DATA EVALUATION RECORD

7/19/2000

MESOTRIONE (ZA1296 (480 g/L SC Formulation))

Study Type: §81-3, Acute Inhalation Toxicity

Work Assignment No. 2-01-52H (MRID 44373517)

Prepared for

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DATA EVALUATION RECORD

STUDY TYPE: Acute Inhalation Toxicity - Rat
OPPTS Number: 870.1300

OPP Guideline Number: §81-3

DP BARCODE: D259369
P.C. CODE: 122990

SUBMISSION CODE: S541375
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): 480 g/L SC Formulation of ZA1296 [40.7% (w:w) ai]

SYNONYMS: None specified

CITATION: Parr-Dobrzanski, R. (1995) ZA1296: 4-hour acute inhalation toxicity study in the rat of a 480 g/L SC formulation. Zeneca Central Toxicology Laboratory, Macclesfield, Cheshire, UK. Laboratory Report No. CTL/P/4822, Study No. HR2275. November 29, 1995. MRID 44373517. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, DE.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 44373517), five young adult Alpk:AP$_f$DS (Wistar-derived) rats/sex were exposed by nose-only inhalation to a 50% aqueous dilution of the 480 g/L SC Formulation of ZA1296 [40.7% (w:w) ai] at 2.83 mg/L for 4 hours. Animals were observed for clinical signs of toxicity and mortality for up to 14 days post-exposure.

Inhalation LC_{50} Males = >2.83 mg/L (observed)
Females = >2.83 mg/L (observed)

The 480 g/L SC Formulation of ZA1296, at a 50% aqueous dilution, is classified as **TOXICITY CATEGORY IV** based on the observed LC_{50} values in both sexes.

No mortality occurred. Clinical effects observed during the 14-day study included hunched posture, piloerection, test substance around snout, wet fur, salivation, irregular breathing, coat stained by test substance, lacrimation, decreased activity, and chromodacryorrhea. Piloerection persisted in males through days 3 or 4 and in females through days 2 to 6. Other effects subsided from all animals by day 2. No treatment-related effect on body weight was observed, and

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necropsy revealed no gross internal abnormalities.

This study is classified **acceptable (§81-3)** and satisfies the guideline requirement for an acute inhalation 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: 480 g/L SC Formulation of ZA1296
   Description: Tannish brown liquid
   Lot/Batch #: WF2381; 15424-50-01
   Purity 40.7% ZA1296 (w:w)
   CAS #: Not provided

2. Vehicle and/or positive control: Due to the high viscosity of the test material, a 50% (v:v) preparation in deionized water was used to generate the test atmosphere.

3. Test animals: Species: Albino rat
   Strain: Specific pathogen free, Alpk:AP$_f$SD (Wistar-derived)
   Age: Young adult
   Weight: 226-246 g males; 208-212 g females
   Source: Alderley Park, Cheshire, UK
   Acclimation period: ≥7 Days
   Diet: Pelleted Porton Combined Diet (Special Diets Services Limited, Witham, Essex, UK), ad libitum, except during exposure
   Water: Tap water, ad libitum, except during exposure
   Housing: Five animals/cage, separated by sex. Cages were contained in one mobile rat rack.
   Environmental conditions:
   Temperature: 19-26 °C
   Humidity: 35-68%
   Air changes: 20-30/hour
   Photoperiod: 12-hour light/dark cycle

B. STUDY DESIGN and METHODS:

1. In-life dates: October 5-19, 1995

2. Exposure conditions: A dynamic cylindrical PERSPEX exposure chamber of Zeneca design (27.6-L volume) was used in the study. The chamber was equipped with radial ports, in which tapered, polycarbonate restraining tubes were securely fitted for nose-only exposure.

Test atmosphere was generated at the top of the exposure chamber using a glass concentric-jet atomizer. The atomizer was operated with filtered, de-humidified compressed air. The total airflow through the exposure chamber (equivalent to that employed for the generation of the test atmosphere) was maintained at 27 L/min (equivalent to 59 chamber turnovers/hour). Animal tubes were affixed to the exposure chamber once the target concentration had been maintained over approximately 30 minutes.

The nominal test atmosphere concentration was calculated at the end of the exposure period by dividing the total amount of material delivered to the chamber by the total volume of air used during exposure. The total particulate concentration of the test atmosphere was measured gravimetrically seven times (at approximately half-hour intervals) during the exposure period. Samples (volume not specified) were drawn from the breathing zone of the animals through a Gelman GLA 5000 PVC filter (25 mm). Following gravimetric determination, the filters were extracted with acetonitrile and aliquots of the extracts were analyzed for ZA1296 (active ingredient) using high-performance liquid chromatography (HPLC) with UV (270 nm) detection. Following active ingredient analysis, the total formulation concentration was back-calculated. The nominal test atmosphere concentration was 14.8 mg/L. The total particulate concentration, actual ZA1296 concentration, and total formulation concentration during the exposure period averaged 2.09, 1.15, and 2.83 mg/L, respectively.

Particle size was determined twice, at 58 and 225 minutes into exposure, using a Marple Cascade Impactor. Samples (volume not specified) were drawn from the animals' breathing zone. The calculated mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) averaged 3.54 and 1.74 µm, respectively.

The temperature and relative humidity were measured at "frequent intervals" during exposure and ranged from 20.6-21.2 °C and 70-73%, respectively. Oxygen levels in the exposure chamber were not reported.

3. Animal assignment and treatment: Five young adult Alpk:AP$_f$SD (Wistar-derived) rats/sex were exposed to a 50% aqueous dilution of the 480 g/L Formulation of ZA1296 at 2.83 mg/L via nose-only inhalation for 4 hours. The animals were observed for signs of toxicity and/or mortality "frequently" during exposure, once immediately following exposure, and once daily thereafter for 14 days. Body weights were recorded on days 0 (prior to exposure), 1, 2, 7 and 14. After 14 days, the surviving animals were sacrificed, necropsied, and examined for gross pathological changes.

4. Statistics: Not applicable.

II. RESULTS AND DISCUSSION:

A. Mortality: All animals survived the 4-hour exposure and 14-day observation periods.

Inhalation LC_{50} Males = >2.83 mg/L (observed)
Females = >2.83 mg/L (observed)

B. Clinical observations: Irregular respiration, wet fur, salivation, and test substance coated around snout were observed in all animals within 150 minutes of exposure initiation. In addition, chromodacryorrhea, lacrimation, and coat stained with test substance were also observed in some animals from 180-210 minutes of exposure initiation (individual data not provided). Clinical effects following exposure included hunched posture (10/10), piloerection (10/10), test substance around snout (10/10), wet fur (10/10), salivation (9/10), irregular breathing (5/10), coat stained by test substance (3/10), lacrimation (2/10), decreased activity (1/10), and chromodacryorrhea (1/10). Piloerection persisted in males through days 3 or 4 and in females through days 2 to 6. Other effects subsided from all animals by day 2.

C. Body Weight: Upon comparison of the 0-, 7-, and 14-day data, no significant effect on body weight was observed during the study. It should be noted that both males and females lost weight the day after exposure, but had a significant recovery by the end of the study period. Overall (0-14 days), the body weight of males and females increased averages of 39% and 17%, respectively.

D. Necropsy: Necropsy after 14 days revealed no internal abnormalities.

E. Deficiencies: Oxygen content in the exposure chamber was not reported, but should not affect the outcome of the study. No other deficiencies were noted.