

8E

DOW CORNING

36-PP

PPCN'

Mar 16, 1992

8EHQ-0392-1047 SUPP 8890000217

TSCA Document Processing Center (TS-790)
Room L-100
Office of Pesticides and Toxic Substances
U.S. Environmental Protection Agency
Attn: TSCA Section 8(e) Coordinator
401 M Street S.W.
Washington, D.C. 20460

Re: Followup Submission to 8EHQ-1191-1047
TSCA Section 8(e) Notification of Substantial Risk
Hexamethoxydisilylethane

Dear Sir:

In accordance with the provisions of Section 8(e) of the Toxic Substances Control Act (TSCA), as interpreted in the Statement of Interpretation and Enforcement Policy (40 FR 11110, March 16, 1978), Dow Corning Corporation is submitting the following final report as a followup to our Notification of Substantial Risk of November 25, 1991 (8EHQ-1191-1047).

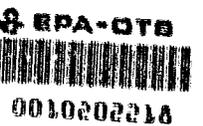
Chemical Substance:

Hexamethoxydisilylethane
CASRN 18406-41-2

89920000077

Manufacturer:

Dow Corning Corporation
2200 West Salzburg Road
Midland, Michigan 48686-0994



Submitted Study:

ACUTE INHALATION TOXICITY STUDY OF DOW CORNING®
X1-6145A ADDITIVE IN DOGS

Background:

On November 25, 1991, Dow Corning submitted a Notification of Substantial Risk under TSCA Section 8(e) concerning preliminary results obtained in an acute vapor inhalation toxicity study of DOW CORNING® X1-6145A Additive, chemically described as hexamethoxydisilylethane (CASRN 18406-41-2), in dogs. At this time, as a followup to that notification (8EHQ-1191-1047), we are submitting a copy of the final report to EPA.

DOW CORNING CORPORATION, MIDLAND, MICHIGAN 48686-0994 TELEPHONE: (517) 496-4000

CONTAINS NO CBI



1992-10000-37039

Project No. 6030-002
Dow Corning® X1-6145A PROPRIETARY

2

Executive Summary:

DOW CORNING® X1-6145A Additive was administered as a vapor via whole-body inhalation to three male beagle dogs at a target concentration of 10 ppm for six hours for two consecutive days, with two dogs being scheduled for sacrifice after the second exposure and the remaining dog being scheduled for sacrifice after a 14-day post-exposure period.

Actual and nominal concentrations agreed very well with the target concentration. No mortality occurred during the two-day exposure period. Clinical signs observed following the first exposure included coughing, salivation, sneezing, corneal opacity and trembling. One dog was removed from the chamber and sacrificed after 3.5 hours of the second exposure due to morbidity. Scheduled sacrifice was performed on the second dog at the termination of the exposure. An unscheduled sacrifice was performed on the third dog 13 hours post-exposure. All dogs lost weight during the study.

Histopathological examination of tissues indicated acute, severe, epithelial cytotoxicity and necrosis, with a subsequent inflammatory response characterized by a neutrophilic and fibrous exudate. The test material induced respiratory tract lesions which demonstrated an anterior-posterior gradient (i.e., lesions were most severe in the nasal passages and least severe in the major bronchi). The ocular lesions (corneal ulceration, keratitis) also suggest that the material is a strong cytotoxicant.

Actions:

Dow Corning will notify EPA of any further pertinent information that may be developed concerning this chemical substance.

If you require further information concerning this notification of substantial risk, please contact Dr. Rhys G. Daniels, Regulatory Compliance Specialist, Dow Corning Product Safety and Regulatory Compliance Department, at the address provided below or by telephone at 517-496-4222.

Sincerely,



Dr. Forrest O. Stark
U.S. Area Vice-President
Director of Health and Environmental Sciences

0 0 0 3

1992-10000-37039

DOW CORNING

H

ACUTE INHALATION TOXICITY STUDY OF
DOW CORNING® X1-6145A ADDITIVE IN DOGS

Dow Corning Corporation
March 12, 1992

DOW CORNING CORPORATION, MIDLAND, MICHIGAN 48686-0994

TELEPHONE: (517) 496-4000

0 0 0 9

1992-10000-37039

Project No. 6030-002
Dow Corning® X1-6145A Additive ADV

PROPRIETARY

- 2 -

1992-10000-37039

REPORT NO.: 1992-10000-37039
FILE NO.: 7486
LOT NO.: BN099001
AUTHORS: ManTech Environmental Technology, Inc.
SUBMITTED BY: Alan L. Himstedt
REVIEWED BY: Gary B. Kolesar
CHECKED BY: Waheed H. Siddiqui
DEPARTMENT: Health and Environmental Sciences
SUPERVISOR: Waheed H. Siddiqui
LOCATION: Midland, Michigan
DATE: March 12, 1992
TITLE: Acute Inhalation Toxicity Study of DOW CORNING® X1-6145A Additive in Dogs

ABSTRACT

DOW CORNING® X1-6145A Additive (hexamethoxydisilyloethane) was administered as a vapor, via whole-body inhalation, to three male beagle dogs at a target concentration of 10 ppm for 6 hours per day for two consecutive days. Two dogs were scheduled to be sacrificed after the second exposure and the remaining dog was to be sacrificed after a 14-day post-exposure period. Actual and nominal concentrations agreed very well with the target concentration. No mortality occurred during the two day exposure period. Clinical signs observed following the first exposure included coughing, salivation, sneezing, corneal opacity and trembling. One dog was removed from the chamber and sacrificed after 3.5 hours of the second exposure due to morbidity. Scheduled sacrifice was performed on the second dog at the termination of the exposure. An unscheduled sacrifice was performed on the third dog 13 hours post-exposure. All the dogs lost weight during the study. Histopathological evaluation of tissues indicated acute, severe, epithelial cytotoxicity and necrosis, with a subsequent inflammatory response characterized by a neutrophilic and fibrous exudate. The test material induced respiratory tract lesions which demonstrated an anterior-posterior gradient (i.e., lesions were most severe in the nasal passages and least severe in the major bronchi). The ocular lesions (corneal ulceration, keratitis) also suggest that the test material is a strong cytotoxicant.

