JUN 4 1990

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

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007957

JUN 4 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Request for Renewal of Experimental Use Permit Number 524-EUP-56 with Temporary Tolerances (for Acetochlor as MON 8437 [Harness] Herbicide).
EPA ID No.: 1G2454 & 524-EUP-56, EPA Record Nos.: 258583 & 258599, MRID Nos.: 40998801 thru 40998805 & 40994401, HED Project No. 0-0563A, Caswell No. 3B.

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

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/24/90
Pharmacologist, Review Section I
Toxicology Branch-Herbicide, Fungicide, Antimicrobial Support/HED (H7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. J M Ioannou 5/24/9
Section Head, Review Section I
and
Marcia van Gemert, Ph.D. Marcia van Gemert 5/25/90
Chief, Toxicology Branch-Herbicide, Fungicide, Antimicrobial Support
Health Effects Division (H7509C)

Registrant: Monsanto Company
1101 17th Street, N.W.
Washington, D.C. 20036

Action Requested: Evaluate request for renewal of temporary tolerances for Acetochlor and renewing EUP Number 524-EUP-56 (for Acetochlor as MON 8437 [Harness] Herbicide).

Recommendations: The Toxicology Branch-Herbicide, Fungicide, Antimicrobial Support has no objection to the renewal of the Temporary Tolerance for Acetochlor and for the EUP for a different formuation of Acetochlor pending the outcome of the carcinogenic risk assessment and the assessment under the Dietary Risk Evaluation System (DRES). This action is deferred to the DRES group. There are no objections to the labeling.
NOTE: This chemical is classified as a Group B2 carcinogen (see page 4).
The Acetochlor Toxicology Database for the technical is complete and will support permanent tolerances (see discussion). One datagap exists for the new formulation (81-3 Acute Inhalation reviewed in this document, not required for EUP with Temporary Tolerance, but would be required for a permanent tolerance).

DISCUSSION:

I. Background

A. General Information

i. Revised Section F - Proposed Temporary Tolerances for Acetochlor (as MON-8437 (Harness) Herbicide)

The following is the proposal from the registrant:

It is proposed that the following temporary tolerances be established for the total combined residues of acetochlor [N-(ethoxymethyl)-2-methyl-6-ethyl-2-chloro-acetanilide] and from the sum of its EMA- (2-ethyl-6-methyl aniline) yielding metabolites and its HEMA- [2-(1-hydroxyethyl)-6-methyl aniline] yielding metabolites (when calculated as acetochlor) as follows:

Field Corn, grain	0.04 ppm
Field Corn, fodder and forage	0.50 ppm
Milk	0.02 ppm
Meat, meat byproducts, and fat of cattle, goats, hogs, horses, sheep	0.04 ppm

ii. Section G - Proposed Experimental Program for Acetochlor

The proposed program will involve the use of MON 8437 (Harness) Herbicide on corn (field, silage) to control annual grass and small-seeded broadleaf weeds and sedges listed on the label. It will be used in the states of Minnesota, South Dakota and Iowa during the spring planting season ranging from April to June at a rate of 1.3 to 3 lbs a.i. per acre with an average of 2 lbs per acre. This will be used with conventional, reduced tillage and no-till systems using a predominantly ground broadcast application during the early preplant, preplant incorporated and preemergence time points. The total number of plots will involve 100 of approximately 40 acres each. This will use 8000 pounds of the active ingredient over the one year period of the experimental plan.

The following data are required for an EUP:
81-1 Acute oral toxicity in rats with EP
81-2 Acute dermal toxicity in rat with EP
81-4 Primary eye irritation in rabbits with EP
81-5 Primary dermal irritation in rats EP

also since this is a food use pesticide with a temporary tolerance request included, the following data using the technical grade of the chemical are required:
82-1 90 day feeding study - rodent
82-1 90 day feeding study - nonrodent
or
83-1 2-year feeding - rodent
83-1 2 year feeding - nonrodent
the above 90 day or 2 year feeding studies must demonstrate a NOEL in both rodent and nonrodent species
83-3 Teratology - one species
84-2 Gene Mutation test in bacteria
84-2 In vitro mammalian cytogenetic test
84-2 Primary DNA damage/repair (UDS) or Sister-chromatid exchange study in mammalian cells

The database for Acetochlor, including the data submitted with this action fully support the EUP, with temporary tolerances, renewal request. Therefore, the Toxicology Branch - Herbicide, Fungicide, Antimicrobial Support has no objection to the renewal of the temporary tolerance requested under the revised Section F Petition and for the renewal of EUP Number 524-EUP-56.

B. Regulatory Considerations

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 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 oncogenicity data.

In respect of the above information the Toxicology Branch - Herbicide, Fungicide, Antimicrobial Support has no objection to the label and the statment **"Restricted Use Pesticide" due to oncogenicity.**

C. Previously Submitted Data on Acetochlor

This compound is a registered active ingredient. The following data were submitted prior to this application.

