DATA EVALUATION RECORD

7/19/2000

MESOTRIONE (ZA1296)

Study Type: §81-3, Acute Inhalation Toxicity

Work Assignment No. 2-01-52G (MRID 44373516)

Prepared for

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

Prepared by

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

Primary Reviewer:
Christie E. Padova, B.S.

Signature: Christie E. Padova
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.

1

David Nixon 7/11/2000

Marion Copley 7/19/2000

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

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

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): ZA1296 (97.3% purity)

SYNONYMS: None specified

CITATION: Rattray, N. (1995) ZA1296: 4-hour acute inhalation toxicity study in the rat. Zeneca Central Toxicology Laboratory, Macclesfield, Cheshire, UK. Laboratory Report No. CTL/P/4739, Study No. HR2273. August 8, 1995. MRID 44373516. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, DE.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 44373516), five young adult Alpk:AP$_f$DS (Wistar-derived) rats/sex were exposed by nose-only inhalation to ZA1296 (97.3% purity) at 4.75 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 = >4.75 mg/L (observed)
Females = >4.75 mg/L (observed)

ZA1296 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, abnormal respiratory noise, decreased activity, salivation, irregular breathing, shaking, mucus secretion from nose, reduced response to sound, splayed gait, labored breathing, head/paw flicking, absence of pinna reflex, ptosis, reduced righting reflex, reduced stability, rubbing chin along floor, and chromodacryorrhea. Most effects subsided by day 1; however, hunched postures, piloerection, irregular breathing,

2

and/or splayed gait showed variable persistence in affected animals through day 2 out to day 9. Effects completely subsided from all animals by day 10. No significant effect on body weight was observed in male animals, who exhibited an overall average increase of 24%. In comparison, 2/5 females exhibited slight weight losses (<2.5% ↓) between 0 and 7 days. All females gained weight between 7 and 14 days, and exhibited an overall mean increase of 13%. Necropsy after 14 days revealed red spots on the lungs of one male.

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: ZA1296
   Description: Light beige solid
   Lot/Batch #: P18
   Purity: 97.3% (w:w)
   CAS #: None specified

2. Vehicle and/or positive control: None employed

3. Test animals: Species: Albino rat
   Strain: Specific pathogen free, Alpk:AP$_f$SD (Wistar-derived)
   Age: Young adult
   Weight: 273-310 g males; 213-246 g females
   Source: Alderley Park, Cheshire, UK
   Acclimation period: ≥5 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
   Environmental conditions:
   Temperature: 19-23 °C
   Humidity: 50 ± 15%
   Air changes: 20-30/hour
   Photoperiod: 12-Hour light/dark cycle

3

B. STUDY DESIGN and METHODS:

1. In-life dates: July 25 - August 8, 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 Wright's Dust Feed mechanism. The dust feeder 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 30 L/min (equivalent to 65 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 apparently not calculated. The total particulate concentration of the test atmosphere was measured gravimetrically ten 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. 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. The total particulate concentration and actual concentration of ZA1296 during the exposure period averaged 5.19 and 4.75 mg/L, respectively.

   Particle size was determined twice, at 70 and 215 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 2.10 and 2.13 µm, respectively.

   The temperature and relative humidity were measured at "frequent intervals" during exposure and ranged from 19.7-22.2 °C and 39-55%, 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 ZA1296 at 4.75 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. In addition, lung weights were recorded.

4

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 = >4.75 mg/L (observed)
Females = >4.75 mg/L (observed)

B. Clinical observations: Irregular respiration, wet fur, salivation, and reduced response to sound stimulation was observed in all animals within 2 hours of exposure initiation. Clinical effects following exposure included hunched posture (10/10), piloerection (10/10), test substance around snout (10/10), wet fur (10/10), abnormal respiratory noise (8/10), decreased activity (2/10), salivation (6/10), irregular breathing (8/10), shaking (3/10), mucus secretion from nose (3/10), reduced response to sound (2/10), splayed gait (2/10), labored breathing (1/10), head flicking (1/10), paw flicking (1/10), absence of pinna reflex (1/10), ptosis (1/10), reduced righting reflex (1/10), reduced stability (1/10), rubbing chin along floor (1/10), and chromodacryorrhea (1/10). Most effects subsided by day 1; however, hunched postures, piloerection, irregular breathing, and/or splayed gait showed variable persistence in affected animals through day 2 out to day 9. Effects had completely subsided from all animals by day 10.

C. Body Weight: Upon comparison of the 0-, 7-, and 14-day data, no significant effect on body weight was observed in male animals 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 increased an average of 24%. In comparison, 2/5 females exhibited slight weight losses (<2.5% ↓) between 0 and 7 days. All females gained weight between 7 and 14 days, and exhibited an overall mean increase of 13%.

D. Necropsy: Necropsy after 14 days revealed red spots on the lungs of one male. No other abnormalities were observed. In addition, no treatment-related effect on lung weight was observed.

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.

5