DATA EVALUATION RECORD

MESOTRIONE (ZA1296) 7/19/2000

Study Type: §81-2, Acute Dermal Toxicity

Work Assignment No. 2-01-52E (MRID 44373514)

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

Prepared by
Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Kimberly S. Woodard, B.S.

Signature: Kimberly S. Woodard
Date: 12/13/99

Project Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L. Menetrez CEP
Date: 12-13-99

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

81

EPA Reviewer: David Nixon, DVM
Registration Action Branch 1/HED (7509C)

Work Assignment Manager: Marion Copley, DVM
Registration Action Branch 1/HED (7509C)

David Nixon 7/11/2000

M Copley 7/19/2000

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - Rat
OPPTS Number: 870.1200 OPP Guideline Number: §81-2

DP BARCODE: D259369 SUBMISSION CODE: S541375
P.C. CODE: 122990 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): ZA1296 (95.1% purity)

SYNONYMS: None specified.

CITATION: Robinson, P. (1994) ZA1296: acute dermal toxicity to the rat. Zeneca Central Toxicology Laboratory, Macclesfield, Cheshire, UK. Laboratory Report No. CTL/P/4503, Study No. CR3171. November 4, 1994. MRID 44373514. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, DE.

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 44373514), five young adult (7.5- to 8.5-wks. old) Alpk:AP$_f$SD (Wistar-derived) rats/sex were dermally exposed to ZA1296 (95.1% purity) at 2,000 mg/kg (limit dose) for 24 hours. The test substance was moistened with distilled water and applied to a 6 cm x 4 cm area of shaved skin. Animals were observed for clinical signs of toxicity, skin irritation, and mortality for up to 14 days postdosing.

Dermal LD_{50} Males = >2,000 mg/kg (observed)
Females = >2,000 mg/kg (observed)

ZA1296 is classified as **TOXICITY CATEGORY III** based on the observed LD_{50} values for both sexes. Precautionary statements are still required since there are no data to indicate the LD_{50} is greater than 5,000 mg/kg.

All animals survived the 14-day study. Stains around nose, urinary incontinence, and salivation were observed in up to 3/10 animals between days 0 and 1. Dermal irritation was generally obscured by yellow staining of the treated area, which persisted in all animals through 14 days. Slight edema and slight desquamation were observed each at 1/10 sites and small scattered scabs

2

were observed at 5/10 sites. No significant treatment-related effect on body was observed, and necropsy after 14 days revealed no gross internal abnormalities.

This study is classified **acceptable (§81-2)** and satisfies the guideline requirement for an acute dermal study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: ZA1296
   Description: Light beige solid
   Lot/Batch #: P11, WRC 14845-32-2
   Purity: 95.1% (w:w)
   CAS #: Not provided

2. Vehicle: Deionized water, 0.8 mL/application

3. Test animals: Species: Rat
   Strain: Alpk:AP$_f$SD (Wistar-derived)
   Age: Young adult (approximately 7.5-8.5 weeks)
   Weight: 260-278 g males; 192-207 g females
   Source: Barriered Animal Breeding Unit, Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK
   Acclimation period: ≥6 Days
   Diet: (PCD) Special Diet Services Limited, Witham, Essex, UK, ad libitum
   Water: Tap water, ad libitum
   Housing: Individually in suspended stainless steel cages
   Environmental conditions:
   Temperature: 21±2 °C
   Humidity: 55±15%
   Air changes: Approximately 25-30 changes/hour
   Photoperiod: 12-Hour light/dark cycle

3

B. STUDY DESIGN and METHODS:

1. In-life dates: July-August 1994

2. Animal assignment and treatment: Fur from the dorso-lumbar areas (approximately 5% of the total body surface area)[1] of five young adult Alpk:APfSD rats/sex was clipped 16-32 hours prior to dermal administration of ZA1296 at 2,000 mg/kg (limit dose). The test substance was weighed, moistened with deionized water (0.8 mL), and applied to the clipped site. Each site was covered with a 4-ply 4-cm x 6-cm gauze patch which was kept in contact with the skin using an occlusive dressing and covered plastic secured with PVC tape. After 24 hours, the coverings were removed, and each application site was gently washed with warm water. The rats were observed for signs of systemic toxicity/gross abnormalities between 1 and 4 hours following treatment, and once daily thereafter for up to 14 days. Dermal irritation was also observed once daily following patch removal. Body weights were recorded at 0 (prior to dosing), 2, 4, 7, and 14 days. At 14 days, the surviving animals were sacrificed, necropsied, and examined for gross pathological changes.