Guideline #	Study Type	Tox.Cat.	Core Classification
Acute Toxicity			
81-1	Acute oral toxicity in rats with technical material there are adequate studies with the MP and EP available	III	Minimum
81-2	Acute dermal toxicity in rabbits with technical material there are adequate studies with the MP and EP available	III	Minimum
81-3	Acute inhalation toxicity in rats with technical material also no studies are available with the MP or EP		DATA GAP [see new data]
81-4	Primary eye irritation in rabbits with technical material there are adequate studies with the MP and EP available	II	Minimum
81-5	Primary dermal irritation in rabbits with technical material there are adequate studies with the MP and EP available	IV	Minimum
81-6	Dermal sensitization - guinea pig with the technical material there are adequate studies with the MP and EP available		Minimum
Subchronic Testing			
82-1	90 day feeding study - rodent		Minimum
82-1	120 day feeding study - dog		Minimum
82-2	21 day dermal - rabbit		Minimum

Chronic Testing	
83-1 2-year feeding - rodent (2 studies)	Minimum
83-1 2 year feeding - dog	Minimum
83-2 Oncogenicity - rat (2 studies)	Minimum
83-2 Oncogenicity - mouse	Minimum
83-3 Teratology - rat	Minimum
83-3 Teratology - rabbits (2 studies)	Minimum
83-4 3 generation reproduction-rat	Minimum
Mutagenicity Testing	
84-2 Dominant Lethal Test in mice	Unacceptable
84-2 In vitro cytogenetic	Acceptable
84-2 Reverse mutation	Acceptable
84-2 DNA damage/repair rat hepatocytes	Acceptable
84-2 HGPRT-CHO	Acceptable
84-2 Salmonella	Acceptable
84-2 Micronucleus assay - mice	Acceptable
Special Testing	
85-1 General metabolism - rat	Acceptable

III: Summary of New Toxicity Data

A. New toxicology Data on Acetochlor

81-1	Acute oral toxicity in rats with new formulation	III	Minimum
81-2	Acute dermal toxicity in rabbits with new formulation	III	Minimum
81-3	Acute inhalation toxicity in rats with technical material		Minimum
81-3	Acute inhalation toxicity in rats with new formulation	II	Supplementary DATA GAP
81-4	Primary eye irritation in rabbits with new formulation	III	Minimum
81-5	Primary dermal irritation in rabbits with new formulation	III	Minimum

The DER's are attached.

Reviewed by : David S. Liem, Ph.D. DSLiem 4/17/90
Toxicology Branch II, Section II
Secondary Reviewer: Steve Dapson, Ph.D. Stephen C. Dapson 5/10/90
Toxicology Branch II, Section I
Tertiary Reviewer: K. Clark Swentzel K. Clark Swentzel 5/14/90
Toxicology Branch II, Section II

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral LD_{50} Study of Harness in Spraque-Dawley Rats

TOX. CHEM. NO.: 0563A MRID NO.: 409988-01 CASWELL #: 03B

TEST MATERIAL: Harness, FD-88-173, Batch/Lot/NBR No. XLI-198; dark purple liquid containing 82.28% acetochlor

SYNONYMS: none

STUDY NUMBER(S): Monsanto #FD-88-173, FDRL #88-2053.015

SPONSOR: Monsanto Company, St. Louis, MO 63167

TESTING FACILITY: Federal & Drug Research Laboratories (FDRL), Waverly, Box 107, Route 17C, NY 14892

TITLE OF REPORT: Acute Oral LD50 Study of Harness in Sprague-Dawley Rats

AUTHOR: E. L. Reagan

REPORT ISSUED: July 8, 1988

CONCLUSIONS: Acute oral LD50 = 1488 ± 666 mg/kg for both sexes combined; Acute oral LD50 = 2381 ± 1290 mg/kg in males and 1101 ± 668 mg/kg in females. This study satisfied the data requirement for Subdivision F Guideline No. 81-1. Toxicity Category III.

Classification: Core-minimum

Quality Assurance Statement: Signed and checked by Quality Assurance Unit

FIFRA GLP Compliance Statement: Signed and dated

Study Title: Acute Oral LD_{50} Study of Harness in Sprague-Dawley Rats

Test Material: Harness, FD-88-173, Batch/Lot/NBR No. XLI-198; 82.28% acetochlor. It was not noted whether this test material is a manufacturing-use or end-use product

Test Animals: Sprague-Dawley rats, 5 males and 5 females/group, weighing 205-360 g at study initiation, were acclimated at least 5 days prior to study initiation and fasted overnight prior to dosing. Age of test animals was not noted.

Feed and Water: Test animals were provided with Rat and Mouse Diet (NIH Open Formula 07) and fresh tap water ad libitum.

Environmental Parameters: Animals were maintained in a controlled environment: 12 hours light-dark cycle; room temperature and humidity ranges were 68-75°F and 40-70%, respectively.

PROCEDURES

Dose Administration: Test animals of 5 male and 5 female rats per group, weighing 205-360 g at study initiation, were fasted overnight prior to dosing. The test compound was administered by gavage to each rat at dose levels of 1000, 3000, and 5000 mg/kg body weight using a Nelaton catheter affixed to a syringe. An additional group of five females were dosed at 500 mg/kg body weight as described above.

