acute oral toxicity with MON5775 (§81-1).

Recommendations: TB II reviewed the "Acute Oral Toxicity Study in Rats with MON 5775" (Springborn Laboratories, Inc. (SLS) for Monsanto Company, SLS Study No. 3044.303; Monsanto Study No. SB-92-131, 1/27/93, MRID No. 427015-01); the following are the conclusions of the review:

Based on the data provided the **acute oral LD_{50} of MON 5775 is greater than 6000 mg/kg.** The study is classified as **Core Guideline Data** with a **Toxicity Category of IV. This study satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.** The acute oral LD50 for alachlor technical is 0.93 g/kg with a toxicity category of III; therefore MON-5775 is less toxic than the parent chemical.

This study is not 6(a)(2) data; the identification of the alachlor polar soil metabolite, MON-5775, was reported as 6(a)(2).

I. Toxicology Profile for Alachlor (40 CFR 180.249)

Technical: Alachlor
Use Pattern: food and non-food
Action Type: data waiver request

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

THIS INFORMATION DOES NOT NECESSARILY REFLECT THE DATA REQUIREMENTS FOR REREGISTRATION.

	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	NO
§82-1(a)90 day feeding study - rat	Yes	NO[1]
§82-1(a)90 day feeding study - rat/metabolite	Yes	Yes
§82-1(b)90 day feeding study - nonrodent	Yes	NO[2]
§82-1(b)90 day feeding study - nonrodent/met.	Yes	NO[2]
§82-2 21 day dermal - rabbit	Yes	Yes
§83-1(a)2-year feeding - rodent	Yes	Yes
§83-1(a)2-year feeding - rodent/stabilized	Yes	Yes
§83-1(b)2 year feeding - nonrodent	Yes	Yes
§83-2(a)Carcinogenicity - rat	Yes	Yes
§83-2(a)Carcinogenicity - rat/stabilized	Yes	Yes
§83-2(b)Carcinogenicity - mouse	Yes	Yes
§83-2(b)Carcinogenicity - mouse/stabilized	Yes	Yes
§83-3(a)Teratology - rat	Yes	Yes
§83-3(b)Teratology - rabbit	Yes	Yes
§83-4 Multigeneration reproduction-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 Dermal penetration (absorption)	Yes	Yes[3]

[1] = satisfied by 2-year chronic feeding study in the rat
[2] = satisfied by 6 month subchronic feeding study in the dog
[3] = based on human and monkey data submitted to the agency

II. Data Gaps

The database for technical Alachlor is not complete:

§81-6 Dermal sensitization - guinea pig

There are acute toxicity study data gaps with the registered formulations. These must be resolved before further additional permanent food use tolerances are granted.

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III. Actions Being Taken to Obtain Additional Information or Clarification

None needed at this time.

IV. Reference Dose

The RfD is 0.01 mg/kg/day based on the chronic feeding study in the dog with a NOEL of 1 mg/kg/day and an uncertainty factor (UF) of 100.

V. Pending Regulatory Actions

None at this time.

VI: Toxicological Issues Pertinent to this Request

This chemical was a registration standard in 1983.

A. New toxicology Data on Alachlor

Discussed above on cover page (DER attached).

B. Carcinogenicity

This chemical has been classified as a Group B2 Carcinogen (Probable Human Carcinogen) by the HED Peer Review Committee (PRC) and the Science Advisory Panel (SAP). This is based on the evidence that administration of alachlor was associated with an increased incidence of benign and malignant tumors in male and female rats in multiple experiments to an unusual degree and at an unusual site (nasal turbinates) and of benign lung tumors in female CD-1 mice. The risk assessment determined a Q1* of 8.0 x 10-2 (mg/kg/day)-1 (in human equivalents) using the nasal turbinate tumor.

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Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 4/23/93
Senior Pharmacologist, Review Section I, TB II/HED H7509C

Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. 4/26/93
Section Head, Review Section I, TB II/HED H7509C

DATA EVALUATION RECORD

Study Type: Acute Oral Toxicity - Rat; Guideline: §81-1

EPA Identification No.s:
EPA MRID No. 427015-01
EPA Pesticide Chemical Code 090501 (Alachlor)
Toxicology Chemical Code 011 (Alachlor)
DP Barcode: D189873

Test Material: MON 5775 (a polar soil metabolite of alachlor)

Synonyms: ethane sulfonate (2-[(2,6-diethylphenyl)-(methoxymethyl)amino}2-oxo-ethane sulfanate)

Sponsor: Monsanto Company, 800 N. Lindbergh Blvd., St. Louis, MO 63167

Testing Facility: Springborn Laboratories, Inc. (SLS), Life Sciences Division, 553 North Broadway, Spencerville, OH 45887

Title of Report: Acute Oral Toxicity Study in Rats with MON 5775

Study Number(s): SLS Study No. 3044.303;
Monsanto Study No. SB-92-131

Author(s): Kimberly L. Bonnette, M.S.