0 0 0 6

1992-10000-37039

Project No. 6030-002
Dow Corning® X1-6145A Additive
March 12, 1992
PROPRIETARY

PROPRIETARY

- 3 -

1992-10000-37039

2

This report constitutes pages 1 through 32 of a ManTech Environmental Technology, Inc. Report.

Reviewed By: Gary B. Kolesar Date: 3/1/92
Gary B. Kolesar, M.S., M.P.H.

Approved By: Waheed H. Siddiqui Date: 3/4/92
Waheed H. Siddiqui, Ph.D.

Forrest O. Stark Date: 3/11/92
Forrest O. Stark, Ph.D.
Director, U.S. Area
Vice President

0 0 0 7

1992-10000-37039

PROPRIETARY

PROPRIETARY

7

MAN
TECH

BIANTECH ENVIRONMENTAL TECHNOLOGY, INC.

0 0 0 8

1 992 10000 37039

PROPRIETARY

PROPRIETARY

(6)

ACUTE INHALATION TOXICITY STUDY OF DOW CORNING® XI-6145A ADDITIVE
IN DOGS

DRAFT FINAL REPORT

PROJECT NO.: 6030-002

TEST MATERIAL: Dow Corning® XI-6145A Additive

Contractor: Mantech Environmental Technology, Inc.
5 Triangle Drive
Research Triangle Park, NC 27709

Sponsor: Dow Corning Corporation
2200 West Salisbury Road
Midland, MI 48640

0 0 0 9

Project No. 6030-002

Dow Corning® X1-6145A Additive

Page 2 of 17

Final Report

PROPRIETARY

ACUTE INHALATION TOXICITY STUDY OF
 DOW CORNING® X1-6145A ADDITIVE IN DOGS
 Test Material: Dow Corning® X1-6145A Additive

Study Initiation Date:
 Initiation of Exposure:
 Completion of In-Life Phase:

October 1, 1991
 November 15, 1991
 November 17, 1991

SUMMARY

Dow Corning® X1-6145A Additive was administered as a vapor, via whole-body inhalation, to three male beagle dogs at a concentration of 10 ppm for 6 hours per day for two consecutive days. The nominal concentrations for exposure day 1 and day 2 were 11.04 and 9.71 ppm, respectively. The actual chamber concentration, as determined by Infrared Analysis, was 10.16 ppm for exposure day 1 and 9.58 ppm for exposure day 2. The dogs appeared normal during the first exposure except for slight ocular discharge noted after 5.5 hours of exposure. At termination of the first exposure, the dogs appeared normal upon removal from the chamber with the exception of slight lacrimation in one dog. Approximately 1 hour post-exposure, the dogs developed coughing, sneezing, salivation and were observed pacing in their cages. Approximately 4 hours post-exposure, the symptoms appeared to decrease in severity. Observations noted prior to the start of the second exposure day included coughing, salivation, trembling and pacing. Within 0.5 hours of the start of the second exposure, the dogs developed salivation and nasal discharge. Salivation, lethargy, ocular discharge, gagging, ocular opacity and vomiting of clear liquid was observed with increasing severity. One dog was removed from the chamber and sacrificed after 3.5 hours of exposure due to the extreme severity of the symptoms. One dog was sacrificed (scheduled) immediately after the second exposure. The remaining dog exhibited salivation, ocular opacity and clear nasal discharge upon removal from the chamber. Approximately 1.5 hours post-exposure, this dog developed nasal congestion, salivation and an ungroomed appearance. At 9 hours post-exposure, the dog exhibited salivation, sneezing, nasal congestion, hoarseness and pacing. At approximately 13 hours post-exposure, the symptoms included dyspnea, rales and depression and the dog was sacrificed to prevent further suffering. All the dogs lost weight during the study. Histopathological evaluation of tissues indicated acute, severe, epithelial cytotoxicity and necrosis, with a subsequent inflammatory response characterized by a neutrophilic and fibrinous exudate. The test material induced respiratory tract lesions demonstrated an anterior-posterior gradient (i.e. lesions were most severe in the nasal passages and least severe in the major bronchi). The ocular lesions (central corneal ulceration, keratitis) also suggests that the test material is a strong cytotoxicant.