Observations: The animals were observed three times on the day of dose administration and twice daily thereafter for pharmacotoxic signs and mortality. Individual body weights were determined prior to dose administration on study day 1, 8, and 15 (terminal sacrifice) or at death.

Postmortem Examination: All animals were subjected to a gross necropsy examination. Surviving animals were sacrificed on day 15 by exposure to CO_2 gas.

Method to determine LD_{50}: The investigator determined the acute oral LD_{50} (male, female and both sexes combined) with 95% confidence interval using the probit method of L.C. Miller and M.L. Tainter (Proc. Soc. Exp. Biol. Med. 57 (1944). The results are expressed as mg/kg test material.

RESULTS

Mortality: The cumulative mortality of test animals is tabulated in Table 1 and the total mortality is summarized as follows:

Dose level (mg/kg)	No. of Deaths Males	Females	Combined
500	Not applicable	0	Not applicable
1000	0	3	3
3000	3	5	8
5000	5	5	10

LD_{50} Determination: Based on the mortality data, the investigator determined that the acute oral LD_{50} of Harness in Sprague-Dawley rats (both sexes combined) was calculated to be 1488 mg/kg body weight with a 95% confidence interval of 822-2154 mg/kg. The LD_{50} in male rats was determined to be 2381 mg/kg with a 95% confidence interval of 1091-3671 mg/kg and in female rats was determined to be 1101 mg/kg with a 95% confidence interval of 433-1769 mg/kg.

Daily Observations: Pharmacotoxic signs noted by the investigator following dose adminstration included: ataxia, decreased activity, diarrhea, labored breathing, salivation and apparent urinary incontinence. Lacrimation, tremors and prostrate animals were also noted after dose administration. All surviving animals appeared normal on study days 3-15.

Gross Necropsy: Gross necropsy findings included: white or red fluid in the intestines, dark or pale areas on the liver, bright/dark red lungs, white fluid in the stomach and thin stomach walls with absent rugae. One male at terminal sacrifice had a dilated pelvis of the right kidney.

Conclusions: The investigator determined that the oral LD_{50} of Harness in Sprague-Dawley rats (both sexes combined) was calculated to be 1488 mg/kg body weight with a 95% confidence interval of 822-2154 mg/kg. The LD_{50} in male rats was determined to be 2381 mg/kg with a 95% confidence interval of 1091-3671 mg/kg and in female rats was determined to be 1101 mg/kg with a 95% confidence interval of 433-1769 mg/kg.

Classification: Core-minimum

ACETOCHLOR Tox R # 007957

Page_____ is not included in this copy.

Pages 10 through 11 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by : David S. Liem, Ph.D. David S. Liem 4/27/90
Toxicology Branch II, Section II
Secondary Reviewer: Stephen Dapson, Ph.D. Stephen C. Dapson 5/10/90
Toxicology Branch II, Section I
Tertiary Reviewer: K. Clark Swentzel K. Clark Swentzel 5/15/90
Toxicology Branch II, Section II

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation Toxicity Study

TOX. CHEM. NO.: 0-0563A CASWELL NO.: 03B MRID NO.: 409944-01

TEST MATERIAL: MON 097; EHL Substance ID No. T880042; Lot No. XLI-187; purity 92.5% acetochlor; a light amber to violet colored oily liquid

SYNONYMS: none

STUDY NUMBER(S): ML-88-107/EHL 88097

SPONSOR: Monsanto Company, St. Louis, MO

TESTING FACILITY: Environmental Health Laboratory, Monsanto Co., St. Louis, MO 63110

TITLE OF REPORT: Acute Inhalation Study of MON 097

AUTHOR(S): C.L. Bechtel

REPORT ISSUED: October 7, 1988

CONCLUSIONS: The LC50 value for MON 097 as administered in the study is considered to be greater than 3.0 mg/l in air. The LC50 was not attained in this study. Although the percent of particles less than 1.0 um was 9.7%, this is considered acceptable because the MMAD was relatively small. Therefore this study satisfies the data requirement for Subdivision F Guideline No. 81-3.

Classification: Core-minimum

Quality Assurance Statement: Signed and dated

FIFRA GLP Compliance Statement: Signed and dated

Study Title: Acute Inhalation Study of MON 097

Test Material: MON 097; EHL Substance ID No. T880042; Lot No. XLI-187; purity 92.5% acetochlor; a light amber to violet colored oily liquid.

Test Animals: One group of 5 male and 5 female Sprague-Dawley rats, about eight weeks old, males weighing approximately 282 g and females weighing approximately 204 g. It was not reported how long these animals were acclimated in the test facility and how they were selected.

Feed and Water: Purina Mills RODENT CHOW No. 5002 and sodium zeolite-conditioned St. Louis public water supply were provided ad libitum. Feed and water were witheld during exposure period.

Environmental Parameters: During non-exposure period, test animals were maintained under controlled environment; light/dark cycle 12 hrs; temperature 68-76°F; relative humidity range 35-60%.

PROCEDURES

Exposure: One group of 5 male and 5 female rats was exposed for 4 hours to an atmosphere of aerosolized MON 097 at a mean analytical concentration of 3.0 mg/l in air. A 300-liter New York University-style stainless steel chamber with a pyramidical top and bottom was used for this study. Exposure was followed by a 14-day recovery period and subsequent necropsy.

