1/24/2001

Glycolic Acid [81-3] Acute Inhalation Toxicity/Rat

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DATA EVALUATION REPORT

STUDY TYPE:	Acute Inhalation/Rat OPPTS 870.1300 [§ 81-3]
DP BARCODE:	D270915
SUBMISSION CODE:	S576708
P.C. CODE:	000101
Case:	062360
TEST MATERIAL:	Glycolic Acid
SYNONYMS:	Hydroxyethanoic acid 70% solution; Acetic acid, Hydroxy-70% solution
CITATION:	Bamberger, J. Glycolic Acid 70% Solution: Inhalation Median Lethal Concentration (LC_{50}) Study in Rats. E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714-0050. Laboratory Project ID: DuPont 1516, Nov. 2, 1998; MRID 449753-02; Unpublished.
SPONSOR:	E.I. du Pont de Nemours and Company, Inc. Wilmington, DE

EXECUTIVE SUMMARY:

In a nose only 4 hour inhalation study [MRID 449753-02], Sprague-Dawley rats [Crl:CD®(SD) IGS BR] were exposed to Glycolic acid (70% a.i.) at a measured concentration of 5.2 [5♂,5♀], 3.8 [10♂], 2.1 [10♂] or 0.60 [10♂] mg/l. During the 14 or 15 day recovery period, animals were weighed and observed for clinical signs of toxicity. Gross pathology was performed on all surviving rats. Microscopic examination was performed on the nose, larynx, pharynx and lungs.

The control group consisting of 10♂ were exposed to air only, 5 of these animals were sacrificed 24 hours after exposure for microscopic examination of the nose, larynx, pharynx and lungs. The remaining 5 rats were allowed to recover for 14 days. The animals were then sacrificed for microscopic pathology of the nose, larynx, pharynx and lungs.

The satellite group consisted of 4 groups [5.2, 3.8, 2.1, or 0.60 mg/l] of 5 male rats that were concurrently exposed to the above concentrations of glycolic acid. These animals were sacrificed ~24 hours after exposure for microscopic examination of the nose, larynx, pharynx and lungs.

The mass median aerodynamic diameter (MMAD) of the aerosol generated ranged from 2.3 to 3.1 µm with 8.0 to 18% of the particles <1 µm, 50 to 62% of the particles were <3 µm and 93 to 99% of the particles <10 µm.

Clinical signs of toxicity immediately following exposure included gasping, lung noise, hunched posture, and nasal and ocular discharge. Clinical signs noted during the recovery period included the above and lethargy, sore eyes, sore noise, sore chin and vocalization.

An exposure of 5.2 mg/l of the test compound produced a 60% mortality (3/5) in the male but no mortality in the female (0/5). Subsequent exposures were conducted with male rats only at 3.8, 2.1 or 0.60 mg/l. Mortality was 60%, 20% and 0% respectively. In both the above studies, animals died either during exposure or within 1 to 12 days following exposure to the test substance.

No mortality was observed in male rats designated as satellite animals or in control animals.

Microscopic changes attributable to tissue irritation were seen in the nose, larynx, and lung of male rats and the nose and larynx of female rats. Mild to severe laryngeal ulceration was present all treated male groups and mild effects were present in the female group.

The 4 hour inhalation LC_{50} in female rats is: >5.2 mg/l, and 3.6 mg/l in male rats. Glycolic acid is classified in Toxicity Category IV in both sexes (LC_{50} >2.0 mg/l).

This acute inhalation study in the rat is **Acceptable** and satisfies the guideline requirement [§ 81-3] for an Acute Inhalation study in the rat.

COMPLIANCE

Statements of Quality Assurance, Good Laboratory Practice compliance and No Data Confidentiality Claims were signed and dated.

I. MATERIALS

A. Test Material, technical

Test Compound:	Glycolic Acid
Purity:	70.58% a.i. (Total acid based on saponification)
Lot:	[Haskell No.] 23274
Synonym:	Hydroxyethanoic acid 70% solution; Acetic acid, hydroxy 70% solution
Description:	Pale-yellow Liquid
Storage:	NA
Stability:	The test substance appeared to be stable under the conditions of the study.