ManTech Environmental Technology

PROPRIETARY

10

STUDY PARTICIPANTS:

Study data were collected by Allen Ledbetter
This Final Report was prepared by Allen Ledbetter

Submitted By:

Allen Ledbetter
Study Director

Date

Approved By:

Mr. Gary Kolesar
Sponsor

Date

ManTech Environmental Technology

PROPRIETARY

PROPRIETARY

TABLE OF CONTENTS

	Page
I. GLP COMPLIANCE STATEMENT.....	5
II. INTRODUCTION.....	6
III. MATERIALS AND METHODS.....	6
A. Test Material.....	6
B. Exposure	6
C. Test Atmosphere Generation.....	6
D. Test Atmosphere Monitoring.....	7
E. Purity Analysis.....	7
F. Animals.....	7
G. Feed and Water.....	8
H. Exercise.....	8
I. Environment.....	8
J. Assignment to Groups.....	8
K. Clinical Observations.....	8
L. Body Weights.....	8
M. Necropsy.....	8
N. Pathology.....	8
IV. RESULTS.....	8
A. Mortality.....	8
B. Exposure	9
C. Nominal Concentration.....	9
D. IR Analysis.....	9
E. Purity Analysis.....	9
F. Chamber Environmental Conditions.....	10
G. Clinical Observations.....	10
H. Body Weights.....	11
I. Gross Pathology.....	11
J. Histopathology.....	11
K. Protocol Deviations.....	11
V. CONCLUSION.....	11
VI. QUALITY ASSURANCE STATEMENT.....	12
VII. TABLES	
Table 1 Exposure Chamber Concentrations.....	14
Table 2 Clinical Observations.....	15
Table 3 Body Weights.....	16
VIII. APPENDIX.....	17
Histopathology Report.....	A-1

PROPRIETARY

I. GLP COMPLIANCE STATEMENT

Study Title: Study Title: Acute Inhalation toxicity of Dow
 Corning® X1-6145A Additive in Dogs

Project Number: 6030-002

Study Director: Allen Ledbetter

ManTech Environmental Technology's portion of this study was conducted in accordance with EPA Good Laboratory Practice Regulations (GLP) as set forth in the Code of Federal Regulations (40 CFR 792.12). There were no significant deviations, in the work conducted by ManTech, from the aforementioned GLP regulations that would have affected the integrity of the study or the interpretation of the test results. The ManTech generated raw data have been reviewed by the Study Director, who certifies that the information contained in this report represents an appropriate and accurate conclusion within the context of the study design and evaluation criteria. Deviations are listed below:

1. The sponsor was responsible for the test substance characterization, stability and homogeneity analysis.
2. On six days during the study the relative humidity in the animal room or exercise room was below the protocol specified limit of 30% (lowest reading 23%) due to a malfunction of the facility humidification system. On three days during the study the temperature was below the protocol specified limit of 68°F with the lowest temperature being 60°F.

All original ManTech generated raw data are retained in the ManTech Environmental Technology's Archives, at 5 Triangle Drive, Research Triangle Park, NC 27709, with a copy of the final study report.

SUBMITTED BY:

Study Director:

Allen Ledbetter

Date

For Sponsor:

Date

ManTech Environmental Technology

PROPRIETARY

13

ACUTE INHALATION TOXICITY STUDY OF
DOW CORNING® X1-6145A ADDITIVE IN DOGS

II. INTRODUCTION

The purpose of this study was to determine the acute toxicity of Dow Corning® X1-6145A Additive in dogs when administered as a vapor, via whole-body inhalation, during two consecutive 6-hour exposures at a target concentration of 10 ppm. Two dogs were scheduled to be sacrificed immediately after the second exposure with the third dog to be held for 14 days of observations.

III. MATERIALS AND METHODS

- A. Test Material: The test material, identified as Dow Corning® X1-6145A Additive was received October 14, 1991. It was a clear liquid which was stored in the sponsor supplied original container, inside a hood, at room temperature (approximately 72°F).
- B. Exposure: The dogs were exposed on two consecutive days (11/15/91 and 11/16/91). Chamber temperature, relative humidity, generator temperature, chamber airflow and static pressure were monitored continuously and recorded every 30 minutes during the exposure. The exposures were conducted in a Hazleton 2000 liter chamber (Lab Products, Maywood, NJ) constructed of stainless steel and glass.
- C. Test Atmosphere Generation: The exposure chamber atmosphere was generated by metering the liquid test material into a heated 1-inch diameter glass U-Tube with 0.5 inch stainless steel Kovar® ends. The liquid test material was delivered to the U-Tube via a Harvard Syringe Drive (Harvard Apparatus, South Natick, MA) which pushed the liquid test material through a 30 ml glass syringe, 1/8" Teflon® and 1/16" stainless steel tubing into the U-Tube. The U-Tube was filled with 5mm glass beads, wrapped with heat tape and covered with insulation. Nitrogen entered counter current to one end of the U-Tube and was heated as it passed over the hot glass beads. A stainless steel Tee was connected to the other end of the U-Tube. Liquid test material entered one port of the Tee, dripped onto the hot beads and was vaporized. The heated nitrogen carried the vapors out the other port in the Tee into a Teflon delivery line connected to the exposure chamber inlet. The test material/air mixture entered the top of the chamber, passed over a round deflection plate, past the dogs and was exhausted at the bottom of the chamber. The chamber exhaust was

0 0 1 4

filtered through a water scrubber prior to being released into the atmosphere.

