

FOR DU PONT USE ONLY

Copies to [REDACTED]

REVISED REPORT

E. I. du Pont de Nemours and Co., Inc.
Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road, P. O. Box 50,
Newark, Delaware 19711

HASKELL LABORATORY REPORT NO. 423-83

MR NO. [REDACTED]

Material Tested

Haskell No.

15,048

INHALATION APPROXIMATE LETHAL CONCENTRATION (ALC)
AND INTRAVENOUS AND INTRAPERITONEAL APPROXIMATE
LETHAL DOSES (ALD) OF [REDACTED]

I. SUMMARY:

A. Inhalation ALC: Groups of 6 male Crl:CD® rats were exposed for single, 4-hour periods to particulate atmospheres of [REDACTED] in air. Lungs from rats which died were examined pathologically.

An ALC for [REDACTED] is 42 mg/m³ (particulate concentration). According to Haskell Laboratory Toxicity Classifications, [REDACTED] is extremely toxic by inhalation.

Pathological examination of rats which died after exposure to 73 mg/m³ revealed elevated lung weights, and severe pulmonary congestion, edema and hemorrhage. These effects appear to be caused by damage to Type I pneumocytes, with consequent increased permeability of alveolar capillaries.

B. I.P. and I.V. Injection: Groups of male Crl:CD® rats were dosed by either I.P. or I.V. injection with various concentrations of [REDACTED] suspended in water. Rats which died were examined pathologically.

No deaths occurred in rats dosed intraperitoneally with up to 50 mg/kg. The ALD by I.V. injection is 500 mg/kg. The cause of death appears to be massive emboli formation in the alveolar capillaries. Rats surviving either I.P. or I.V. injection showed no significant adverse effects.

II. INTRODUCTION: The initial purpose of this study was to determine an inhalation ALC for [REDACTED]. Secondly, because of the marked difference between [REDACTED] oral and inhalation toxicity [REDACTED] has very low toxicity by oral dosing; [REDACTED] the I.P. and I.V. routes were investigated.

III. PROCEDURES:

A. Animal: Male Crl:CD® rats were housed singly in 5" x 11" x 7" stainless steel, wire-mesh cages. Purina Certified Rodent Chow® #5002 and water were available ad libitum. Rats were weighed and observed for general suitability for 1 week prior to testing.

B. Test Material:

Purity: [REDACTED]

Composition: [REDACTED]

Contaminants: [REDACTED]

Synonyms: [REDACTED]

Other Codes: [REDACTED]

Submitted by: [REDACTED]

Chemicals & Pigments Department
Jackson Laboratory

C. Inhalation Procedures:

1. Protocol: Groups of 6 rats, 1- to 8-weeks old and weighing between 228-267 grams, were restrained in perforated, stainless steel holders. Rats were exposed nose-only for one 4-hour exposure to particulate atmospheres of [REDACTED] in air. Rats were weighed and observed daily for 14 days post exposure, weekends included when deemed necessary.

2. Generation: Liquid [REDACTED] was syringe-driven into a Spraying Systems® nebulizer. Air introduced at the nebulizer aerosolized the test material and swept it into a cyclone. The cyclone removed non-respirable particles by inertial impaction, whereas respirable particles passed through the cyclone and into the chamber. The cyclone and nebulizer were heated to 100°C during the generation of the highest [REDACTED] concentration.

3. Analytical: At 10- to 30-minute intervals, calibrated volumes of chamber atmosphere were drawn through pre-weighed, glass-fiber filters. Filters were weighed on a Cahn® 26 Automatic Electrobalance. Atmospheric concentration was determined from the filter weight differential before and after sampling.

Chamber temperature was monitored with a thermometer. Particle size (mass median diameter) and percent of respirable particulate were determined with a Sierra® Cascade Impactor during representative exposures.

4. Pathology: Some rats which died after exposure to 73 mg/m³ were necropsied for examination of the lungs. Lungs were weighed at necropsy, then fixed and examined microscopically.