B. Test Animals

Species:	Rat
Strain:	Sprague-Dawley [Crl:CD®(SD)IGS BR]
Source:	Charles River Laboratories, Inc., Raleigh, NC
Groups:	Nine (9) groups consisting of LC_{50}, satellite and control groups.
Feed:	PMI Certified Rodent LabDiet® 5002, *ad-libitum*
Water:	*ad-libitum*
Weight:	♂: 237 to 295 gm, ♀: 198 to 202 gm at time of exposure
Age:	≈8 weeks old at time of exposure
Acclimatization:	6 days prior to testing
Housing:	Animals were housed singly or in pairs in
elevated	stainless steel cages with wire mesh flooring.
Environmental:	Temperature: 23° ± 1° C Relative humidity 50% ± 10% Photoperiod: 12 hour light/dark cycle

II. METHODS

In life dates: start: 7/14/98; end: 8/28/98

Introduction

In a nose only, 4 hour inhalation study, rats [Crl:CD®(SD) IGS BR] were exposed to measured chamber concentrations of: 5.2 [5♂,5♀], 3.8 [10♂], 2.1 [10♂] or 0.60 [10♂] mg/l of glycolic acid. During the 14 or 15 day recovery period, animals were weighed and observed for clinical signs of toxicity. Gross

pathology was performed on all surviving rats. Microscopic examination was performed on the nose, larynx, pharynx and lungs.

The control group consisting of 10♂ were exposed to air only, 5 of these animals were sacrificed 24 hours after exposure for microscopic examination of the nose, larynx, pharynx and lungs. The remaining 5 rats were allowed to recover for 14 to 15 days. The animals were then sacrificed for microscopic pathology of the nose, larynx, pharynx and lungs.

The satellite group consisted of 4 groups of 5♂ rats were concurrently exposed to 5.2, 3.8, 2.1 or 0.60 mg/l of glycolic acid. These animals were sacrificed ~24 hours after exposure for microscopic examination of the nose, larynx, pharynx and lungs.

A. Atmosphere Generation/Chamber Parameters/Analysis/etc.

1. Atmosphere Generation (See MRID 449753-02 for diagram of generation apparatus)

Chamber atmospheres were generated by aerosolization of the test substance in air with a Spraying Systems nebulizer. The test substance was metered into the nebulizer with a Harvard Apparatus Model 22 Syringe Infusion Pump. Filtered [baseline] air, induced at the nebulizer, atomized the test substance and carried the aerosol into the exposure chamber. Chamber concentrations of glycolic acid were controlled by varying the test substance feed rate to the atmosphere generator.

The control atmosphere was generated by passing high pressure air through the Spraying Systems nebulizer and into the exposure chamber.

Test atmosphere were exhausted through a cold trap followed by an MSA charcoal/HEPA filter cartridge prior to discharge into the fume hood.

2. Chamber Construction and Design

The exposure chamber was constructed of glass (cylindrical) with a nominal volume of 34 L. A dispersion plate inside the chamber promoted uniform distribution of the test atmosphere.

3. Exposure Mode

During exposure, rats were individually restrained in perforated stainless steel cylinders with conical nose pieces. The re-strainers were inserted into the polymethylacrylate faceplate of

the exposure chamber so that only the nose of each rat extended into the chamber.

4. Characterization of Chamber Atmosphere

During the trails for generation methods, a study of chamber distribution of aerosol concentration was performed. No statistical differences were observed with the Student's ($p<0.05$), when samples taken a 3 locations in the face plate were compared to 4 samples taken from the sampling port. Therefore, the test substance was considered to be homogeneously distributed throughout the exposure chamber.

5. Test Substance Sampling and Analysis

The atmospheric concentration of glycolic acid was determined by gravimetric analysis at approximately 30 or 45 minute intervals during each exposure. Known volumes of chamber atmosphere were drawn from the reference sampling port through a 25 mm filter cassette that contained a pre-weighed Gelman glass fiber (Type A/E) filter. The filters were weighed on a Cahn Automatic Electrobalance, placed in a desiccator for 1 or 2 days, and reweighed on the same balance. The atmospheric concentration of glycolic acid was calculated from the difference in the pre- and post-sampling dry filter weights divided by the volume of chamber atmosphere sampled.

Chamber concentrations of: 5.2, 3.8, 2.1 or 0.60 mg/l of glycolic acid were recorded by gravimetric analysis.

6. Particle Size Distribution

Two samples were used to determine particle size distribution, mass median aerodynamic diameter (MMAD) and percent particles <1.3 and <10 µm diameter) were taken during each exposure with a Sierra® Series 210 Cyclone Preseparator/Cascade Impactor and Sierra® Series 110 Constant Flow Air Sampler.

The MMAD of the aerosol generated ranged from 2.3 to 3.1 µm with 8.0 to 18% of the particles <1 µm, 50 to 62% of the particles were <3 µm and 93 to 99% of the particles were <10 µm.