14

- D. Test Atmosphere Monitoring: The nominal concentration in the exposure atmosphere was determined by dividing the quantity of test material consumed by the volume of air passed through the chamber during each exposure period. The actual chamber concentration was determined by Infrared Analyses (IR) (Miran 1A, Foxboro Analytical, South Norwalk, CT). The IR was calibrated prior to the start of the first exposure using a Dynacalibrator® (Model 450, VICI Metronics, Santa Clara, CA). The Dynacalibrator consists of a glass lined oven with an inlet port for dilution gas and an exhaust port to carry the vapor to an exposure chamber or an analytical instrument. Glass diffusion tubes, comprised of a reservoir and an outlet neck (5 mm), generates vapors at a consistent rate for a given temperature and pressure. By varying the dilution flow in the oven, a range of concentrations can be generated. Liquid test material was placed in a glass diffusion tube and placed in the Dynacalibrator (oven temperature 230°F) which was exhausted into the inlet of the IR. The diffusion tube was weighed periodically to determine the amount of test material being vaporized over a known period of time. The vaporized test material was diluted with measured amounts of nitrogen to deliver concentrations of approximately 0.9 to 15.0 ppm to the IR. The IR response, expressed in recorder chart lines, was determined for each known concentration of the test material vapor. Exposure chamber atmosphere was drawn through the IR, via Teflon lines, under similar conditions as the calibration, and a continuous chart recording made during each 6-hr exposure.
- E. Purity Analysis: The vaporized test material was analyzed with a Perkin-Elmer Model 8700 Gas Chromatograph (GC) (Perkin-Elmer Ltd., Buckinghamshire, England) and compared to the neat material to ensure that no decomposition of the material occurred during the heating of the test material.
- F. Animals: Male beagle dogs, approximately 5 months of age, were purchased from Harlan Sprague Dawley (Ridgell Farms, Inc. Mount Horeb, WI, License No. 35-A-9) for use in this study. After arrival on October 10, 1991, the dogs were held in quarantine for approximately 4 weeks and examined carefully to ensure their health and suitability as test subjects. The dogs were identified by tattoos (tattooed by the supplier) on the inside of one ear.

0 0 1 5

PROPRIETARY

- G. Feed and Water: Certified Dog feed (Purina® Certified Dog Chow 5006, St. Louis MO) and water bowls were available ad libitum, except during the actual inhalation exposure periods.
- H. Exercise: The dogs were removed from their cages and allowed to exercise and socialize together in an empty animal room for at least 1-hour per day. Food and water was available during the exercise periods.
- I. Environment: During the quarantine and post-exposure observation periods the dogs were housed individually in suspended stainless steel 952 in³ (28" X 34" X 32") cages. During the exposure, the dogs were housed in compartments measuring 1034 in³ (47" X 22" X 12"). The animal rooms (housing and exercise) were maintained at approximately 72°F (range 60-76°F) and 40% (range 22-76%) relative humidity. Fluorescent lighting was provided automatically on a 12 hours light: 12 hours dark regimen.
- J. Assignment to Groups: All three dogs (I.D. Nos. XLL1, SHL1 and USL1) were exposed to the test material vapor. There was no control group. The dog in the best physical condition at the end of the second exposure was to be held for 14-days of observations while the other two dogs were to be sacrificed immediately after the second exposure.
- K. Clinical Observations: All dogs were observed during the exposure periods, immediately upon removal from the exposure chamber, hourly for at least two hours after the exposure, and the remaining dog frequently until it was sacrificed.
- L. Body Weights: All dogs were weighed before the exposure and at necropsy.
- M. Necropsy: All dogs were subjected to a gross necropsy conducted by Pathology Associates Incorporated.
- N. Pathology: Histopathological evaluation of the respiratory system and eyes was conducted by Pathology Associates Incorporated.

IV. RESULTS

- A. Mortality: No deaths occurred during the study, however due to the severity of clinical observations, one dog (USL1) was sacrificed after 3.5 hours of exposure on exposure day 2. One dog (XLL1) was sacrificed, as scheduled, immediately after the second exposure. One

ManTech Environmental Technology

PROPRIETARY

dog (SHL1) was sacrificed 13 hours after the second exposure due to severe respiratory distress. 16

- B. Exposure: The exposures were conducted on 11/15/91 and 11/16/91. The generator temperature ranged from 270-283° F on exposure day 1 and 254-294° F on exposure day 2. The exposure time for first exposure was 360 minutes but due to shutting the exposure down for 13 minutes to remove a dog, the second exposure was only 347 minutes.
- C. Nominal Concentration: The amount of test material consumed during exposure day 1 and exposure day 2 was 23.8 and 20.2 grams, respectively. The nominal concentration was 11.04 and 9.71 ppm for exposure day 1 and 2 respectively. Fresh test material was used for each exposure.
- D. IR Analysis: The IR was calibrated just prior to the start of the first exposure using the Dynacalibrator. The calibration range was 0.974 to 14.611 ppm. The exposure chamber concentration was monitored, via IR, for 320 minutes (sixteen 20-minute periods) during exposure day 1 and 260 minutes (thirteen 20-minute periods) during exposure day 2 (Table 1). The mean \pm standard deviation (SD) for exposure day 1 was 10.16 \pm 0.54 ppm with a relative standard deviation (RSD) of 5.3 %. For exposure day 2 the mean \pm SD was 9.50 \pm 0.31 ppm (RSD = 2%). The IR settings for the calibration and exposure chamber analysis were:

Pathlength: 20.25 meters	Wavelength: 3.48 microns
Absorbance: 0.25	Slit: 1
Meter Response: 40	Gain: X 10

- E. Purity Analysis: GC analysis of the neat test material indicated two major peaks, with retention times of approximately 6.2 and 7.4 minutes. The peak at 7.4 minutes was the largest (93%) and assumed to be the test material. The GC analysis of the chamber atmosphere indicated the ratio of the two peaks remained constant. An unknown peak (retention time 4.9 min), which was unresolved in the neat test material and calibration standards, was resolved in the chamber atmosphere samples. The GC column and settings were:

Column: Phase SE-30 30 meters, ID 0.54 mm, Film Thickness- 1.2 microns, Supplier- Alltech Associates
 GC Detector: Flame Ionization (FID)
 Carrier Gas: Helium
 Carrier Flow: 15 ml/min
 Air Pressure: 30 PSI
 Hydrogen Pressure: 20 PSI

Oven Temperature Program:
Initial Oven Temperature: 50°C
Initial Oven Time: 1.5 minutes
Oven Temperature Ramp Rate: 30°C/minute
Oven Temperature Final Temperature: 130°C
Oven Temperature Final Time: 5.9 minutes
Injector Temperature: 150°C
Detector Temperature: 250°C

- F. Chamber Environmental Conditions: The mean chamber temperature was 71°F (69-72°F) and 70°F (68-71°F) for exposure day 1 and 2, respectively. The mean chamber relative humidity was 49% (45-54%) for exposure day 1 and 50% (48-56%) for exposure day 2. The time weighted average exposure chamber air flows was 544 and 543 l/min for exposure day 1 and 2, respectively. The static (negative) pressure in the chamber during exposure day 1 ranged from 0.64 to 0.68" H₂O and 0.63 to 0.66" H₂O for exposure day 2.
- G. Clinical Observations: The dogs appeared normal during the first exposure except for slight ocular discharge noted after 5.5 hours of exposure. The dogs appeared normal upon removal from the chamber after the first exposure with the exception of slight lacrimation in one dog (Table 2). After approximately 1-hour post-exposure, the dogs developed coughing, sneezing, salivation and were pacing in their cages. Approximately 4-hours post-exposure, the severity of the symptoms appeared to decrease. Observations noted prior to the start of the second exposure included coughing, salivation, trembling and pacing. Within 0.5 hours of the start of the second exposure, the dogs developed salivation and nasal discharge. Salivation, lethargy, ocular discharge, gagging, ocular opacity and vomiting of clear liquid was observed and this condition increased in severity during the exposure. To prevent any further suffering, one dog (USL1) was removed from the chamber and sacrificed after 3.5 hours of exposure due to extreme gagging, vomiting, tearing and salivation. One dog (XLL1) was sacrificed, as scheduled, immediately after the second exposure. The remaining dog (SHL1) exhibited salivation, ocular opacity and clear nasal discharge upon removal from the chamber. Approximately 1.5 hours post-exposure, the dog exhibited nasal congestion, salivation and rough hair coat. At 2 hours post-exposure, the dog exhibited salivation, sneezing, nasal congestion, hoarseness and pacing with increasing severity. This dog developed dyspnea, rates and depression and to prevent undue suffering, the dog was sacrificed at approximately 13 hours post-exposure.

0 0 1 A

17

18

- H. Body Weights: All dogs lost weight (Table 3) during the study. The dogs were not observed to eat or drink after the first exposure.
- I. Gross Pathology: The gross pathology summary is included in the Appendix.
- J. Histopathology: The histopathology report is included in the Appendix.
- K. Protocol Deviations: On six days during the study the relative humidity in the animal room or exercise room was below the protocol specified limit of 30% (lowest reading 23%) due to a malfunction of the facility humidification system. On three days during the study the temperature was below the protocol specified limit of 60°F with the lowest temperature being 60°F.

V. CONCLUSION: Dow Corning® X1-6145A Additive when exposed to dogs at a concentration of 10 ppm for up to six hours on each of two consecutive days resulted in severe irritation of the upper respiratory tract and ocular opacity in all dogs. One dog had to be sacrificed during the second exposure due to the severity of the respiratory irritation. The dog that was to be held for 14 days of post-exposure observations had to be sacrificed 13 hours after the second exposure due to severe respiratory irritation and ocular ulceration. Histopathological evaluation indicated that test material induced respiratory tract lesions were most severe in the nasal passages and least severe in the major bronchi. Ocular lesions also suggest that the test material is a strong cytotoxicant.

Project No. 6030-002
 Dow Corning® X1-6145A Additive
 Page 12 of 17
 Final Report

PROPRIETARY

VI. QUALITY ASSURANCE STATEMENT

Study Title: Acute Inhalation toxicity of Dow Corning® X1-6145A Additive in dogs

Project Number: 6030-002

Study Director: Allen Ledbetter

Report Audit Dates:

This study has been subjected to inspections and the report has been audited by ManTech Environmental Technology's Quality Assurance Unit. The report describes the methods and procedures used in the study and the reported results accurately reflect ManTech's raw data. ManTech's raw data and a copy of the final report will be stored in room 210 in the NET building at Research Triangle Park, NC. The sponsor was responsible for the test material characterization, stability and homogeneity analyses.

