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INITIAL SUBMISSION: LETTER FROM LOCTITE CORP TO USEPA RE ACUTE INHALATION STUDIES ON ADHESIVE 3311 AND N,N-DIMETHYLACRYLAMIDE, WITH ATTACHMENTS AND DATED 11/25/98 (SANITIZED)		
Chemical Category		
N,N-DIMETHYLACRYLAMIDE		

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LOCTITE

Loctite Corporation
Environmental Health & Safety Affairs
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November 25, 1998

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TSCA Section 8(e) Coordinator
Document Processing Center
U.S. Environmental Protection Agency
Office of Pollution Prevention and Toxics (7407)
401 M Street, S.W.
Washington DC 20460

COMPANY SANITIZED

Re: TSCA Section 8(e) Submission on N,N Dimethylacrylamide (CAS # 2680-03-7) and Related Adhesive Formulation

Dear Sir or Madam:

Loctite Corporation makes this submission under TSCA Section 8(e), forwarding information from a report just received by Loctite concerning a study of N,N Dimethylacrylamide ("DMAA") (CAS # 2680-03-7) and a related adhesive formulation containing N,N Dimethylacrylamide and several commercially available materials including an acrylate monomer. The study reports are enclosed as Attachments 1A and 1B and summarized below.

As discussed below in Sections I and II, the reported findings may not reflect "substantial risk of injury to health or the environment" under § 8(e), in light of the low volatility of N,N Dimethylacrylamide and the adhesive formulation, and the resulting low probability of human exposure to meaningful concentrations of these materials. Moreover, as discussed in Section III below, we believe that lung irritation, the reported potential effect, already is a well known effect with respect to acrylates, and thus would not be reportable under § 8(e). Loctite nevertheless is providing this information to EPA in an abundance of caution.

One note of explanation is appropriate regarding the format of the enclosed test results. We are submitting the test results as one report because the outside testing laboratory discussed test results and findings for both studies in the Histopathology Report (Appendix B of Attachments 1A and 1B). Each study will be discussed separately in this letter. The results appear in a single report because the outside testing laboratory which conducted the tests provided its findings to Loctite in this manner. For EPA's convenience, however, we have summarized the results of separate studies separately.

I. **Acute Inhalation Study on N,N,-Dimethylacrylamide (CAS # 2680-03-7)**

An independent testing laboratory engaged by Loctite, (Stillmeadow Incorporated, "Stillmeadow") conducted an acute inhalation toxicity study of N,N-dimethylacrylamide using albino rats. The animals were exposed for one hour to a concentration of 776 ppm, which was the maximum achievable concentration at 35°C. The animals were then observed for 14 days, during which time there were no fatalities, demonstrating that the LD_{50} would be well in excess of the saturation concentration at room temperature.

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The animals exhibited no clinical signs during either exposure or the observation period. On the 14th day, all animals were sacrificed and necropsied. The histopathology evaluation of the lungs indicated that interstitial pneumonia occurred, as well as varying degrees of inflammatory changes in the lung tissue and surrounding blood vessels.

While this precise toxicological information apparently may not be previously known for N,N-dimethylacrylamide, because its vapor pressure is very low (0.7 mm Hg at 25°C), it is highly questionable whether this effect could occur under real-world exposure conditions.

II. Acute Inhalation Study on an Adhesive Formulation Containing (CAS # 2680-03-7) and Additional Ingredients, Including an Acrylate Monomer

A companion study to the one described in Section II above was conducted by Stillmeadow using Adhesive 3311, a mixture containing approximately 70% of a high-boiling acrylate monomer (CAS # 5888-33-5) and an aliphatic urethane acrylate oligomer, less than 25% N,N-Dimethylacrylamide [2680-03-7], less than 3% of a phosphine compound, less than 3% of a photoinitiator [24650-42-8] and less than 3% of a substituted silane. The exact composition of this mixture is provided in Attachment 2 hereto, which is hereby claimed as CONFIDENTIAL BUSINESS INFORMATION pursuant to 40 C.F.R. Part 2. Adhesive 3311 is sold only into the industrial marketplace, and is dispensed in small quantities between two substrates immediately prior to polymerization (curing) via ultraviolet light to bond them together.