7. Environmental Monitoring

Chamber air flow was set at the beginning to achieve a least 12 air changes per hour and was monitored every 30 minutes during each exposure. Chamber temperature was targeted at 22±2° C. And recorded every 30 minutes. Chamber relative humidity was targeted

5

at 50±10% and recorded 3 times during the exposure. Chamber oxygen concentration was targeted at 19% and recorded 3 times during each exposure.

Chamber temperature ranged from 20° to 25° C., the oxygen concentration was 21% and the relative humidity ranged from 53 to 56%.

III. RESULTS

A. Biological

1. Mortality/Clinical observations

Animals in the LC_{50} group were observed for mortality and clinical signs. Control and satellite animals were not observed for clinical signs.

An exposure of 5.2 mg/l produced a 60% mortality (3/5) in the male but no mortality in the female (0/5). One of the male rats died during the exposure and the remaining 2 male rats died 9 and 12 days following exposure. Subsequent exposures were conducted with male rats only at 3.8, 2.1 or 0.60 mg/l. Mortality was 60%, 20% and 0% respectively. In both the above studies, animals died either during exposure or within 1 to 10 days following exposure.

The 4 hour inhalation LC_{50} in female rats was >5.2 mg/l, in male rats 3.6 mg/l. Glycolic acid is classified in Toxicity Category IV.

Clinical signs of toxicity were collected for the rats designated for the LC_{50} determinations. Clinical signs of toxicity could not be assessed during the exposure because the density of the atmosphere prevented the observation of the rats in the restrainers. Clinical signs of toxicity immediately following exposure included gasping, lung noise, hunched posture, and nasal and ocular discharge. Clinical signs noted during the recovery period included the above and lethargy, sore eyes, sore noise, sore chin, and vocalization.

2. Body Weights

During the 14 or 15 day recovery period, LC_{50} animals were weighed at least once per week. Moderate to severe body weight loss was noted the day after exposure, except for the female rats at 5.2 mg/l which experienced weight losses of <5.1%. During the recovery period, a single rat in the 5.2 mg/l group and all rats

in the 3.8, 2.1, or 0.60 mg/l groups generally experienced an overall weight gain.

Recovery and satellite animals were not weighed.

3. Pathology

All surviving rats designated for LD_{50} determinations were sacrificed by CO_2 asphyxiation and exsanguination.

(a) Gross

No gross pathology was performed on the satellite or control animals.

Four (4) male animals at 3.8 mg/l were not examined for gross necropsy. Lack of a gross evaluation in these animals did not affect the outcome of the study.

(b) Microscopic Observations

Microscopic examination, using H&E staining, was performed on the nose, larynx, pharynx and lungs of the LC_{50} animals at 14 or 15 days and satellite animals 24 hours after exposure. Control animals were examined both at 24 hours after exposure or at 14 to 15 days after exposure. [Note: In both the control and satellite animals, both the 24 hour after exposure and the 14 to 15 day after exposure animals were combined into one table [Table 9, pp. 32 to 34] in the original report]. The discussion below is a composite of these 2 time periods for the LC_{50} and satellite groups.

Test substance associated microscopic changes attributable to tissue irritation were seen in the nose, larynx, and lungs of male rats and nose and larynx of female rats. Minimal to mild nasal lesions seen in all treated groups consisted of degeneration/regeneration of respiratory and/or olfactory epithelium.

In the respiratory region, changes were in the mucosa lining the dorsal, middle and ventral meatuses and on the septum and turbinates of the anterior nose. The changes consisted of loss of columnar and/or transitional cells and denudation of mucosal epithelium or presence of degenerate acidophilic cells or basophilic regenerative cells.

In the olfactory region, changes were on the septum and ethmoid turbinates and ranged from segmental loss of neuroepithelial

cells, the usual, to occasional loss of neuroepithelial sustentacular cells, resulting in mucosal denudation.

Mild to severe laryngeal ulceration was present all treated male groups and mild effects were present in the female group. There was no clear dose response in regard to lesion severity at lower exposure levels, but exposure to 3.8 mg/l and above was associated with severe ulcerations.

Minimal to mild subacute\chronic inflammation was present in lungs exposed to 2.1, 3.8, and 5.2 mg/l of glycolic acid.

Control animals at both time periods were considered to be unremarkable.

IV. CONCLUSION

The 4 hour inhalation LC_{50} in female rats is: >5.2 mg/l, and 3.6 mg/l in male rats. Glycolic acid is classified in Toxicity Category IV in both sexes (LC_{50} >2.0 mg/l). Test substance associated microscopic changes attributable to tissue irritation were seen in the nose, larynx, and lungs of male rats and nose and larynx of female rats. Mild to severe laryngeal ulceration was present all treated male groups and mild effects were present in the female group.