D. I.V. and I.P. Procedures:

1. Protocol: The test material was suspended in water and administered by intraperitoneal (I.P.) or intravenous (I.V.) injection to groups of 1-5 male Crl:CD® rats. Rats were 7-8 weeks old and weighed between 213-251 grams. Dose levels were chosen based on the calculated body load at the inhalation lethal concentration. This body load was determined to be 6.5 mg/kg.¹ Rats were held for 1 day after dosing, and were observed periodically for toxic signs.

2. Pathology: Rats which died after dosing were examined pathologically. Trachea, lungs, thyroid, parathyroid, esophagus, heart, kidneys, liver, thymus, and spleen were examined microscopically.

IV. RESULTS

A. Inhalation ALC: During exposures, a very slight mist was visible in a beam of light when the laboratory was darkened. Wet and dry filter comparisons indicated that all water was stripped from the particles when [REDACTED] was aerosolized. Chamber temperature ranged between 24.8-25.5°C.

¹ The [REDACTED] body load at the inhalation ALC was calculated based on the atmospheric concentration, the typical average respiratory rate and volume for rats, the duration of exposure, and the rats' average body weight. One hundred percent absorption of the test material is assumed.

Calculation:

$$\begin{aligned} \text{Lethal body load (mg/kg)} &= (0.042 \text{ mg [REDACTED] L atmosphere}) \times \\ & (1.2 \times 10^4 \text{ L/breath}) \times (120 \text{ breaths/min.}) \times (240 \text{ min.}) \div \\ & (0.230 \text{ kg/rat}) = 6.5 \text{ mg/kg} \end{aligned}$$

REVISED

1. Data:

Particulate Concentration (mg/m ³) ^a			% Respirable ^b	Mass Median Diameter of Respirable Particulate	Mortality (# Deaths/# Exposed)
Mean	S.D.	Range			
16	6.6	5.0-26	97	1.7 um	0/6
31	7.2	22-47	-	-	0/6
42	7.8	24-52	98	1.6 um	3/6
59	26	10-100	-	-	6/6
73 ^c	25	27-120	97	1.9 um	6/6

- ^a Particulate concentration represents combined [redacted] and [redacted] concentration.
^b [redacted]
^c Percent by weight of particles with diameter less than 10 um. During this exposure, the cyclone and nebulizer were heated to 100°C

2. Observations:

During Exposure: All exposed rats responded to a tail pinch throughout the exposures. When released from restrainers after 4 hours of exposure, some rats exposed to 42, 59 and 73 mg/m³ had labored breathing and decreased activity.

Post Exposure: No adverse clinical signs were seen in rats exposed to 16 mg/m³. Some rats exposed to 31 mg/m³ had slight to moderate weight loss for 1 day post exposure, followed by normal weight gain. At 42 mg/m³, 3 rats were found dead the morning after exposure; surviving rats had slight to moderate weight loss for 1 day. At 59 mg/m³, 4 rats died within 1 day post exposure. The remaining 2 rats exhibited severe weight loss, red nasal, ocular and oral discharges, hunched posture, lethargy and ruffled fur before they died 2 days post exposure. At 73 mg/m³, 3 rats died within 1 day post exposure; the remaining 3 rats exhibited moderate to severe weight loss and lung noise until they died 2 days post exposure.

3. Pathology²: The 3 rats exposed to 73 mg/m³ which died within 1 day post exposure had elevated lung weights, and severe pulmonary congestion, edema and hemorrhage. These effects appear to be caused by damage to Type I pneumocytes, with consequent increased permeability of alveolar capillaries.

² Lee, Ki Poong and James G. Aftosmis, "Pathology Report No. [redacted] H-15,048, September 26, 1983.