During an acute inhalation toxicity study of Adhesive 3311, albino rats were exposed for one hour to a maximum achievable concentration of 513 ppm of N,N-Dimethylacrylamide at 35°C; airborne concentrations of the other components were not measured. The animals were then observed for 14 days, during which time there were no fatalities, demonstrating that the LD_{50} would be well in excess of the saturation concentration at room temperature.

The animals exhibited no clinical signs during either exposure or the observation period. On the 14th day, all animals were sacrificed and necropsied. The histopathology evaluation of the lungs indicated that interstitial pneumonia occurred, as well as varying degrees of inflammatory changes in the lung tissue and surrounding blood vessels. These effects, which appeared to be of greater severity than those observed for the rats in the study consisting of N,N-Dimethylacrylamide alone (described above), appear consistent with studies for similar acrylate materials detailed in Section III below.

III. Comments and Precautionary Steps Taken

The precise toxicological information summarized above was obtained from the enclosed new study of N,N-Dimethylacrylamide and the related adhesive formulation containing N,N-Dimethylacrylamide and several acrylates. However, there are numerous citations in the scientific literature that describe the irritancy of several similar acrylates. For example, acute inhalation toxicity studies of ethyl acrylate showed that at high concentrations, pneumonic involvement was exhibited (*J. Ind. Toxicology*, 31(6), 311-316, 1949) and lung hemorrhages were found at necropsy (*ECETOC Joint Assessment of Commodity Chemicals*, No. 28, 1994). Similar studies using methyl acrylate which were conducted with rabbits and guinea pigs, as well as with rats, again showed severely congested lungs with areas of hemorrhagic extravasation (*J. Industrial Hygiene and Toxicology*, 31(6), 317-326, 1949). Lastly, more recent inhalation toxicity studies with high concentrations of n-butyl acrylate produced pulmonary hemorrhage and emphysema (*ECETOC Joint Assessment of Commodity Chemicals*, No. 27, 1994). Thus, the effects seen in the above-described study of Adhesive 3311 appear to be consistent with previously reported effects.

Loctite has received no reports of nose, throat or respiratory irritation from either employees or customers who have used either the N,N-Dimethylacrylamide or the adhesive formulation. Based on the low vapor pressure at room temperature for N,N-Dimethylacrylamide (0.7 mm Hg at 25°C) and the estimated low vapor pressure for the adhesive formulation, we do not believe this material poses a high inhalation hazard in the workplace.

Loctite has learned of other § 8(e) studies submitted with respect to N,N,-Dimethylacrylamide which cite its significant adverse dermal absorption properties and resulting adverse reactions [8EHQ-0692-5340, 8EHQ-0692-5343]. On the basis of the foregoing test results and the other § 8(e) reports, Loctite's MSDS

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and labels have been revised to reflect all new information required by OSHA's Hazard Communication Standard. Additionally, Loctite workers handling bulk quantities of N,N-Dimethylacrylamide have been retrained concerning the proper personal protective equipment (PPE) to be used when handling this chemical. Loctite has provided copies of the Stillmeadow report on N,N-Dimethylacrylamide to the distributors that supply us with this chemical (Economy Polymers and Aceto Corporation), and will supply a copy to the manufacturer in Japan (Kohjin).

Please contact Margaret A. Rakas, Ph.D., Manager, Safety, Health & Regulatory Affairs, Loctite Corporation, at (860) 571-5355, should there be any questions.

Sincerely,

Margaret A. Rakas, Ph.D.
Manager, Safety, Health & Regulatory Affairs

ATTACHMENT 2-
Composition of Adhesive 3311

CAS Number	WT %

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STILLMEADOW
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N, N-Dimethylacrylamide

FINAL REPORT

ACUTE INHALATION TOXICITY STUDY IN RATS

OSHA Regulation 29 CFR 1910

AUTHOR - Jerry E. Bennick

STUDY INITIATION DATE: June 1, 1998
STUDY COMPLETION DATE: November 10, 1998

CONDUCTED BY:

STILLMEADOW, Inc.
12852 Park One Drive
Sugar Land, TX 77478

LABORATORY STUDY NUMBER

4329-98

VOLUME 1 OF 1 OF STUDY

PAGE 1 OF 18

SUBMITTED TO:
Loctite Corporation
1001 Trout Brook Crossing
Rocky Hill, CT 06067

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QUALITY ASSURANCE STATEMENT

Study Number: 4329-98
Test Substance: N, N-Dimethylacrylamide
Study Title: Acute Inhalation Toxicity Study in Rats

The study has been inspected and the report and data have been audited in accordance with STILLMEADOW, Inc. Standard Operating Procedures (SOP's). The findings from the inspection and audit were reported to the Study Director and Management as follows:

Phase of Study Inspected	Date Inspected	Reported to Study Director	Reported to Management
Dosing Observations	6/24/98 7/01/98	6/24/98 7/02/98	6/24/98 7/02/98
Report/Data Audit	9/18/98	9/18/98	9/18/98

Lynne Magee
Lynne Magee, B.S.
Quality Assurance Unit
STILLMEADOW, Inc.