Chamber Parameters: Chamber airflow, temperature, and relative humidity were monitored continuously and recorded every 30 minutes. Oxygen level in the chamber was measured once.

Determination of Exposure Concentration: Atmospheric analytical sampling was conducted 4 times per exposure at approximately one-hour intervals. Gas chromatography with flame ionization detector was used for this analysis. The nominal concentration was calculated once for each exposure.

Particle Size Determination: Conducted once during the exposure using an Anderson Cascade Impactor. The mass of material collected on each stage was determined gravimetrically and was also used to determine mass median aerodynamic diameter (MMAD), geometric standard deviation, and percentage of particles less than 10 microns.

In-life Observations: Animals were observed hourly during exposure, immediately after exposure, and once daily during the 14-day post-exposure period. Animals were checked for mortality and moribundity twice daily.

Body Weights: Individual body weights were measured on exposure day (prior to exposure), and 2, 7 and 14 days following exposure.

Macroscopic Pathology: All animals were subjected to gross necropsy. No microscopic examination was performed.

RESULTS

Chamber Parameters: Mean Temperature: 20.9°C; Mean Relative Humidity: 66%; Mean Airflow: 76.6 l/min; O2 Level: 21%

Particle Size Data: The Mass Median Aerodynamic Diameter (MMAD) was 2.1 microns with geometric standard deviation of 1.8 microns. Percent particles of less than 10 microns was 99.6%, and for particles of less than 1.0 micron was 9.4%. The particle size distribution was not presented.

Exposure Concentration: The analytical concentration for the exposure was 3.0 ± 0.3 mg/l. The mean analytical and nominal exposure concentrations were 3.0 and 5.6 mg/l, respectively.

Symptoms and Mortality: No death was observed. During exposure salivation and perinasal wetness were observed. Immediately after exposure (day 0), only perioral wetness was noted. Thereafter all animals appeared normal.

Body Weights: All but one animal lost weight by post-exposure day 2. By post-exposure day 7 all animals were gaining weight and exceeded their pre-exposure body weights.

Macroscopic Examination: No gross necropsy findings were noted.

LC50 Determination: No deaths were achieved at the highest attainable mean analytical exposure concentration of 3.0 mg/l. Thus no LC50 could be calculated.

Conclusions: LC50 of tested material is greater than 3.0 mg/l. Despite the low percentage of particles (9.4%) of less than 1.0 micron in the test atmosphere, this is considered acceptable because of the low MMAD (2.1 um). This study satisfies the data requirement for Subdivision F Guideline No. 81-3. Tox. Category III.

Classification: Core-minimum

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Toxicology Branch II, Section I
Tertiary Reviewer: K. Clark Swentzel K. Clark Swentzel 5/15/90
Toxicology Branch II, Section II

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation Toxicity Study

TOX. CHEM. NO.: 0-0563A CASWELL NO.: 03B MRID NO.: 409944-01

TEST MATERIAL: MON 097; EHL Substance ID No. T880042; Lot No. XLI-187; purity 92.5% acetochlor; a light amber to violet colored oily liquid

SYNONYMS: none

STUDY NUMBER(S): ML-88-107/EHL 88097

SPONSOR: Monsanto Company, St. Louis, MO

TESTING FACILITY: Environmental Health Laboratory, Monsanto Co., St. Louis, MO 63110

TITLE OF REPORT: Acute Inhalation Study of MON 097

AUTHOR(S): C.L. Bechtel

REPORT ISSUED: October 7, 1988

CONCLUSIONS: The LC50 value for MON 097 as administered in the study is considered to be greater than 3.0 mg/l in air. The LC50 was not attained in this study. Although the percent of particles less than 1.0 um was 9.7%, this is considered acceptable because the MMAD was relatively small. Therefore this study satisfies the data requirement for Subdivision F Guideline No. 81-3.

Classification: Core-minimum

Quality Assurance Statement: Signed and dated

FIFRA GLP Compliance Statement: Signed and dated

Study Title: Acute Inhalation Study of MON 097

Test Material: MON 097; EHL Substance ID No. T880042; Lot No. XLI-187; purity 92.5% acetochlor; a light amber to violet colored oily liquid.

Test Animals: One group of 5 male and 5 female Sprague-Dawley rats, about eight weeks old, males weighing approximately 282 g and females weighing approximately 204 g. It was not reported how long these animals were acclimated in the test facility and how they were selected.

Feed and Water: Purina Mills RODENT CHOW No. 5002 and sodium zeolite-conditioned St. Louis public water supply were provided ad libitum. Feed and water were witheld during exposure period.

Environmental Parameters: During non-exposure period, test animals were maintained under controlled environment; light/dark cycle 12 hrs; temperature 68-76°F; relative humidity range 35-60%.

PROCEDURES

Exposure: One group of 5 male and 5 female rats was exposed for 4 hours to an atmosphere of aerosolized MON 097 at a mean analytical concentration of 3.0 mg/l in air. A 300-liter New York University-style stainless steel chamber with a pyramidical top and bottom was used for this study. Exposure was followed by a 14-day recovery period and subsequent necropsy.

