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Tox. Branch II, Section IV (H7509C)
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Tox. Branch II, Section IV (H7509C)

DATA EVALUATION REPORT

| | |
|---|---|
| STUDY TYPE: | Acute Inhalation Toxicity Study (81-3) |
| MRID NO.: | 421695-01 |
| TEST MATERIAL: | 7-oxabicyclo [2.2.1] heptane - 2,3 dicarboxylic acid |
| SYNONYMS: | Endothall Technical |
| SPONSOR: | ATOCHEM North America<br>Three Parkway<br>Phila. PA 19102 |
| TESTING FACILITY: | Life Science Research Limited<br>Eye, Suffolk, England 1P23 7PX |
| REPORT NUMBER: | 88/PSV024/0598 |
| TITLE OF REPORT: | Enothall Technical: Acute Inhalation Toxicity Study in the Rat; Final report |
| AUTHOR: | S. Cracknell |
| REPORT ISSUED: | July 20, 1990 |
| QUALITY ASSURANCE: | Quality assurance documentation was provided on p. 3. |
| CONCLUSIONS: | $LC_{50}$ (4 hour, inhalation): males - 1.27 mg/l; females - 2.20 mg/l;<br>males and females combined - 1.51 mg/l. |
| CLASSIFICATION: | Core - guideline<br><br>This study satisfies the guideline requirements (81-3) for an "Acute Inhalation Toxicity Study". |
| TOXICITY CATEGORY: | -III- as per 40 CFR 156.10 p. 79, 7/1/89. |

A. MATERIALS

| | | |
|---|---|---|
| Test Compound: | Chemical: | 7-oxabicyclo [2.2.1] heptane - 2,3 dicarboxylic acid |
| | Label: | Endothall Technical |
| | Lot No. | B14-37 |
| | Description: | fawn crystalline, lumpy powder |
| | Purity: | 89.47% a.i. at start of the study |
| | Stability: | stable at room temperature |

Purity

The material, as received, had a purity of 89.47% a.i. The purity was again reverified at the end of the study and found to be 90.8%, showing that the material was stable under the test conditions.

| | | |
|---|---|---|
| Test Animal: | Animal: | albino rat |
| | Strain: | CD Sprague-Dawley derived |
| | Groups: | four (4) groups of 10 animals/sex |
| | Weight: | males 244-275 gm; females 230-259 gm at start of the study |
| | Age: | approximately 7-12 weeks of age at start of the study |
| | Source: | Charles River Laboratories (U.K.) |

Animal Husbandry

Rats were conditioned for a least 6 days prior to the study initiation. All animals received LAD 1 chow, Labsure, Manea, Cambridgeshire, England and water ad libitum at all times except during the exposure.

Statistics

The method of Finney (probit analysis) was used to calculate the $LC_{50}$ and 95% confidence limits.

The Students "t" test was used to calculate "the significance of inter-group differences in organ weight for animals that survived the exposure." Values for the male survivors in the 1.678 and 2.472 mg/l groups were pooled before analysis because of the high mortality rate in these groups.

B. STUDY DESIGN

Forty (40) animals per sex were assigned to 4 test groups and exposed to the test material by inhalation at concentrations of 0.446, 1.678 mg/l and 2.472 mg/l of air for 4 hours; the control group received clean dry air for the 4 hour period.

The day of exposure was counted as day 1, Animals were observed for a total of 14 days and weighed on day 15.

Table 1

Animal Test Group Assignments[1]

| Group | Treatment | Conc. (mg/l[2]) |
|---|---|---|
| 1 | Control | 0.0 |
| 2 | Enothall | 0.446 |
| 3 | Endothall | 1.678 |
| 4 | Endothall | 2.472 |

[1]Adapted from original report, Vol 2 p. 10.
[2]mg of the test compound per liter of air.

Exposure Chamber

The exposure chamber consisted of a 60 liter aluminum alloy cylinder. The cylinder contained numerous exposure ports that could be mated to polycarbonate restraint tube(s) containing the rat. Since only the animal's snout protruded from the restraint tube which was attached to the exposure port, a "nose only" exposure of the animal was effected.

A large cabinet equipped with an exhaust fan and collection filter enclosed the exposure cylinder and generation apparatus.

The chamber was equilibrated for 5.5 minutes, the theoretical time required for the dust concentration to reach 90% of the nominal value, after which the 4 hour exposure period was then started.

