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

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012578

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Memorandum

4/8/98

Subject: Atrazine - Review of Dominant Lethal study in the mouse.

DP Barcode: D242767
Case: 003213
Submission: S536785
Caswell No. 063
PC No. 080803
Registrant: Novartis Crop Protection
P.O. Box 18300
Greensboro, N.C.
27419-8300

From: Roger Hawks, Ph.D. Roger Hawks 4-15-98
Toxicology Branch II
Health Effects Division (7509c)

Thru: Stephen Dapson, Ph.D. Stephen C. Dapson 4/15/98
Branch Senior Scientist
Toxicology Branch II (7509c)

To: Cathrine Eiden
RCAB, Health Effects Division (7509c)
and
Jeff Morris
SRRD (7508w)

Action requested: Review Dominant Lethal study in mouse using atrazine (MRID 42637003) to see if it fulfills guideline 84-2.
Response: The study has been reviewed and found to be acceptable. The study does fulfill the guideline 84-2 for atrazine.

Reviewers:
Oakridge National Laboratories: Primary reviewer - C.B. Bast, Ph.D.
Secondary reviewer - B.L. Whitfield, Ph.D.
EPA: Primary reviewer - Roger Hawks, Ph.D.
Work assignment manager - Sinjivani B. Diwan, Ph.D.

DATA EVALUATION REPORT SUMMARY

ATRAZINE TECHNICAL

STUDY TYPE: DOMINANT LETHAL – MOUSE (84-2)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer:
C. B. Bast, Ph.D., D.A.B.T.

Signature: C B Bast
Date: 3-25-98

Secondary Reviewers:
B. L. Whitfield, Ph.D.

Signature: RHR for B L Whitfield
Date: 3-25-98

Robert H. Ross, M.S., Group Leader

Signature: RHR
Date: 3-25-98

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: Lee Ann Wilson
Date: 3-25-98

Disclaimer

This Data Evaluation Report may have been altered by the Health Effects Division subsequent to signing by Oak Ridge National Laboratory personnel.

Managed by Lockheed Martin Energy Research Corp., for the U.S. Department of Energy under Contract No. DE-AC05-96OR22464.

EPA Reviewer: R. Hawks, Ph.D. Roger Hawks, Date 4/8/98
Toxicology Branch 1 (7509C)
EPA Secondary Reviewer: S. Diwan, Ph.D. Sanjay Diwan, Date 4/8/98
Toxicology Branch 1 (7509C)

DATA EVALUATION RECORD **012578**

STUDY TYPE: Rodent dominant lethal assay in mice; OPPTS 870.5450 [§84-2]

DP BARCODE: D242746 SUBMISSION CODE: S536785
P.C. CODE: 80803 TOX. CHEM. NO.: 063

TEST MATERIAL (PURITY): Atrazine Technical (97.1%)

SYNONYMS: G 30027 technical

CITATION: Hertner, T. (1993) Atrazine Structural Chromosomal Aberration Test. Dominant Lethal Test, mouse 8 weeks. Ciba-Geigy Limited, Plant Protection, Basle, Switzerland. Study No. 911247. January 7, 1993. MRID 42637003. Unpublished

SPONSOR: Plant Protection, Ciba-Geigy Corporation, Post Office Box 18300, Greensboro, NC 27419.

EXECUTIVE SUMMARY:

In a mouse dominant lethal assay (MRID 42637003), groups of 30 male Tif: MAGf (SPF)mice were treated orally by gavage with Atrazine technical (97.1% a.i., batch #SG8029BA10) at doses of 0, 500, 1000, 2000, or 2400 mg/kg body weight in a volume of 10 mL/kg. The vehicle was corn oil. Starting immediately after dosing, each male was mated with 2 untreated females per interval for days 1-4, days 4-8, and days 8-12. Each male was then mated with 2 untreated females per week for weeks three through eight.

Atrazine technical was tested at an adequate dose. There were signs of toxicity after dosing as evidenced by piloerection and decreased locomotor activity. The females were sacrificed on gestation day 13-15 and the uteri examined for the number of alive, early, and late dead embryos and resorptions. Cyclophosphamide served as the positive control. **There was no significant difference between the control group and treated groups with respect to post-implantation mortality of embryos. Under the conditions of this study atrazine technical did not induce dominant lethal mutations in male mice at doses as high as 2400 mg/kg.**

This study is classified as acceptable (guideline). It does

satisfy the requirement for FIFRA Test Guideline 84-2 for rodent dominant lethal data.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. A Flagging Statement was not provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material:Atrazine technical
   Description: white powder
   Lot/Batch #: SG8029BA10
   Purity: 97.1% a.i.
   Stability of compound: "stable"
   CAS #:1912-24-9
   Structure: not provided
   Solvent used: corn oil

2. Control Materials:

   Vehicle/Final volume/Route of administration: corn oil/ 10 mL/kg/ oral gavage

   Positive/Finaldose(s)/Route of administration: cyclophosphamide/133 or 400 mg/kg in 0.5% carboxymethylcellulose/ oral gavage