9 Nov 98
Date

SUMMARY

N, N-Dimethylacrylamide was evaluated for its acute inhalation toxicity potential in albino rats. Five males and five females were exposed for one hour to a vapor generated from the liquid test substance at a level of 776 ppm. There was no mortality during the study. There were no clinical signs of toxicity observed during the study. Body weights were unaffected by exposure. The gross necropsy revealed no observable abnormalities, except discolored lungs in three animals. As indicated by the data, the acute inhalation LC_{50} for N, N-Dimethylacrylamide is greater than 776 ppm.

INTRODUCTION

The objective of this study was to determine the acute inhalation toxicity potential of the test substance in accordance with US OSHA Regulation: 29 CFR 1910.1200. This study was conducted for Loctite Corporation, according to the approved protocol and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. The original protocol, raw data, and this report are kept on file in the STILLMEADOW, Inc. archives. The the animals were expo. . as follows:

Beginning of 1 Hour Exposure					Termination of In-Life Observations	
Dose (ppm)	Males		Females		Date	
	Date	Time	Date	Time	Males	Females
776	7/01/98	9:40	7/01/98	9:40	7/15/98	7/15/98

TEST SUBSTANCE

Identification:	N, N-Dimethylacrylamide Lot # 7H147 Ref: X202181
Date and Quantity Received:	May 29, 1998; 2 liters
Physical Description:	Clear colorless liquid
Storage:	Room temperature
Purity and Composition:	Certificate of Analysis not provided by sponsor
Stability:	Not provided by sponsor

Records pertaining to stability, characterization, and verification of test substance identity are the responsibility of the sponsor.

TEST SYSTEM

Experimental Animals	
Species and Strain:	Rat; HSD:Sprague-Dawley
Justification of Species:	The rat is a representative rodent species preferred by various regulatory agencies for use in acute inhalation toxicity studies.
Source:	Harlan Sprague Dawley, Inc., Indianapolis, IN
Quarantine Period:	Five days
Date Received:	June 25, 1998
Quantity and Sex:	5 males and 5 females (nulliparous and non-pregnant)
Animal Identification:	Ear punch and cage cards
Weight When Tested:	Males (230-258 g); Females (175-213 g)
Date of Birth:	May 1, 1998
Animal Husbandry	
Cage Type:	Suspended, wire bottom, stainless steel
Housing:	One per cage
Environmental Controls Set to Maintain:	•Temperature Range: 22°C ± 3° •Humidity Range: 30-80% •12-hour light/dark cycle •10-12 air changes/hour
Food:	PMI™ Lab Diet Formula #5008, available *ad libitum* except during the exposure period
Water Type:	Municipal water supply from automatic water system, available *ad libitum* except during the exposure period

Animal husbandry and housing at STILLMEADOW, Inc. comply with Animal Welfare Act Regulations. No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

PROCEDURES

Prestudy Testing

Trial assays were conducted to determine which method(s) of vaporizing the test substance into the exposure chamber would produce an acceptable concentration.

Exposure Chamber

A 15.5L nose-only stainless steel, dynamic flow inhalation chamber was utilized in this experiment. The body of the chamber has 16 ports in 3 rows. Polycarbonate tubes are inserted into 10 designated individual ports. The test substance is introduced through the opening in the top of the chamber. The bottom section has a corresponding air outlet and a drain valve for cleaning the chamber. The individual polycarbonate tubes are tapered at one end to fit the shape of the animal's head and the back portion is sealed with a polycarbonate cap. The tubes containing the animals fit tightly into the ports, and are sealed with "O" rings.

PROCEDURES (cont.)