Chamber Parameters: Chamber airflow, temperature, and relative humidity were monitored continuously and recorded every 30 minutes. Oxygen level in the chamber was measured once.

Determination of Exposure Concentration: Atmospheric analytical sampling was conducted 4 times per exposure at approximately one-hour intervals. Gas chromatography with flame ionization detector was used for this analysis. The nominal concentration was calculated once for each exposure.

Particle Size Determination: Conducted once during the exposure using an Anderson Cascade Impactor. The mass of material collected on each stage was determined gravimetrically and was also used to determine mass median aerodynamic diameter (MMAD), geometric standard deviation, and percentage of particles less than 10 microns.

In-life Observations: Animals were observed hourly during exposure, immediately after exposure, and once daily during the 14-day post-exposure period. Animals were checked for mortality and moribundity twice daily.

Body Weights: Individual body weights were measured on exposure day (prior to exposure), and 2, 7 and 14 days following exposure.

Macroscopic Pathology: All animals were subjected to gross necropsy. No microscopic examination was performed.

RESULTS

Chamber Parameters: Mean Temperature: 20.9°C; Mean Relative Humidity: 66%; Mean Airflow: 76.6 l/min; O2 Level: 21%

Particle Size Data: The Mass Median Aerodynamic Diameter (MMAD) was 2.1 microns with geometric standard deviation of 1.8 microns. Percent particles of less than 10 microns was 99.6%, and for particles of less than 1.0 micron was 9.4%. The particle size distribution was not presented.

Exposure Concentration: The analytical concentration for the exposure was 3.0 ± 0.3 mg/l. The mean analytical and nominal exposure concentrations were 3.0 and 5.6 mg/l, respectively.

Symptoms and Mortality: No death was observed. During exposure salivation and perinasal wetness were observed. Immediately after exposure (day 0), only perioral wetness was noted. Thereafter all animals appeared normal.

Body Weights: All but one animal lost weight by post-exposure day 2. By post-exposure day 7 all animals were gaining weight and exceeded their pre-exposure body weights.

Macroscopic Examination: No gross necropsy findings were noted.

LC50 Determination: No deaths were achieved at the highest attainable mean analytical exposure concentration of 3.0 mg/l. Thus no LC50 could be calculated.

Conclusions: LC50 of tested material is greater than 3.0 mg/l. Despite the low percentage of particles (9.4%) of less than 1.0 micron in the test atmosphere, this is considered acceptable because of the low MMAD (2.1 um). This study satisfies the data requirement for Subdivision F Guideline No. 81-3. Tox. Category III.

Classification: Core-minimum

007257

Reviewed by : David S. Liem, Ph.D. David Liem 4/26/90
Toxicology Branch II, Section II
Secondary Reviewer: Stephen Dapson, Ph.D. Stephen C. Dapson 5/10/90
Toxicology Branch II, Section I
Tertiary Reviewer: K. Clark Swentzel K. Clark Swentzel 5/11/90
Toxicology Branch II, Section II

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation Toxicity Study

TOX. CHEM. NO.: 0-0563A CASWELL NO.: 03B MRID NO.: 409988-05

TEST MATERIAL: Harness (Toxicology Test Sample), Monsanto Study No. BD-88-174, Lot # XLI-198; purple liquid formulation containing 82.28% acetochlor.

SYNONYMS: none

STUDY NUMBER(S): Monsanto Study No. BD-88-174; Biodynamics Inc. Study No. 88--8072

SPONSOR: Monsanto Agricultural Company, St. Louis, MO 63167

TESTING FACILITY: Bio/dynamics Inc., Mettlers Rd., East Millstone, NJ 08875

TITLE OF REPORT: An Acute Inhalation Toxicity Study of Harness in the Rat

AUTHOR(S): Gary M. Hoffman

REPORT ISSUED: October 31, 1988

CONCLUSIONS: This study as presented is not acceptable, because the investigator failed to keep a consistent chamber test material concentration, failed to generate respirable particles (since MMAD was >1 um, at least 25% of the particles must be 1 micron or less), and did not indicate why smaller respirable particle could not be generated in the chamber. Variation of test animal ages is considered too great. The mean body weight difference between group I and group III males at the start of the study exceeded 20%.

Classification: Core-supplementary

Quality Assurance Statement: Signed and dated

FIFRA GLP Compliance Statement: Signed and dated

Study Title: An Acute Inhalation Toxicity Study of Harness in the Rat

Test Material: Harness (Toxicology Test Sample), Monsanto Study No. BD-88-174, Lot # XLI-198; purple liquid formulation containing 82.28% acetochlor.

Test Animals: Sprague-Dawley rats (3 group of 5 animals/sex/group), age 7-11 weeks old, body weight of males 205-346 g and of females 184-236 g, were acclimated between 1-3 weeks prior to dosing. Mean body weight difference between males group 1 and 3 exceeded 20%.

