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# DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation Toxicity Study Guideline: 81-3

HED PROJECT NO.: 1-1237 CASWELL NO.: 545E MRID NO.: 417994-04

TEST MATERIAL: Sulfluramid (98.2% linear and 1.8% branched isomers)

SYNONYMS: N-Ethyl perfluoro-octane-sulfonamide

STUDY NUMBER(S): Hazelton UK Study No. 6443-788/1

SPONSOR: Griffin Corp., P.O. Box 1847, Valdosia, GA 31603-1847

TESTING FACILITY: Hazelton UK, Otley Rd., Harrogate, England

TITLE OF REPORT: Acute Inhalation Toxicity Study - $LC_{50}$ Rats (4 Hours Exposure); Test article: Sulfluramid

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REPORT ISSUED: November 14, 1990

CONCLUSIONS:

Two groups of 5 male and 5 female rats/dose group, one group was exposed to aerosolized Sulfluramid (98.2% linear and 1.8% branched isomers) in acetone and the other group was exposed to aerosolized acetone for four hours, and observed for a period of 14 days.

Signs of toxicity observed included clinical signs such as piloerection, lethargy, salivation, nasal secretion, and sore ear. A slight reduction of body weight gain occurred in the treated females, and kidney nephrosis was observed in four control males, eyesore in two treated females, and fur loss in one treated male.

Since no deaths occurred at the maximum practical concentration used in the study, the acute $LC_{50}$ could not be accurately computed. The acute median LC50 is assumed to be greater than 4.379 mg/L and this is close to the limit concentration of 5 mg/L. Toxicity category III.

This study satisfies data requirement for an acute inhalation toxicity study in rats, Subdivision F guideline 81-3.

Classification: Core-minimum

Study Title: Acute Inhalation Toxicity Study-$LC_{50}$ Rats (4 Hours Exposure). Test article: Sulfluramid

Test Material: Sulfluramid consisting of 98.2% linear and 1.8% branched isomers; white crystalline powder; Batch # RO92789EH-1; Vehicle used was acetone.

Test Animals: Crl:CD(SD)BR rats, age 6-8 weeks old on arrival and body weight ranging from 180 to 200 g were acclimated for at least five days prior to dosing.

HUSBANDRY OF TEST ANIMALS (during non-exposure periods)

Feed and Water: SQC Rat and Mouse Maintenance Diet no. 1, Expanded (from Special Diets Services Ltd, Witham) and local tap water were provided ad libitum. Food and water were withheld during exposure period.

Environmental Parameters: Maintained under controlled environment; a 12-hour light/dark cycle; temperature range of 19 - 25°C, and relative humidity 30-70%; minimum air exchanges of 15 changes/hour. Rats were housed in groups of five in stainless steel wire mesh cages.

PROCEDURES

Test Article Formulation: The test article was mixed with acetone to form a 66% solution in order to produce an aerosol of small particles.

Selection of Test Animals: Test animals were assigned by sex on arrival, one to each cage, until each cage contained a maximum of five rats. Cages were also arbitrarily allocated to study. Five males and five females per dose group were used as the control and the treated groups.

Exposure: The test article was administered by whole body inhalation for a period of four hours.

Experimental Design: An initial group was exposed at a chamber concentration of 4.379 mg/L. The nominal concentration was 9.388 mg/L of test article and 4.708 mg/L of acetone vehicle. These concentrations were determined to be the most practical in view of the potential flammability and toxicity of acetone. The controls were exposed under similar conditions to an atmosphere of acetone. All survivors were held for a 14-day observation period and then they were sacrificed.

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<u>Chamber Parameters</u>: Exposures were conducted in an exposure chamber (1.4 $m^3$) using a continuous flow exposure system. Two Sachsse nebulizers, supplied with compressed air, were used alternately to produce the atmosphere of the test article. Two nebulizers were used to prevent test article crystallization during nebulization. Only one nebulizer was used to produce the vehicle (acetone) dose group atmosphere. The chamber flow rates were monitored and recorded at half-hourly interval. Exposure chamber temperature, relative humidity, and oxygen were measured continuously and recorded at half-hourly intervals throughout the four hours exposure period.

<u>Determination of Exposure Concentration</u>: The analytical exposure level was determined gravimetrically by hourly sampling using a filter paper over a 3-minute period. The filter was weighed before and after sampling and the measured concentration of the test atmosphere calculated, by dividing the total weight gain (mg) by the volume (liter) of the sample. The concentration of the vehicle (acetone) was determined every half hour using a Miran 1A infra-red gas analyzer. The nominal concentration of the test article in the exposure chamber was calculated by dividing the weight of the test article (mg) time % test article (w/) in solution by airflow rate (L/min) times duration (min) time 100.

