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KBR 3023

Acute Inhalation Study (870.1300)

EPA Reviewer: John E. Whalan
Registration Action Branch 2 (7509C)

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EPA Work Assignment Manager: S. Diwan, PhD
Registration Action Branch 1 (7509C)

DATA EVALUATION RECORD

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

OPP Guideline Number: §81-3

DP BARCODE: D241232
P.C. CODE: 070705
EPA REG. NO.: 3125-LRE

SUBMISSION CODE: S534142
TOX. CHEM. NO.:

TEST MATERIAL (PURITY): KBR 3023 (99.1% purity)

SYNONYMS: 2-(2-Hydroxyethyl)-1-piperidinecarboxylic acid; 1-(1-methylpropoxycarbonyl)-2-(2-hydroxyethyl)piperidine; 1-methylpropyl 2-(2-hydroxyethyl)-1-piperidine-carboxylate

CITATION: Pauluhn, J. (1990) KBR 3023: study for acute inhalation toxicity in the rat to OECD Guideline No. 403. Bayer AG, Department of Toxicology, Wuppertal, Germany. Laboratory Study Number T1033186. June 13, 1990. MRID 44408709. Unpublished.

SPONSOR: Bayer Corporation, Agricultural Division, 17745 S. Metcalf, Stilwell, KS.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 44408709), groups of five young adult SPF-bred Wistar rats/sex were dynamically exposed by nose-only inhalation to KBR 3023 (99.1% purity) aerosol at analytical concentrations of 2.153 or 4.364 mg/L for 4 hours. The test substance was formulated as a 75% concentration with polyethylene glycol 400:ethanol (1:1, v:v). Historical vehicle control data using ten animals/sex were provided. Animals were observed for clinical signs of toxicity and mortality for up to 14 days postexposure.

Inhalation LC_{50} >4.364 mg/L (males and females)
NOAEL = 4.364 mg/L (slight body weight anomalies)

KBR 3023 is classified as **TOXICITY CATEGORY IV** based on the observed LC_{50} values in both sexes.

All animals survived and appeared normal during the 14-day observation period. Overall, a slight dose-dependent relationship on body weight gain was apparent in both sexes. Males from the control, 2.153-, and 4.364-mg/L groups gained averages of 38, 29, and 26%, respectively, and

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females from the three groups gained averages of 6.4, 5.9, and 4.4%, respectively. Necropsy after 14 days revealed no treatment-related gross abnormalities.

This study is classified **Acceptable (§870.1300)** 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: KBR 3023
   Description: Clear colorless liquid
   Lot/Batch #: 19009/89
   Purity: 99.1%
   Density: 1.134 g/mL (temperature not specified)
   CAS #: 119515-38-7

2. Vehicle and/or positive control: The test substance was diluted to 75% in polyethylene glycol 400:ethanol (1:1, v:v) prior to use.

3. Test animals: Species: Rat
   Strain: Bor:WISW(SPF-Cpb)
   Age: Young adult (2-3 months)
   Weight: 171-193 g males; 171-191 g females (test and control groups)
   Source: Winkelmann, Borchen, Kreis Paderborn
   Acclimation period: ≥7 Days
   Diet: Altromin R 1324 Diet for Rats and Mice, *ad libitum*
   Water: Tap water, *ad libitum*
   Housing: Five/cage
   Environmental conditions:
   Temperature: 22 ± 2°C
   Humidity: Approximately 50%
   Air changes: Approximately 10/Hour
   Photoperiod: 12-Hour light/dark cycle

B. STUDY DESIGN and METHODS:

1. In-life dates: September 7-22, 1989

2. Exposure conditions: An cylindrical dynamic 20-L nose-only exposure chamber (Rhema Laboratories, Germany) constructed of PVC and equipped with radial animal ports was used in the study. During exposure, plexiglass tubes, each containing a single animal, were attached to the chamber with the nose portion of the cone protruding into the chamber. The exposure tubes (Rhema Labs) were designed so that the rat's tail was outside the tube, whereby preventing hyperthermic effects.

To generate test atmosphere, 75% KBR 3023 in polyethylene glycol 400:ethanol was delivered via a Braun infusion pump into a binary jet atomizer (Rhema Labs) using conditioned (water, dust and oil were removed) compressed air. The resultant aerosol was drawn through a 2-L baffling chamber prior to entering the top of the exposure chamber. During all exposures, the airflow through the chamber was maintained at approximately 10 L/min (equivalent to 27 chamber turnovers/hour), and the time required for 95% equilibration was about 6 minutes.