HUSBANDRY OF TEST ANIMALS (during non-exposure periods)

Feed and Water: Purina Rodent Laboratory Chow Brand Animal Diet #5001 and local tap water were provided ad libitum. Food and water were witheld during exposure period.

Environmental Parameters: Maintained under controlled environment; a 12-hour light/dark cycle; temperature range of 67-76°F, and relative humidity 30-70%.

PROCEDURES

Selection of Test Animals: Test animals were arbitrarily selected from Bio/dynamics' in-house population based on acceptable pretest physical examinations and body weights.

Exposure: Three groups of five male and five female rats were exposed to an atmosphere containing the test material for 4 hours. The mean exposure concentrations were 0.94, 3.2 and 5.3 mg/l. Each group was dosed on subsequent week. All survivors were held for a 14-day post-exposure observation period and survivors were sacrificed.

Chamber Parameters: Exposures were conducted in plexiglass exposure chambers with a total volume of 100 liters and were operated dynamically at a calibrated airflow rate of 20 liters per minute. This flow rate will provide one complete air change every 5 minutes and a 99% equilibrium time of 23 minutes. The chamber environmental conditions were checked 8 times during the exposure period. Readings were as follows: temperature 68-78°F and relative humidity 30-75%. The oxygen level in the chamber was not measured.

Determination of Exposure Concentration: The analytical exposure level was determined gravimetrically using Whatman glass microfibre filter paper (Type GF/F, 3.7 cm) mounted in a Millipore filter holder. Samples were withdrawn once per hour from normal sampling portal and once from the distribution sampling portal. The wet and dry gravimetric concentrations in mg/l were calculated by dividing the weight differences in milligrams by the volume of air sampled in liters.

Particle Size Determination: Samples for particle size distribution assessment were drawn once per hour using a Delron CI-6 cascade impactor.

LC_{50} Determination: A calculation of median lethal concentration and 95% confidence limits was performed according to the method of Litchfield and Wilcoxon.

Observations during Exposure: All animals were observed individually immediately prior to exposure and as a group at about 15 minutes interval during the first hour of exposure and hourly for the remainder of the exposure period. All survivors were observed individually upon removal from the chamber and hourly for two hours post-exposure.

Post-exposure Observations Period: Test animals were observed daily from day 2 through day 15 (terminal sacrifice). Body weights were taken on days 1 (immediately prior to exposure), 2, 3, 5, 8, and 15 (just prior to sacrifice).

Macroscopic Pathology: Postmortem gross examinations were performed on all test animals; this included examination of the nasal passages, trachea, all orifices, the cranial cavity, the brain and spinal cord, the thoracic, abdominal and pelvic cavities, and their viscera and cervical tissues and organs.

RESULTS

Chamber Parameters: Chamber temperatures were generally within or slightly above the protocol-specified range of 60-75°F. Chamber relative humidities were around 50% during Group III exposure and were above 70% during Groups I and II exposures. Oxygen level in the exposure chamber was not reported.

Chamber Monitoring and Mortality: The analytical exposure concentrations were determined gravimetrically and calculated on a formulation basis. Total formulation, nominal, and gravimetric wet/dry exposure concentrations (mg/l), and mortality of test animals were as follows:

Group	Exposure Concentration (mg/l)				Mortality (#Death/#Exposed)		
	Gravimetric		Total Formulation	Nominal	Male	Female	Total
	Wet	Dry					
I	5.1	5.0	5.3	61	1/5	3/5	4/10
II	3.0	3.1	3.2	29	3/5	0/5	3/10
III	0.91	0.87	0.94	6.1	0/5	0/5	0/10

The percentage of solids was determined to be 95%, therefore slight differences were noted between the dry and wet filter weight values. As seen from the table the difference between the nominal and the analytical exposure concentrations was large. The investigator considered that this was due to impaction or sedimentation of the aerosol on the surfaces within the exposure chamber.

Particle Size Determination: The results of particle size determination are presented on the attached Tables 2-1/2/3. As seen from these tables, although between 94% to 98% of particles were less than 10 um, but far smaller percentages of particles were less than 1 um; the percentages were 8%, 4% and 11% for groups I, II, and III, respectively. The particle size distribution of the test material was not reported. The MMAD values were larger than 1 um, namely 3.0, 3.4, and 2.4 um, respectively. Based on these facts, contrary to what the report said, the test atmosphere was not highly respirable to the test animals. It is an established fact that only particle size of 1 um or less can reach the lung alveoli. Furthermore, the group I 165 to 169 minutes gravimetric samples indicate that the investigator had difficulties in maintaining a constant chamber concentration (Table 2-1).

Mortality and LC_{50}: Death occurred within the first week after exposures in group I and II, and no mortality occured in group III. It is interesting to note that in group II, 3 males out of 5 died while none died in group II females. In contrast 1 male and 3 females died in group I.

Based on the mean analytical exposure concentration of this study and the resultant mortality, the investigator determined the LC_{50} values and 95% confidence limits as follows:

Sex	LC50 (mg/l)	95% Confidence Limits (mg/l)
Males	5.0	0.63 to 39
Females	4.7	2.6 to 8.3
Both sexes	6.7	3.9 to 12

In-life Animal Observations:

During Exposure: Decreased activitiy, eyes closed, and labored breathing were observed in all three groups.