Generation of Test Atmosphere

The vapor was generated by bubbling air through fritted tubes into 4 Erlenmeyer flasks, each containing 300 mL of the test substance. The air was heated prior to entering flasks by heating tape wrapped around the air tubes to approximately 35° C. The vapor was pulled from the flasks through the exposure chamber. Air flow into the chamber was maintained through the use of a calibrated orifice plate at a rate of 21.9 air changes per hour. Air flow was recorded just prior to and after the exposure period, and was sufficient to ensure an oxygen content of at least 19% of the exposure atmosphere. Temperature and humidity were recorded prior to and after the exposure period from a Solomat hygrometer located in the exposure chamber.

Test Substance Administration

Healthy albino rats were released from quarantine, and five males and five females were selected for testing. The animals were exposed to a vapor generated from the liquid test substance for a period of one hour. A visible coating was observed on the inside of the sample delivery flask, sample delivery line and inhalation chamber. When 99% concentration (t-99) was attained, the animals which were individually housed in polycarbonate exposure tubes were inserted into a 15.5L stainless steel nose-only inhalation chamber for the specified exposure period. At the termination of the exposure period, the animals were returned to their stock laboratory cages.

Determination of Concentration

The concentration of test substance in the exposure atmosphere (taken from the breathing zone of the animals) was determined analytically twice during the exposure. The analytical determination was made using a Varian Model 3700 gas chromatograph (Appendix A). The nominal concentration was determined by dividing the loss in weight of the test substance after the exposure by the total volume of air which passed through the chamber.

In-life Observations

Observations for mortality and signs of pharmacologic and/or toxicologic effects were made frequently on the day of exposure and at least once daily thereafter for 14 days (Day 0 is day of exposure). Observations include skin, fur, eyes, mucous membranes, somatomotor activity and behavior pattern, with particular attention to convulsions, coma, diarrhea, lethargy, sleep, salivation and tremors. Individual body weights were recorded just prior to the inhalation exposure and on Days 7 and 14.

PROCEDURES (cont.)

Postmortem Observations

At study termination, each animal was euthanized by an intraperitoneal injection of Fatal Plus® (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy, and all abnormalities were recorded. Gross necropsy includes observations of external surfaces and orifices; thoracic, abdominal and pelvic cavities, and major organs. The lungs were preserved and submitted for histopathological interpretation.

Statistical Analysis

In order to calculate a mean exposure, the Mean Value Theorem of Calculus was used to properly weight the concentration, since the concentrations could not be measured continuously (see Table 4). This method weights concentrations based on the time span of each concentration. A concentration can be calculated for each minute, which better represents the exposure concentration received by each animal.

RESULTS AND DISCUSSION

Mortality/Estimated LC_{50} Values

There was no mortality during the study. As indicated by the data, the acute inhalation LC_{50} for N, N-Dimethylacrylamide is greater than 776 ppm.

Body Weights

Individual body weights are presented in Table 1. Body weight gain of surviving animals was unaffected by the administration of the test substance.

Clinical Signs

Clinical signs are presented in Table 2. All animals appeared normal for the duration of the study.

Necropsy Findings

Individual necropsy findings are presented in Table 1. The gross necropsy conducted on each animal at termination of the study revealed no observable abnormalities, except for red lungs in three females. Histopathological results are presented in Appendix B.

RESULTS AND DISCUSSION (cont.)

Inhalation Chamber Conditions

Chamber operating parameters are presented in Table 3. Concentration determinations and calculations are presented in Table 4. Pretest data are presented in Table 5.

CONCLUSION

N, N-Dimethylacrylamide was evaluated for its acute inhalation toxicity potential in albino rats. As indicated by the data, the acute inhalation LC_{50} for N, N-Dimethylacrylamide is greater than 776 ppm in males and females.

Jerry E. Bennick
Study Director
STILLMEADOW, Inc.

10 Nov 98
Date

STUDY PERSONNEL

Technical Staff

Liangbao Rao, B.S.
Paul H. Siemens, B.A.
Carol Morris, B.A.
Hector Fuentes
Chris Ontiveros
Stephen McGary
Weston Anderson, B.S. Pharm.
Charles A. Montgomery, D.V.M.