The nominal and analytical chamber concentrations are presented in Table 1. The actual test atmosphere concentration was determined analytically following equilibration, at mid-test, and towards the end of each exposure period. Samples (10 L) were collected from the animals' breathing zone using glass tubes filled with cotton wool. The cotton wool was extracted with carbon tetrachloride, and aliquots of the extracts were analyzed for KBR 3023 by gas chromatography in conjunction with flame-ionization detection (GC/FID). Results were adjusted for purity (99.1%).

TABLE 1. Exposure conditions

Nominal Conc. (mg/L)	Mean Analyt. Conc. (mg/L)	Mean Vehicle Conc. (ppm)	MMAD (µm)	GSD	Particles ≤5 µm
Control	0.0	20	N/A	N/A	N/A
15.0	2.153[a]	20	1.62	1.44	100
37.5	4.364[a]	50	1.80	1.49	100

[a]>Limit concentration

Particle size was apparently determined only once during each test exposure using a TSI-APS 3300 aerodynamic particle sizer equipped with a laser velocimeter. Each sample was collected for 30 seconds from the animals' breathing zone. The mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and percentages of particles ≤5 µm were calculated; values are reported in Table 1.

The temperature, recorded at 10-minute intervals, averaged 22 °C for both test exposures. The relative humidity, also recorded at 10-minute intervals, averaged 15.0% for the 2.153-mg/L exposure and 27.9% for the 4.364-mg/L exposure. Although not monitored, the turnover rate (27/hour) ensured an oxygen content of ≥19%.

3. Animal assignment and treatment: Animals were assigned to the test groups noted in Table 2. Rats were exposed to either 75% KBR 3023 or vehicle via nose-only inhalation for 4 hours. Animals were observed for signs of toxicity and/or mortality several times following exposure and twice daily thereafter for up to 14 days. Body weights were recorded at 0 (prior to exposure), 3, 7, and 14 days. At 14 days, all survivors were sacrificed, necropsied, and examined for gross pathological changes.

Table 2. Mortality/animals treated

Mean Analytical Conc. (mg/L)	Male	Female	Combined
Control[a]	0/10	0/10	0/20
2.153	0/5	0/5	0/10
4.364	0/5	0/5	0/10

[a]Vehicle control studies are conducted every 3 months.

4. Statistics: Body weight gains were evaluated by means of an analysis of variance. The homogeneity of the variances between the groups was checked with the Box test, and if a difference was noted, a pairwise *post hoc* comparison of the groups was made using Games and Howell's modification of the Tukey-Kramer significance test.

II. RESULTS AND DISCUSSION:

A. Mortality: Mortality data are presented in Table 2. All animals survived the 4-hour exposure and 14-day observation periods.

Inhalation LC_{50} >4.364 mg/L (males and females)

B. Clinical observations: No signs of toxicity were observed in test or control groups.

C. Body Weight: The mean percent change in body weights during the study is presented in Table 3. Upon comparison with the control group, statistically-significant ($p = 0.05$)

decreases were observed in males and females exposed at 2.153-mg/L between 3-7 days, and in males exposed at 4.364-mg/L between 0-3 and 3-7 days. Overall (0-14 days), a slight dose-dependent relationship was apparent in both sexes, whereas males from the control, 2.153-, and 4.364-mg/L groups gained averages of 38, 29, and 26%, respectively, and females from the three groups gained averages of 6.4, 5.9, and 4.4%, respectively.

Table 3. Body Weight Changes (%)

Mean Analytical Conc. (mg/L)	Interval (Days)			
	0-3	3-7	7-14	0-14
Male				
Control	6.4	15	13	38
2.153	5.1	4.0*	17	29
4.364	0.96*	8.2*	15	26
Female				
Control	0.83	1.4	4.0	6.4
2.153	2.0	-1.9*	5.8	5.9
4.364	-0.97	0.33	5.1	4.4

[a] Percentages derived from data on pages 39-51 in the study report.
* Significantly different from control group at 0.05 level.

D. Necropsy: Necropsy after 14 days revealed no treatment-related gross abnormalities.

E. Deficiencies: Particle size determination should have been conducted hourly during each exposure period. In this study, only one sampling/exposure was collected. It was apparent from the limited data that the aerosol was within the ideal MMAD range of 1-4 µm. Therefore, this deficiency is considered minor.

Although the humidity levels during both test exposures (averages of 15 and 28%) were less than the 40-60% limits set forth in Subdivision F guidelines, this deficiency should have no significant effect on the results of the study and is considered minor.