Upon Removal from Chamber: Upon removal from exposure chamber and up to two hours thereafter labored breathing and moist rales were still observed in all three exposure groups. Lacrimation, nasal discharge and salivation were also seen. Test material contamination on fur was observed in the high exposure group.

Post-Exposure Observation: All mortalities occured between day 2 and day 8. Signs observed during the first week after exposure included: excess lacrimation, eyes closed, mucoid and dried red nasal discharges, noisy and dried rales, labor breathing, and discolor ano-genital areas. After the first week these signs decreased in incidence and/or became sporadic among surviving animals.

Body weights: Weight losses were observed following exposure, especially at the high dose level. At study termination most surviving animals weighed more than their pre-exposure weights.

Macroscopic Findings: The lungs and nasal turbinates were red in some spontaneously death and in terminally sacrificed animals. Group I and II animals had discolored skin and matted coat. The significance of these signs are unknown. Microscopic examination was not performed.

DISCUSSIONS

The large MMAD values and the low percentages of particle size of less than 1 um in the test atmosphere, suggest that very little test material was respirable to the test animals. The major route of exposure would have been orally via the mucociliary transport and through the nasopharyngeal areas. There was no evidence that the investigator attempted to generate at least 25% respirable particle of one micron or less.
Mean body weight difference between group I and group III males at the start of the study exceeded 20%. The guideline calls for weight variation of animals or between groups of animals of not more than 20% of the mean weight for each sex.
Variation in the ages of test animals, which ranged between 1-4 weeks was too great.

CONCLUSIONS

This study as presented is not acceptable because of the following reasons:

- Not enough respirable particles of test material were generated into the test atmosphere (at least 25% particle size must be of 1 um or less).
- The investigator did not attempt to generate or indicate why smaller particles could not be generated.
- Failure to maintain a consistent chamber concentration.
- Variation in the ages of the test animals was too great.

In this study it appeared that the route of exposure would have been orally via mucociliary transport and through the nasopharyngeal surfaces.
The red colored respiratory tissues (lungs and nasal turbinates) in both sacrificed and spontaneously dying animals and other sporadic findings were not considered clearly compound-related.

Classification: Core-supplementary

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007957

Reviewed by: David S. Liem, Ph.D. 4/12/90
Toxicology Branch II, Section II
Secondary Reviewer: Stephen Dapson, Ph.D. 5/10/90
Toxicology Branch II, Section I
Tertiary Reviewer: K. Clark Swentzel 5/14/90
Toxicology Branch II, Section II

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation Study

TOX. CHEM NO.: 6-0563A CASWELL NO.: 03B MRID NO.: 409988-04

TEST MATERIAL: Harness, Monsanto No. FD-88-173, XLI-198; a dark purple viscous liquid; assay = Acetochlor 82.28%

SYNONYMS: none

STUDY NUMBER(S): Monsanto Study No. FD-88-173; Food & Drug Research Laboratories (FDRL) Study NO. 88.2053.018

SPONSOR: Monsanto Company, St. Louis, MO 63167

TESTING FACILITY: Food and Drug Laboratories (FDRL), P.O. Box 107, Route 17C, Waverly, NY 14892

TITLE OF REPORT: Primary Dermal Irritation Study of Harness in New Zealand White Rabbits

AUTHOR(S): E. L. Reagan

REPORT ISSUED: July 8, 1988

CONCLUSIONS: Test material caused slight to well-defined erythema in all six (6/6) and very slight to slight edema in two of six (2/6) animals. Dermal irritation was not observed 10 days after dose administration.
This study satisfies the data requirement subdivision F Guideline No. 81-5. Toxicity category III.

Classification: Core-minimum

Quality Assurance Unit Statement: Signed and dated

FIFRA GLP Compliance Statement: Signed and dated

STUDY TITLE: Primary Dermal Irritation Study of Harness in New Zealand White Rabbits

Test Materials: Harness, Monsanto No. FD-88-173, XLI-198; a dark purple viscous liquid; assay = Acetochlor 82.28% PH of test material was not noted in the report. It was not noted whether this test material is a manufacturing-use or an end-use product.

Test Animals: Young adult New Zealand white rabbits were acclimated to the laboratory environment for at least 5 days prior to study initiation. For this study, six healthy rabbits weighing between 2 to 3 kg, were randomly selected from the acclimated colony.

Feed and Water: Test animals were provided with certified NIH 09 Rabbit Ration and local tap water ad libitum.

Environmental Parameters: Test animals were kept in a controlled environment; a 12 hrs light/dark cycle; room temperature 68-75°F; relative humidity 40% to 60 %. Rate of air exchanges in the room was not noted.

PROCEDURES

Treatment: Dorso-lumbar area was shaved 24 hours prior to test material application. Test material (0.5 ml) was applied topically to each of two intact dorsal test sites per rabbit. Then test sites were semi-occluded with a gauze patch and held in place with Micropore tape. The animals were collared to prevent removal of the patches. The patches and collars were removed four hours after dose administration and the exposure sites were gently wiped with gauze to remove the non-absorbed test material.