Report Issued: January 27, 1993

Conclusions:

Based on the data provided the **acute oral LD_{50} of MON 5775 is greater than 6000 mg/kg.**

Core Classification: Core Guideline Data

Toxicity Category: IV

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

A. Materials and Methods

A copy of the "materials and methods" section from the investigators report is appended.

Test Compound: Purity: 90.7 % + 6.6 % H_2O
Density: not provided
Description: pinkish white powder
Lot No.: NPD-9203-3974-T
Receipt date: April 28, 1992
Other provided information: supplier - Monsanto
Contaminants: not provided

Vehicle(s): distilled water as needed

Test Animal(s): Species: Albino Rat
Strain: Fischer 344-CDF®
Source: Charles River Laboratories, Inc.
Kingston, NY
Age: not provided
Body Weight: 138 g for males, 123 g for females

Animals were kept under standard animal care conditions and received a "commercial rodent feed and purified water" *ad libitum*. A range finding study was conducted with the following doses:

Treatment Level (mg/kg)	Dose Volume (ml/kg)	Concentration (% w/v)	No. of Animals Males	Females
5000	10	50	1	1
3000	10	30	1	1
1000	10	10	1	1
500	10	5	1	1
100	10	1	1	1

Rats were fasted overnight before dosing. Test material was administered orally by gavage using a ball tipped stainless steel gavage needle. Animals were weighed individually prior to fasting, then on days 1, 8 and 15. They were observed for mortality twice daily, also observed frequently on day of dosing for clinical signs and then once daily for the duration of the study. All animals were subjected to a gross necropsy at time of death or at scheduled sacrifice. The following are the dose levels tested (limit tests):

Treatment Level (mg/kg)	Dose Volume (ml/kg)	Concentration (% w/v)	No. of Animals Males	Females
5000	10	50	5	5
6000	10	60	5	5

B. Results:

1. Mortality

According to the investigator all mortality occurred by study day 3; one male and one female of the 5000 mg/kg group died on day 3, and two females of the 6000 mg/kg group died on day 2 .

2. Clinical Signs

Clinical signs of toxicity included decreased activity, wobbly gait, rigid upon handling, respiratory abnormality, apparent hypothermia, salivation, decreased defecation, diarrhea, soft stools, mucoid material in cage/tray, piloerection, rough coat, unkempt appearance, fecal/urine stains, emaciation, dehydration, dark material around facial area, clear nasal discharge, and lacrimation along with noted hairloss in the urogenital and abdominal region.

3. Body Weights

DAY:	-1	1	8	15
		Males		
5000 mg/kg	139[a]	123	147	172
6000 mg/kg	137	118	150	169
		Females		
5000 mg/kg	123	110	131	143
6000 mg/kg	123	110	130	139

[a] = grams

No treatment related effect was noted. According to the investigator: *One surviving 5000 mg/kg male rat exhibited body weight loss during the day 1-8 study interval. All other surviving animals exhibited weight gain during the test period (days 1-15), although only a slight weight gain was noted in one male at the 6000 mg/kg dose level by study termination.*

4. Gross Necropsy

According to the investigators: *For animals surviving until necropsy on study day 15, one male at the 6000 mg/kg/dose level exhibited reduced adipose tissue. For animals found dead during the study, necropsy findings included colored mucoid/fluid contents and reddened mucosa of the digestive tract, red linear striations of the glandular mucosa of the stomach, congested meningeal vessels of the brain, dark red/tan mottled lungs and reddened thymus.*

C. Discussion and Conclusions

Based on the data provided the acute oral LD_{50} of MON 5775 is greater than 6000 mg/kg.

Core Classification: Core Guideline Data

Toxicity Category: IV

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

Alachlor

RIN 4444-96

Page_____ is not included in this copy.

Pages 8 through 10 are not included.

The material not included contains the following type of information:

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✓ FIFRA registration data.

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