B. I.P. and I.V. Injections:

1. Data:

<u>Dose</u> <u>(mg/kg)</u>	<u>Dose</u> <u>(mL)</u>	<u>Suspension</u> ^a <u>(mg/mL)</u>	<u>Average</u> <u>Initial Body</u> <u>Weight (g)</u>	<u>Mortality</u> <u>(# Deaths/#Dosed)</u>
<u>I.P. Injection:</u>				
5.0	0.46	2.5	231	0/5
50	0.47	25	234	0/5
<u>I.V. Injection:</u>				
5.0	0.47	2.5	233	0/5
50	0.46	25	229	0/5
120	0.24	125	237	0/1
250	0.49	125	244	0/3
500	0.47	250	237	1/5
960	0.49	480 ^b	245	1/1

^a Concentration of [REDACTED]
^b 40% suspension as supplied

2. Observations: Rats dosed by I.P. injection exhibited no adverse clinical signs at either dose level. Rats dosed with 5.0 and 50 mg/kg by I.V. injection were hypersensitive for 2 hours after dosing. Rats dosed with 120 and 250 mg/kg by I.V. injection showed no adverse signs. At 500 mg/kg, 1 rat died 3 minutes after dosing. Surviving rats at 500 mg/kg showed no adverse signs. The 1 rat dosed at 960 mg/kg (test material as supplied) died within seconds after dosing.

3. Pathology³: Pathological examination of the 2 rats which died revealed the cause of death to be massive emboli formation in the alveolar capillaries, which prevented gaseous exchange through the air-blood barrier. These emboli are suspected to be undissolved (insoluble) [REDACTED]

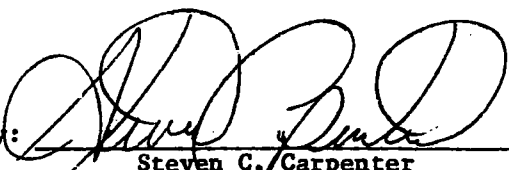
³ Lee, Ki Poong and James G. Aftosmis, "Pathology Report No. [REDACTED]
[REDACTED] H-15,048, September 26, 1983.

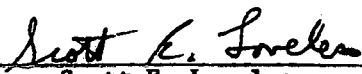
REVISED

V. CONCLUSIONS: An Inhalation Approximate Lethal Concentration for [REDACTED] is 42 mg/m³ of particulate. The cause of death after inhalation exposure appears to be damage to Type I pneumocytes, with consequent increased permeability of alveolar capillaries. According to Haskell Laboratory Toxicity Classifications, this material is extremely toxic by inhalation.

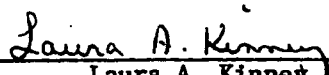
In contrast [REDACTED] appears to have low toxicity by I.V. and I.P. injections. Deaths occurred only at concentrations of 500 and 960 mg/kg by I.V. injection, doses which are well above the calculated lethal mg/kg body load by inhalation. Furthermore, the cause of death from I.V. injection appears to be physical blockage of alveolar capillaries due to the test material's insolubility.

Work by:

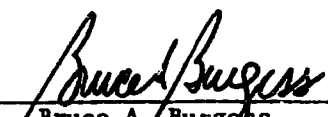

Steven C. Carpenter
Technician


Scott E. Loveless
Research Toxicologist

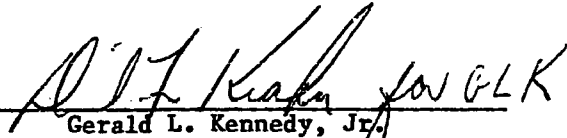
Supervision and Report by :


Laura A. Kinney
Chemist

Study Director:


Bruce A. Burgess
Research Toxicologist

Approved by:


Gerald L. Kennedy, Jr.
Section Supervisor
Acute Investigations

LAK:jrg:11.24

Date Issued: November 23, 1983

Study Initiated/Completed: 8/12/83-9/1/83

[REDACTED]
Haskell Lab. Report No. 423-83

Number of pages in this report: 6

Date Reissued: April 2, 1985