The following are the inspection dates, and the dates inspection reports were submitted:

<u>Date(s) of Inspection</u>	<u>Study Director</u>	<u>Inspection Report(s) Submitted to:</u> <u>Management</u>
11/13/91	11/18/91	11/18/91
11/16/91	11/18/91	11/18/91
12/26/91	12/26/91	12/26/91

Michael Rey
 Michael Rey
 Manager,
 Quality Assurance

February 9, 1992
 Date

ManTech Environmental Technology

1992-10000-37039

Project No. 6030-002

Dow Corning® X1-6145A Adhesive

Page 13 of 17

Final Report

PROPRIETARY

02

VII. TABLES

0021

PROPRIETARY

Table 1

Exposure Chamber Concentrations

<u>Exposure Day 1</u>		<u>Exposure Day 2</u>	
<u>IR Chart Lines¹</u>	<u>Conc. ppm</u>	<u>IR Chart Lines¹</u>	<u>Conc. ppm</u>
38.25	9.29	36.25	8.78
40.00	9.75	39.50	9.62
39.50	9.62	39.50	9.62
39.25	9.55	39.50	9.62
39.50	9.62	39.50	9.62
39.50	9.62	40.00	9.75
41.50	10.14	40.50	9.88
41.00	10.04	40.50	9.88
41.75	10.20	38.25	9.29
43.00	10.53	38.25	9.29
43.25	10.59	39.25	9.55
43.75	10.72	40.00	9.75
44.50	10.92	40.50	9.88
44.50	10.92		
43.50	10.66		
42.75	10.46		
Mean	10.16		9.58
SD ²	0.54		0.31
% RSD	5.28		3.22
N	16 ³		13 ⁴

¹ Each period equals 20 minutes of continuous sampling

² Standard Deviation

³ Total of 320 minutes sampled

⁴ Total of 260 minutes sampled

ManTech Environmental Technology

Y
2/

PROPRIETARY

22

TABLE 2
Clinical Observations

Observation	Incidence		
	Total Incidence	First 24-Hours ¹	Second 24-Hours ²
Normal	0/3 ³	0/3	0/3
Coughing	3/3	3/3	1/3
Lacrimation	1/3	1/3	0/3
Sneezing	2/3	2/3	0/3
Salivation	3/3	3/3	3/3
Pacing	3/3	3/3	1/1
Trembling	1/1	1/3	0/3
Clear Nasal Discharge	1/1	0/3	1/1
Ocular Opacity	3/3	0/3	3/3
Nasal Congestion	2/3	3/3	1/1
Hoarse	1/1	0/3	1/1
Depression	1/1	0/3	1/1
Foaming	1/1	0/3	1/1
Lethargic	3/3	0/3	3/3
Ungroomed Appearance	1/1	0/3	1/1

- ¹ Observations noted from start of first exposure to start of second exposure.
- ² Observations noted from start of second exposure until the final dog sacrificed.
- ³ Number of animals alive when observation was noted.

0 0 2 3

TABLE 3

Body Weights (grams)

<u>Animal Number</u>	<u>Pre-Exposure Body Weight</u>	<u>Terminal Body Weight</u>	<u>Weight Change¹</u>	<u>Necropsy Date</u>
USL1	7778.4	7285.4	-493.0	11/16/91 ²
XLL1	9650.4	9165.2	-485.2	11/16/91 ²
SHL1	9653.8	8503.4	-1150.4	11/17/91 ³

¹ Pre-Exposure Body Weight minus Terminal Body Weight

² Unscheduled Necropsy

³ Scheduled Necropsy

1992-10000-37039

Project No. 6030-002
Dow Corning® XI-5145
Page 17 of 17
Final Report

PROPRIETARY

Handwritten initials

VIII. APPENDIX

PAI

Pathology Associates, Inc.

4915 D Prospectus Drive
Durham, NC 27713
(919) 544-5257
Fax: (919) 544-3218

1992-10009-37039

PROPRIETARY

25

**Acute Inhalation Toxicity
Study of
Dow Corning® X1-6145A Additive
in Dogs**

FINAL PATHOLOGY REPORT

Prepared By:

**Thomas M. Monticello, DVM, PhD
Diplomate, A.C.V.P.
Pathology Associates, Inc.
4915 D Prospectus Drive
Durham, NC 27713**

Prepared For:

**ManTech Environmental Technology, Inc.
2 Triangle Drive
Research Triangle Park, NC 27709**

January 27, 1992

0 0 2 6

26

TABLE OF CONTENTS

I.	Pathology Narrative	A - 3
	Reports Code Table	A - 8
II.	Project Summary Table -	A - 9
III.	Tabulated Animal Data -	A - 11
IV.	Quality Assurance Statement	A - 12

0 0 2 7

PROPRIETARY**I. Pathology Narrative**

27

INTRODUCTION

This pathology report submitted by Pathology Associates, Inc. (PAI) to ManTech Environmental Technology, Inc. (METI), Research Triangle Park, NC represents the histopathology findings for the study designated as "Acute Inhalation Toxicity Study of Dow Corning® X1-6145A Additive in Dogs".

EXPERIMENTAL DESIGN AND METHODS

PAI performed necropsies on 3 male beagle dogs that had been exposed to 10 ppm X1-6145A 6h/day for up to 2 days. The study was terminated early since the dogs appeared to be suffering. The summary of the experimental design is shown in Table 1.

A complete list of tissues taken at necropsy included the entire respiratory tract: lungs, trachea, larynx, and nasal turbinates; the eyes, and any gross lesion. The tissues were formalin-fixed, trimmed, processed, embedded, sectioned, and stained with hematoxylin and eosin using standard methods as per Pathology Associates SOP's. Prior to sectioning, the nasal passages were first decalcified in 5% formic acid.

Microscopic findings are summarized in the Project Summary Tables. The microscopic findings for individual animals are presented in the Tabulated Animal Data Tables. All codes used as entries in these tables are explained in the Reports Code Table.