3. Statistics: Not applicable to this study.

II. **RESULTS AND DISCUSSION**:

A. Mortality: All animals survived the 14-day observation period.

Dermal LD_{50} Males = >2,000 mg/kg (observed)
Females = >2,000 mg/kg (observed)

B. Clinical observations: Clinical effects included stains around nose (3/10), urinary incontinence (3/10), and salivation (2/10) between days 0 and 1. All effects subsided by day 2.

In all animals, yellow staining of the treated area was observed throughout the study and in some cases prevented a complete assessment of dermal irritation (slight or moderate erythema would be obscured). Slight edema and slight desquamation were observed each at 1/10 sites; small scattered scabs were also observed at 5/10 sites.

C. Body Weight: No significant treatment-related effect on body was observed. All animals gained weight during the study, with mean overall (days 0-14) increases of 32% in males and 18% in females.

---

[1]Percent body surface area calculated by reviewer using $(BW)^{2/3}$ conversion.

D. Necropsy: Gross necropsy of animals sacrificed after 14 days revealed yellow staining of the hair in all rats. No internal abnormalities were observed.

E. Deficiencies: The test substance application area was approximately 5% of the total body surface area. After discussions with the registrant, subsequent studies were modified to increase the application area to 10% of the total body surface area. Due to the low toxicity of the test substance, this deficiency should have no effect on the outcome of the study. No other deficiencies were noted.

5

ZENECA

Zeneca Ag Products
1800 Concord Pike
P.O. Box 15458
Wilmington, DE 19850-5458

Telephone (302) 886-1000
(302) 886-1553

VIA E-MAIL

March 17, 2000

TO: Mr. James M. Stone
Product Management Team 25
U.S. Environmental Protection Agency

FROM: Barbara J. Kaminski
Regulatory Manager
Zeneca Ag Products

RE: PHONE REQUEST FOR INFORMATION REGARDING MESOTRIONE ACUTE DERMAL STUDIES

Question from EPA on mesotrione (1)

Acute Dermal Studies

With reference to reports CTL/P/4503 (ZA1296: Acute dermal toxicity to the rat) and CTL/P/4810 (Acute dermal toxicity to the rat of a 480 g/l SC formulation)

After the animals were shaved, was the test compound spread over the entire area that was shaved or only over the small area under the patch? If under the patch area only, what was the size of the area ?

The protocol for acute dermal toxicity studies calls for approximately 10% of the total body surface area of the animal to be used as the application site for the test compound. The amount of compound applied is based on the individual body weights of each animal at the time of dosing.

In all cases an area on the dorso-lumbar region of each animal, slightly larger than the calculated 10% of the total surface area, is shaved. Liquid test substances are applied directly to this area and are spread evenly to cover an area equivalent to 10% of the surface area of the animal and equal to the selected patch size, allowing the application site to be entirely covered by the patch. Solid test substances are moistened with a suitable vehicle and are applied evenly to the patch which is then applied to the shaved area of the animal.

In the case of the two studies mentioned, the weight range of the animals and the patch size used was as follows:

6

Report Number	Date of study	Weight of animals	Area of patch
CTL/P/4503	June 1994	Males 260-278 g Females 192-207 g	6cm x 4cm
CTL/P/4810	September 1995	Males 267-291 g Females 221-234 g	7cm x 7 cm

Between the conduct of the first and second study the criteria for assessing the total surface area of the rat changed as a result of discussions between industry and the EPA as detailed in ref. 1. As a result, the area of exposure equivalent to approximately 10% of total surface area of the animal was defined as 'from the scapular to the wing of the ileum and halfway down the flank on each side of the animal'. Patch sizes were, therefore, increased from approximately 25 cm^2 to 50cm^2 for animals weighing up to 300 g.

In conclusion, in acute dermal toxicity studies the area dosed is equivalent to 10% of the surface area of the animal and is the same as the patch size used. The specific patch size used in each of the studies mentioned is summarised in the above table and is specified in the methodology section of the reports. The change in patch size used between the first and second study was as a result of discussions which took place between the EPA and industry.

Ref:

1. **Acute Tox Rejection Rate Project - Final Correspondence Memo from P.F Paul to T. Levine Sept 20th 1996**