Sample Preparation and Dust Generation

The test substance was passed through an 80 um screen of an ultracentrifuge mill and then hand-milled in a mortar and pestle. The test material was packed into a Wright Dust Feed Mechanism to produce the test atmosphere.

Concentration Measurements

The actual concentration was determined by gravimetric analysis based on samples taken at 5 intervals. Samples were collected at a flow rate of 4 l/min.

Particle Size Determination

Particle size distribution of the test material aerosol was determined each hour during the exposure period at a flow rate of 2 l/min. through a cascade impactor located on a spare animal exposure port.

Inhalable diameter particles (<6.0 um equivalent aerodynamic diameter) were as follows: Group 2, 38.3 um, std. dev. ±2.8; Group 3, 33.7 um, std. dev. ±2.0; Group 4, 38.8 um, std. dev. ±5.2.

Airflow, Chamber Temperature and Relative Humidity

The chamber was operated at a flow rate of 25 l/min.

During the 4 hour study, the temperature ranged between 23.1 and 23.7° C. while relative humidity ranged from 37.3% in the control group to 43.1% in the high dose level group.

C. METHODS AND RESULTS

Observations

Animals were observed immediately before exposure, after exposure at 15 and 30 minutes and at 30 minute intervals during the 4 hour study. After the exposure, animals were observed each 30 minutes for the first 3 hours and then 2 times daily until the completion of the 14 day observation period.

Mortality

All deaths occurred after the 4 hour exposure period (Table 2).

Table 2

Mortality and Time of Death During the 14 Day Study[1,2]

| Day | Exposure Concentration (mg/l) Level 0 (M,F) | 0.446 (M,F) | 1.678 (M,F) | 2.472 (M,F) |
|---|---|---|---|---|
| 1 | -,- | 0,0 | 2,1 | 2,2 |
| 2 | -,- | 0,1 | 6,1 | 7,4 |
| 3 | -,- | -,- | -,- | -,- |
| 7 | -,- | -,- | -,- | -,1 |
| 8-14 | -,- | -.- | -,- | -,- |
| Total (M) | 0/10 | 0/10 | 8/10 | 9/10 |
| (F) | 0/10 | 1/10 | 2/10 | 7/10 |

[1]Adapted from Vol 2, p. 24.
[2]Total of 10 animals per group;
"-" = no deaths.

Signs During the 4 Hour Exposure

The rate of respiration was reduced in all groups treated with the test compound. Signs noted in the 1.678 and 2.472 mg/l dose groups were peripheral vasodilation, struggling and exaggerated respiratory movements. The authors note that these signs "were consistent with the inhalation of a highly irritating particulate atmosphere."

Signs During the Observation Period

During the 3 hours following exposure, exaggerated respiratory movements, reduced respiratory rate, rales, and hypoactivity occurred.

By day 10, the 0.446 mg/l and 1.678 mg/l concentration level animals had generally recovered from the major signs of toxicity. The one male animal that survived the 2.472 mg/l concentration group was noted to have exaggerated respiratory movements and a swollen abdomen until day 14.

Body Weight

Body weight was recorded daily throughout the study.

Moribund animals lost body weight before death. Body weight loss was noted for up to 4 days for males and up to 6 days for females

following exposure in the survivors. Female surviving animals regained their body weight by the end of the study. The 2 surviving male animals at 1.678 and the 1 surviving animal at 2.472 mg/l showed a decrease in the rate of weight gain when compared to the control animals on day 15. The absolute body weights at all dose levels at the end of the study were not remarkable (Table 3,4).

Table 3

Absolute Mean Body Weight(gm) in the Male[1]

| | Exposure Concentration Level (mg/l) | | | |
|---|---|---|---|---|
| Day | 0 | 0.446 | 1.678 | 2.472 |
| 1 | 256 | 253 | 258 | 262 |
| 2 | 261 | 227 | 214 | 221 |
| 4 | 275 | 238 | 223 | 209 |
| 5 | 284 | 253 | 234 | 200 |
| 12 | 326 | 305 | 289 | 285 |
| 15 | 346 | 327 | 308 | 312 |
| Rate of Body Weight Change | | | | |
| day 1 to 4 | 19 | -15 | -35 | -53 |
| day 4 to 15 | 71 | 89 | 85 | 103 |
| day 1 to 15 | 90 | 74 | 50 | 50 |
| Absolute Body Weight, day 15 | | | | |
| % | -- | - 6 | -11 | -10 |

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[1]Adapted from original report, p. 44.