28

TABLE 1

SUMMARY OF EXPERIMENTAL DESIGN

Animal ID	Hours of Exposure	Hours on Test (prior to sacrifice)
USL1	10 (6 + 4)	28
XLL1	12 (6 + 6)	30
SML1	12 (6 + 6)	46

GROSS FINDINGS

USL1 - A clear mucoid exudate was present in the external nares, posterior nasal cavity and within the trachea. The tonsils and laryngeal mucosal surfaces were mottled tan and dull red. The left and right diaphragmatic lung lobes contained multiple, 2 mm, dull tan foci. The spleen was enlarged, compatible with terminal congestion, due to euthanasia (barbiturate effect); this was considered an incidental finding, therefore, no spleen sections were taken for histopathology.

XLL1 - A yellow mucoid exudate was present in the medial canthus of both eyes. The anterior and posterior nasal cavity contained a clear mucoid exudate. The tonsils were mottled red and tan as was the laryngeal mucosa, which also contained a clear mucoid exudate on the surface. The left middle lung lobe had several 2 mm, dark brown foci. The right diaphragmatic lung lobe contained many 5 mm, dark brown foci.

SML1 - The right and left eyes had corneal opacities and the left cornea contained a central defect, compatible with an erosion. A clear mucoid exudate was present in the external nares. The nasal turbinates appeared swollen. The laryngeal mucosa was swollen and mottled red and tan. The tonsils were swollen and out of their crypts. Whitish froth was present in the trachea. The left and right middle lung lobes had areas of red and tan discoloration. The major airways contained froth.

0-0 2 9

PROPRIETARY

29

HISTOPATHOLOGY RESULTS AND DISCUSSION

Compound-induced lesions were present in 3/3 animals. Lesions were confined to the respiratory tract and corneas of the eye. The respiratory tract lesions exhibited an antero-posterior severity gradient; most severe lesions were present in the nasal passages and larynx, with less severe lesions present in the trachea and mainstem bronchi. The corneal lesions consisted of central ulceration and were usually associated with a keratitis.

Nasal Passages

Exposure to X1-6145A resulted in a locally extensive to diffuse necrosis of the surface nasal epithelium with partial to complete sloughing of the necrotic epithelium into the nasal lumen. Also present in the nasal lumen and associated with the lesions, was an abundant amount of fibrin admixed with neutrophils. The fibrin mats formed a scaffold-like structure between the nasal turbinates. Large portions of the subjacent lamina propria and nasal glands were necrotic, and had a neutrophilic inflammatory cell infiltrate.

Larynx

Inhalation of the test article induced locally extensive to diffuse necrosis of the epithelium which lines the larynx, resulting in ulceration. Necrotic debris admixed with aggregates of neutrophils oftentimes formed an overlying serocellular cap. Also, there was edema, hemorrhage and a neutrophilic infiltrate of the lamina propria.

Trachea

The tracheal epithelial lesions were not as severe as those observed in the nasal passages and larynx. An antero-posterior severity grade was present. Compound-induced lesions were segmental (i.e. patchy areas), and consisted of individual cell necrosis of the respiratory epithelium which lines the trachea. There was marked pyknosis and karyorrhexis of respiratory epithelial cell nuclei. Many intraepithelial vacuoles, which contained necrotic cellular debris and some inflammatory cells, were present throughout the epithelium. Individual respiratory cell necrosis was present distally to the tracheal bifurcation (carina) and also extended into the main stem bronchi (see description of lung, below). There was a mild inflammatory cell infiltrate present in the lamina propria. Squamous metaplasia was evident in one animal (SHL1).

B O E O

30

Lung

Compound-induced lung lesions consisted of mild necrotizing bronchitis of the mainstem bronchi, and a varying degree of suppurative bronchopneumonia. There was individual cell necrosis, with similar characteristics as described above for the trachea, in the mainstem bronchi; these lesions were not present in the smaller airways.

Suppurative bronchopneumonia was characterized by the filling of small airways with neutrophils, segmental necrosis of bronchial walls, and an outpouring and flooding of neutrophils into the adjacent alveolar air spaces oftentimes resulting in the consolidation of parenchyma. In addition, there were fibrin mats and proteinaceous material present in alveoli. The bronchopneumonia was attributed to secondary infections from the disruption and/or loss of the mucociliary apparatus induced by the inhalation exposure of the test compound.

Tonsil

The stratified epithelial surface of the tonsil had a slight increase in the number of migrating neutrophils present in addition to small aggregates of neutrophils present in the tonsillar fossulae. There is usually a slight background of migrating neutrophils in the tonsils of control animals and the lesions described in the present study, therefore, were interpreted to be mild.

Eye

Compound related lesions of the eye were present in the cornea. There were large central corneal ulcers evidenced by the loss of corneal epithelium, slight swelling (odema) of the corneal stroma, and the presence of neutrophils infiltrating the stroma from the limbal region. The distribution of the ulcers suggests an exposure-like keratitis.

0 0 3 1

CONCLUSIONS

Based on the distribution and nature of the compound-induced lesions, inhalation exposure to X1-6145A induced acute, severe, epithelial cytotoxicity and necrosis, with a subsequent inflammatory response characterized by a neutrophilic and fibrinous exudate. Compound-induced respiratory tract lesions demonstrated an anterior-posterior gradient (i.e. lesions were most severe in the nasal passages and least severe in the major bronchi). The predominant lesions were necrosis and sloughing of the epithelium which lines the nasal passages and larynx, and individual cell necrosis of the respiratory epithelium lining the trachea and mainstem bronchi. The bronchopneumonia was attributed to sequelae of the exposure (e.g., loss of the mucociliary apparatus) and most likely was not directly due to the test compound. The ocular lesions (corneal ulceration, keratitis) also suggest that the test compound is a strong cytotoxicant.