3. Test compound administration:
   Volume of test substance administered: 10 mL/kg

   Route of administration: oral gavage

   Dose levels used: 500, 1000, 2000, or 2400 mg/kg

4. Test animals: (males only were treated)
   a. Species mouse Strain Tif:MAGf (SPF)
      Age adult Weight male 31-45 g

      Source: Ciba-Geigy

   b. No. animals used per dose: 30 males
      Mated to 2 untreated females for days 1-4, 4-8, and 8-12. Mated to 2 untreated females per week for weeks 3-8
   c. Properly maintained? Yes

B. TEST PERFORMANCE

1. Treatment:
   a. Test compound and solvent control
   Dosing: X once _____ twice (24 hr apart)
   _____ other (describe):

2. Mating: Starting the day of treatment, each atrazine-treated male (30/dose group) or positive control male (20/dose group) was mated over night with two untreated virgin females per mating period (Table 1).

Table 1. Mating Schedule

Atrazine Treated Animals		Cyclophosphamide Treated Animals	
MATING PERIOD	TIME INTERVAL	MATING PERIOD	TIME INTERVAL
I	Day 1-4	I	Week 1
II	Day 4-8	II	Week 2
III	Day 8-12	III	Week 3
IV	Week 3	IV	Week 4
V	Week 4	V	Week 5
VI	Week 5	VI	Week 6
VII	Week 6	VII	Week 7
VIII	Week 7	VIII	Week 8
IX	Week 8		

Each morning females were examined for the presence of a vaginal plug. Females with a vaginal plug were marked and housed in groups in separate cages. Those without a vaginal plug were mated again the next night with the same male for a maximum of 7 days. If mating had not occurred within 7 days, a new series of two virgin females were mated with each male.

3. Caesarian procedures: Thirteen to fifteen days after the observation of a vaginal plug or, in the absence of a vaginal plug, 17 days after the first opportunity to mate, females were sacrificed. The uteri were examined for the number of alive, early, and late dead embryos. Uteri without embryos were placed in an ammonium sulfide solution for 5 minutes to detect resorptions. The number of corpora lutea were not determined since this

study was designed to detect only post-implantation loss due to genetic damage.

4. Evaluation Criteria: A positive response was defined as "the occurrence of a dose-related increase in the incidence of one or more indicators of post-implantation dominant lethality with at least two dose levels" or "a statistically significant increase in the incidence of one or more indicators of post-implantation dominant lethality of the highest dose with respect to the vehicle control." A negative response was defined if the criteria for a positive response were not met. Data were evaluated with respect to treatment group and mating period.

5. Statistical methods: Nonparametric statistical tests were performed separately for each mating period. Linear-by-Linear Association (LLA) tests with linear score were used for the number of fertilizations, while LLA with mean rank score was used for the number of embryos per male and the proportion of total/early/late dead embryos per male.

II. REPORTED RESULTS

A. Preliminary toxicity assays:

Tolerability Test: Groups of two male mice were administered single gavage doses of 1400, 1600, 1800, 2000, 2200, or 2400 mg/kg atrazine technical in corn oil and observed for up to 8 days. One animal each from the 1400 and 1800 mg/kg groups and both animals from the 2200 mg/kg group died. All other mice exhibited piloerection, decreased activity, ventral recumbency, hunched posture, unkempt fur, and/or tremor. Body weight loss was also observed and did not resolve by the end of the observation period.

Fertility Test: Groups of two males were administered single gavage doses of 0, 200, 400, 800, 1200, 1600, or 2000 mg/kg of atrazine technical in corn oil. They were then mated with two females per week for three consecutive weeks. Thirteen to fifteen days after mating (as evidenced by the presence of a vaginal plug), the females were sacrificed and pregnancy determined by macroscopic examination of the uterus. Signs of toxicity in the treated males were similar to those observed in the tolerability test at similar doses. There was no treatment-related effect on either mating frequency or fertility.

B. Dominant lethal assay: Piloerection was observed in 5/30 males in the 1000 mg/kg group, 2/30 males in the 2000 mg/kg group, and 13/30 males in the 2400 mg/kg group. Decreased locomotor activity was observed in 2/30 animals treated with 1000 mg/kg atrazine, 0/30 in the 2000 mg/kg group, and 12/30 animals treated with 2400 mg/kg. No signs of toxicity were observed in the 500 mg/kg group.

No treatment-related effects were observed on mating frequency, pregnancy rate, number of implantations, number of uteri with only deciduomatas, or embryo lethality at any dose level or mating period. Statistically ($p<0.05$) significant increases in embryonic deaths were observed during mating periods III and IX; however, the study author attributes this to exceptionally low negative control values (2.4 and 3.8%) at these time intervals compared to the negative controls of other mating periods (5.6-11.1%). Results are presented in Appendix Table 1 (MRID 42637003, pp. 45-47). The positive control responded appropriately.

III. REVIEWER'S DISCUSSION/CONCLUSIONS:

A. This is an acceptable study. The experimental protocol was acceptable. A sufficient number of animals were utilized and the highest dose produced toxicity. Although there were increases in embryonic deaths at mating periods III and IX, the author's attribution of these effects to low negative controls seems appropriate.

B. STUDY DEFICIENCIES - None identified.

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APPENDIX A

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T&T Review 012578

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