Observation and Body Weights: Test animals were observed twice daily for mortality at least 5 hours apart. Body weights were taken on day 1, prior to dose administration.

Dermal Irritation Evaluation and Grading: Treated skin was examined on day 1 (30 minutes after patch removal), 2, 3, 4, 7 and 10. Erythema and edema were graded and scored according to the Skin Reaction Code (Draize method) shown in Appendix I.
Individual animal scores were obtained at each scoring interval by adding the total erythema and eschar formation scores from both application sites to the total edema formation scores from both sites and divided by two. The mean primary irritation scores was calculated at each scoring interval from individual scores obtained from the test animals.

RESULTS AND DISCUSSIONS: The numerical scores of skin reactions are presented on Table 1. Test material caused slight to well-defined erythema in all six (6/6) and very slight to slight edema in two of six (2/6) animals. Dermal irritation was not observed 10 days after dose administration. No other signs of systematic toxicity were observed.
The investigator weighed the test animals one day prior to dose administration, but this data was not included in the report.

CONCLUSIONS: Test material caused slight to well-defined erythema in all six (6/6) and very slight to slight edema in two of six (2/6) animals. Dermal irritation was not observed 10 days after dose administration. The treatment sites were not rinsed and washed using water to remove residual test material as recommended by Subdivison F Guideline No. 81-5. The test material is rated as Toxicity Category III.

Classification: Core-minimum

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037927

Reviewed by : David S. Liem, Ph.D. 4/17/90
Toxicology Branch II, Section II
Secondary Reviewer: Stephen Dapson, Ph.D. 5/20/90
Toxicology Branch II, Section I
Tertiary Reviewer: K. Clark Swentzel 5/14/90
Toxicology Branch II, Section II

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation

TOX. CHEM. NO.: 0-0563A CASWELL No.: 03B MRID NO.:409988-03

TEST MATERIAL: Harness, Monsanto Study FD-88-173, XLI-198; a dark purple viscous liquid; Assay = acetochlor 82.28%

SYNONYMS: None

STUDY NUMBER(S): Monsanto Study No.: FD-88-173; Food and Drug Research Laboratories (FDRL) No.: 88.2053.017

SPONSOR: Monsanto Company, St. Louis, MO 63167

TESTING FACILITY: Food & Drug Research Laboratories (FDRL) P.O. Box 107, Route 17C, Waverly, NY 14892

TITLE OF REPORT: Primary Eye Irritation Study of Harness in New Zealand White Rabbits

AUTHOR(S): E.L. Reagan

REPORT ISSUED: July 8, 1988

CONCLUSIONS: Harness caused corneal opacity and conjunctival irritation with blistering in all rabbit after test material instillation. Corneal opacity was not present 7 days after dose administration. At day 14 examination, all eyes appeared normal. The test material is rated as Toxicity Category III. This study satisfies the data requirement for Subdivision F Guideline No. 81-4.

Classification: Core-minimum

Quality Assurance Statement: Signed and checked by QAU

FIFRA GLP Compliance Statement: Signed and dated

Study Title: Primary Eye Irritation Study of Harness in New Zealand White Rabbits

Test Material: Harness, Monsanto Study FD-88-173, XLI-198; a dark purple viscous liquid; Assay = acetochlor 82.28% It was not noted whether this test material is a manufacturing-use or end-use product. PH of the test material was not noted in the report.

Test Animals: Young adult New Zealand White rabbits were acclimated to the laboratory environment for at least 5 days prio. to study initiation.

Feed and Water: Test animals were provided with a certified NIH 09 Rabbit Ration and fresh tap water ad libitum.

Environmental Parameters: Test animals were maintained in a controlled environment with temperature and relative humidity range of 68-75o F and 40-60%, respectively.

PROCEDURES

Treatment: The eyes of each animal were examined prior to study initiation. The test material (0.1 ml) was instilled into one eye of each animal; test material was placed into the lower everted eyelid, then held together for 1 second. Following scoring at 24 hours after dose administration, any residual material was rinsed from the eye with physiological saline.

Eye Irritation Scoring: Treated and untreated eyes were examined at 1, 24, 48, and 72 hours and 7 and 14 days after test material instillation. The cornea, iris and conjunctiva were scored according to the Draize method given in Appendix A.

Systemic Toxicity: All animals were observed twice daily at least 5 hours apart.

Body weights: Body weights were obtained on study day 1. These data were not reported in the report.

RESULTS

All rabbits exhibited conjunctival irritation at one hour and corneal opacity at 24 hours after test material instillation. In one rabbit corneal opacity persisted for 72 hours. Five animals exhibited slight conjunctival redness for 7 days after test material instillation. On day 14, all eyes appeared normal. Individual eye irritation scores are presented in Table 1.

Conclusions: Harness caused corneal opacity and conjunctival irritation with blistering in all rabbit after test material instillation. Corneal opacity was not present 7 days after dose administration. At day 14 examination, all eyes appeared normal.
The test material is rated as Toxicity Category III.
This study satisfies the data requirement for Subdivision F Guideline No. 81-4.

Classification: Core-minimum

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