Thomas M. Monticello

Thomas M. Monticello, DVM, PhD
Diplomate, ACVP

0 0 3 2

1992-10000-37039

Pathology Report
Inhalation Study of X1-6145A in Dogs

PROPRIETARY

2
3

PATHOLOGY ASSOCIATES, INC.
ACUTE INHALATION TOXICITY STUDY
OF X1-6145A ADDITIVE IN DOGS

REPORTS CODE TABLE

N - Tissues within normal histological limits

P - Present

SUPP - Suppurative

NEC - Necrotizing

1 - Minimal

2 - Mild

3 - Moderate

4 - Marked

0 0 3 3

PATHOLOGY ASSOCIATES, INC.
ACUTE INHALATION TOXICITY
OF X1-6145A ADDITIVE
IN DOGS

PROPRIETARY

33

Project Summary Table

SUMMARY: Incidence of NEOPLASTIC and NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: X16145A	DATES: ALL
GROUP:	10PPM
NUMBER OF ANIMALS:	3

	# Ex	#
NOSE		
RHINITIS, NECROTIZING	3	3
EXUDATE, FIBRINOSUPPURATIVE	3	3
LARYNX		
LARYNGITIS, NECROTIZING	3	3
TRACHEA		
TRACHEITIS, NECROTIZING	3	3
SQUAMOUS METAPLASIA	1	1
LUNG		
BRONCHIT, BRONCHITIS, NEC	3	3
BRONCHOPNEUMONIA, SUPP, FOCAL	2	2
BRONCHOPNEUMONIA, SUPPURATIVE	1	1
FOSSIL		
FUNGUSLEPTIS, NEUTROPHILIC	2	2
EYE		
CORNEA, KERATITIS, NEUTROPHILIC	2	2
CORNEA, ULCERATION	1	1

(End of Report)

21-Jan-1992

PATHOLOGY ASSOCIATES, INC.
ACUTE INHALATION TOXICITY
OF X1-6145A ADDITIVE
IN DOGS

PROPRIETARY

Severity Summary Table

PROJECT ID. NO: X16145A FATES: ALL
GROUP: 10PPM
NUMBER OF ANIMALS: 3

	# EA	#	SEV
NOSE		3	
RHINITIS, NECROTIZING		3	4.00
EXUDATE, FIBRINOSUPPURATIVE		3	4.00
LARYNX		3	
LARYNGITIS, NECROTIZING		3	4.00
TRACHEA		3	
TRACHEITIS, NECROTIZING		3	2.67
SQUAMOUS METAPLASIA		1	0.67
LUNG		3	
BRONCHI, BRONCHITIS, NEG		3	2.00
BRONCHOPNEUMONIA, SUPP, FOCAL		2	1.00
BRONCHOPNEUMONIA, SUPPURATIVE		1	1.00
TONSIL		3	
TONSILLITIS, NEUTROPHILIC		2	1.33
EYE		3	
CONJUNCTIVA, KERATITIS, NEUTROPHILIC		2	1.67

* Severity calculated by the number of tissues examined.

(End of Report)

28-Jan-1992

0 0 3 5

1932-10000-37039

PATHOLOGY ASSOCIATES, INC.
 ACUTE INHALATION TOXICITY
 OF XI-6145A ADDITIVE
 IN DOGS

PROPRIETARY

MS

Tabulated Animal Data

PROJECT ID: X16145A GROUP: 10PPM
 PAGES: ALL

ANIMAL ID:	SHLT	USC1	NR1
NOSE			
RHINITIS, NECROFIZING	4	4	4
EXUDATE, FIBRINOSUPPURATIVE	4	4	4
LARYNX			
LARYNGITIS, NECROFIZING	4	4	4
TRACHEA			
TRACHEITIS, NECROFIZING	3	3	2
SQUAMOUS METAPLASIA	2	-	-
LUNG			
BRONCHI, BRONCHITIS, NEG	2	2	2
BRONCHOPNEUMONIA, SUPP, FOCAL	-	1	2
BRONCHOPNEUMONIA, SUPPURATIVE	3	-	-
TONSIL			
TONSILITIS, NEUTROPHILIC	3	-	2
EYE			
CORNEA, KERATITIS, NEUTROPHILIC	2	-	3
CORNEA, ULCERATION	2	2	2

(End of Report)

20 Jan 1992

039

Y
BS

1992-10000-3703

PROPRIETARY

AMENDED QUALITY ASSURANCE STATEMENT

This histopathology project has been audited by the quality assurance unit in accordance with EPA Good Laboratory Practice Standards. Results of these activities indicate that the portions of the study performed by Pathology Associates, Inc. conformed with EPA GLP regulations and applicable Standard Operating Procedures. The pathology narrative report is an accurate reflection of the recorded data. The following is a record of the audit performed and reported by the QAU.

<u>Date of Audit</u>	<u>Phase Audited</u>	<u>Date Findings Reported to Management and Study Pathologist</u>
1-6-92	Draft Narrative Report	1-6-92
2-10-92	Final Narrative Report	2-10-92

Deborah R. Belk
Deborah R. Belk, QA Specialist
Quality Assurance Unit
Pathology Associates, Inc.

10 February 1992
Date

Study Title: Acute Inhalation Toxicity Study of Dow Corning © X1-6145A Additive in Dogs

Study Sponsor: ManTech Environmental Technology, Inc.

PAI Study Number: 38

0 0 3 7