Table 4

Absolute Mean Body Weight and Change (gm) in the Female[1]

| Day | Exposure Concentration Level (mg/l) 0 | 0.446 | 1.678 | 2.472 |
|---|---|---|---|---|
| 1 | 243 | 243 | 236 | 243 |
| 2 | 240 | 221 | 211 | 212 |
| 6 | 244 | 241 | 217 | 196 |
| 7 | 246 | 241 | 223 | 208 |
| 12 | 251 | 246 | 248 | 242 |
| 15 | 258 | 248 | 254 | 248 |
| Rate of Body Weight Change | | | | |
| day 1 to 6 | 1 | -2 | -19 | -47 |
| day 6 to 15 | 14 | 7 | 37 | 52 |
| day 1 to 15 | 15 | 5 | 18 | 5 |
| Absolute Body Weight, day 15 | | | | |
| % | -- | - 4 | -2 | - 4 |

[1]Adapted from the original report, p. 45.

Pathology

Surviving animals were anaesthetized with sodium barbital and sacrificed by exsanguination. All animals that died or were sacrificed during the study had specific organs weighed and were necropsied for gross pathology.

Organ Weight

The lungs with bronchi, liver and kidneys were weighed at the terminal sacrifice.

The lung weight of moribund animals appeared higher than the controls. The reviewer notes, however, that this effect might have been produced from the agonal events preceding death and, therefore, was not considered to be of biological significance.

In the 1.678 and 2.472 mg/l dose level females, lung weights and lung/body weight ratios of the survivors were higher than the corresponding control values. Male animals at the same dose level also showed an increase in these parameters, however, statistical significance was noted only sporadically at the 1.678 mg/l when compared to the corresponding controls (Table 5, 6).

Absolute liver and kidney weights of the male animals showed a non-statistically significant dose related decrease when compared to the controls (Table 5).

Table 5

Mean Organ Weight of Surviving Male Rats Treated with the Test Compound[1]

| Conc. (mg/l) | B.W.[2] (gm) | Lungs Abs. (gm) | Lungs Rel. (%) | Liver Abs. (gm) | Kidneys Abs. (gm) |
|---|---|---|---|---|---|
| 0 | 339 | 1.34 | 0.39 | 14.19 | 2.53 |
| 0.446 | 323 | 1.29 | 0.40 | 13.18 | 2.37[a] |
| 1.678+ | 301 | 1.49[c] | 0.50 | 11.98 | 2.36 |
| 2.472* | 303 | 1.53 | 0.50 | 12.48 | 2.15 |

[1]Adapted from the original report, p. 46.
[2]B.W. = body weight
* Values from 1 animal only.
+ values from 2 animals only.
[a]Significantly different from controls, $p<0.05$.
[c]Significantly different from the controls, $p<0.001$.

Table 6

Mean Lung Weight of Surviving Female Rats Treated with the Test Compound[1]

| Conc. (mg/l) | B.W.[2] (gm) | Lungs Weight Abs. (gm) | Lungs Weight Rel. (%) |
|---|---|---|---|
| 0 | 255 | 1.14 | 0.45 |
| 0.446 | 245 | 1.16 | 0.47 |
| 1.678 | 251 | 1.32[a] | 0.53[a] |
| 2.472 | 243 | 1.50[a] | 0.62[a] |

[1]Adapted from the original report, p. 47.
[2]B.W. = body weight
[a]Significantly different from the controls, $p<0.001$.

Incomplete collapse of the lung was seen in 3 moribund and 1 surviving animal exposed to 2.472 mg/l. The reviewer notes, that the gross pathology might have been produced from non-specific agonal events rather than from a true compound related effect. Other gross pathological observations in both treated and control animals were considered to be unremarkable.

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Summary

Under conditions of the study, the inhalation $LC_{50}$ (4 hours) for Endothall, technical per liter of air was calculated as follows:

Males: 1.267 mg/l (95% confidence limits 0.813-1.722 mg/l),
Females: 2.196 mg/l (95% confidence limits 0.862-3.530 mg/l),
Males and females combined: 1.514 mg/l (95% confidence limits 1.113-1.916 mg/l).

CONCLUSIONS:

$LC_{50}$ (4 hours, inhalation): males - 1.27 mg/l;
females - 2.20 mg/l;
males and females combined - 1.51 mg/l.