<u>Particle Size Determination</u>: Samples for particle size distribution assessment were drawn once per hour using a Sierra Marple Cascade Impactor, with six separators corresponding to the mass median aerodynamic diameters of 0.5, 0.9, 1.6, 3.5, 6.0, and 9.8 μm. The cumulative percentage by weight was plotted and the point at which the cumulative distribution crossed the 50 percentile was determined to be the mass median aerodynamic diameter.

<u>$LC_{50}$ Determination</u>: A calculation of median lethal concentration and 95% confidence limits was performed according to the standard method of Litchfield and Wilcoxon.

<u>Observations during Exposure</u>: All animals were observed immediately prior to exposure, hourly during exposure and during the remainder of the day, and then once daily thereafter for 14 days. Individual body weights were recorded prior to and after exposure, on days 8 and 15 of the study and at necropsy.

<u>Pathology</u>: Postmortem gross examinations were performed on all test animals, which included nasal passages, all respiratory tracts, and a full internal and external examination. Lung, bronchi and trachea were weighed. All gross lesions were fixed in formalin for further histopathological evaluation.

## RESULTS

Chamber Parameters: Chamber temperatures were between 18 - 21°C and the relative humidities were around 41% to 51%. The oxygen level in the exposure chamber ranged from 20.9 to 21.2% for the control and 20.8 - 20.9% for the treated animals. The exposure chamber diluent air flow rates were 300 L/min for both the control and the treated groups.

Chamber Monitoring and Mortality: The nominal and mean measured concentrations (mg/L), and mortality of test animals were as follows:

| Group | Nominal Concentration (mg/L) | Mean Measured Concentration (mg/L ± SD) | Mortality |
|---|---|---|---|
| I<br>Acetone | 4.910 | 4.470 ± 1.067 | 0 |
| II<br>Test Article<br>Acetone | <br>9.388<br>4.708 | <br>4.379 ± 0.418<br>5.162 ± 0.177 | <br>0<br>0 |

mg = milligram; L = Liter; SD = Standard Deviation

As seen from the above Table, the mean measured concentration of the atmosphere of the test article was 4.379 ± 0.418 mg/L expressed in terms of gravimetric concentration. This was close to limit concentration of 5 mg/L. The nominal concentration in term of the test article was 9.388 mg/L. The measured acetone concentration for the test article (5.162 ± 0.177 mg/L) and control (4.470 ± 1.067 mg/L) groups were comparable. All animals survived through termination.

Particle Size Determination: The particle size distribution and the estimated percentages of particles which were less than 1μm are as follows:

| | Mass Median Diameter (μm) | | | | MMAD (μm ± SD) |
|---|---|---|---|---|---|
| | 1st hr | 2nd hr | 3rd hr | 4th hr | |
| Group II | 1.41 | 1.48 | 1.18 | 1.42 | 1.37 ± 0.13 |
| Estimated % of Particles of < 1μm | 33 | 28 | 38 | 28 | 32 ± 5 |

MMAD = Mean of the Mass Median Aerodynamic Diameter; SD = Standard Deviation.

As seen from the Table on the previous page, the mean MMAD of the particle in the atmosphere for the treated group was 1.37 ± 0.13 μm. The amount of particle size of less than 1μm averaged 32%. This indicates that the mean diameter of the aerosol droplets was within the rats' respirable range.

Mortality and $LC_{50}$: As indicated earlier, no mortality occurred at the maximum practical concentration used in the study, hence acute $LC_{50}$ could not be calculated. It is assumed that the acute median $LC_{50}$ is greater than 4.379 mg/L.

Clinical Signs: During the post-exposure period the following were observed in the treated rats: piloerection (all 5♂ and 5♀), lethargy (all 5♂ and 5♀), salivation (1♀), nasal secretion (1♂), and sore ear (1♀). These signs abated after 24 hours.

Body weights: Individual body weights are presented in Appendix A. As seen from this Appendix, body weight losses were observed following exposure. During week one the control and treated male groups gained 12 and 3 percent, respectively. During the same week, control females gained 6 percent while the the treated females loss 3 percent of their body weight. Except for one treated female, all rats gained weight during week two of the study.

Lung Weights: The lung weight data is presented in Appendix B. As seen from this Appendix, there were no differences in lung weights that could be considered as treatment-related.

Macroscopic Pathology: Gross pathology findings are presented in Appendix C. Kidney nephrosis was observed in four control males, eyesore in two treated females, and fur loss in one treated male.

DISCUSSIONS AND CONCLUSIONS

Although the mean MMAD was slightly larger than 1μm in the test atmosphere, but since more than 25% respirable particles of one micron or less were generated, this study is acceptable. Signs of toxicity observed were slight, including clinical signs and a slight reduction of body weight gain in the treated females.

Since no deaths occurred at the maximum practical concentration used in the study, the acute LC50 could not be accurately computed. The acute median $LC_{50}$ is assumed to be greater than 4.379 mg/L.

A FIFRA GLP Compliance Statement and a Quality Assurance Statement were provided, signed and dated.

Classification: Core-minimum