Data Services

Connie Pavatte, Report Preparation

Table 1
ACUTE INHALATION TOXICITY STUDY IN RATS
Body Weights, Time of Death, and Gross Necropsy
Test Substance: N, N-Dimethylacrylamide
Exposure Concentration: 776 ppm

Animal Number	Body Weights (g)			Time of Death*	Gross Necropsy Findings
	Day 0	Day 7	Final		
21-M	236	271	312	Day 14	NOA
22-M	258	275	308	Day 14	NOA
23-M	240	293	331	Day 14	NOA
24-M	230	269	302	Day 14	NOA
25-M	252	284	319	Day 14	NOA
26-F	198	212	217	Day 14	NOA
27-F	213	219	230	Day 14	Lungs red.
28-F	198	210	234	Day 14	Lungs light red
29-F	196	207	229	Day 14	Lungs light red.
30-F	175	187	192	Day 14	NOA

* - Day of dosing considered Day 0; Day 14 is terminal sacrifice.
M - Male; F - Female; NOA - No Observable Abnormalities

Table 2
ACUTE INHALATION TOXICITY STUDY IN RATS
Pharmacologic and/or Toxicologic Signs
Test Substance: N, N-Dimethylacrylamide
Exposure Concentration: 776 ppm
Sex: Males and Females

	Time After Exposure Begins																		
	HOURS					DAYS													
Reaction and Severity	0.5	1.0	2.5	4.5	6.0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Males																			
Fur coated with feces/urine	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Females																			
Fur coated with feces/urine	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

v - very slight; s - slight; m - moderate; e - extreme
Note: Digits indicate number of animals exhibiting reaction.

Table 3
ACUTE INHALATION TOXICITY STUDY IN RATS
Chamber Operating Parameters
Test Substance: N, N-Dimethylacrylamide

Exposure Concentration: 776 ppm

Time (Hour)	Temp. (°F)	RH (%)	Air Flow (Lpm)
Pre-exposure	67	73	5.66
Post-exposure	67	73	5.66
Mean:	67	73	5.66

t-99 Determination

Initial Chamber Air Flow	5.66 Lpm
Exposure Chamber Size	15.5 L
Baffling Chamber	Not used
t-99 Value	13 min

Table 4
ACUTE INHALATION TOXICITY STUDY IN RATS
Analytical Concentration Calculations
Test Substance: N, N-Dimethylacrylamide

Standard Curve

Standard	Conc. (mg/mL)	Area
A	8.921	1392821
B	4.460	774946
C	2.230	348283
D	1.115	186896

Corr (r) = 0.997561 y intercept = 24947.2 slope = 155635

Calculation for 776 ppm Conc

Sample Number	Peak Area	Conc. (mg/mL)	X	Multi. Factor*	Chamber Conc. (ppm)
1	343220	2.04499	x	1.51	759
2	358592	2.14376	x	1.51	795

* - Multiplication factor (mL/L) calculated from figures in Appendix A using following formula:

$$\frac{\text{Solvent volume}}{(\text{Duration})(\text{Sample rate})} = \text{Multifactor}$$

Table 4 (cont.)
ACUTE INHALATION TOXICITY STUDY IN RATS
Analytical Concentration Determination
Test Substance: N, N-Dimethylacrylamide

	Dose Level: 776 ppm	
Event*	Time Period	Concentration
Start-up	9:27	
t-99 (begin exposure)	9:40	
Extrapolation calculated	9:40- 9:55	759 ppm
Sample 1 taken	9:55-10:05	759 ppm
Interpolation calculated	10:05-10:15	777 ppm
Sample 2 taken	10:15-10:25	795 ppm
Extrapolation calculated	10:25-10:40	795 ppm
End exposure	10:40	
MEAN EXPOSURE CONC.		776 ppm
Nominal Concentration		1120 ppm

* - Sample # taken is the concentration measured during the sampling period.
Extrapolation is the measured concentration of the adjacent event period carried over to the present event period.
Interpolation is the concentration calculated as the average of the measured concentration before and after the present event period.
Mean exposure concentration is the sum of the actual time weighted concentrations divided by the sum of elapsed times and represents the mean value of the exposure concentration.

Table 5
ACUTE INHALATION TOXICITY STUDY IN RATS
Pretest Data
Test Substance: N, N-Dimethylacrylamide

Trial assays were conducted to ascertain results, summarized below, under different chamber conditions.

Nominal Conc (ppm)
626
722

Exposure concentration - 776 ppm with a nominal conc. of 1120 ppm

Appendix A
ACUTE INHALATION TOXICITY STUDY IN RATS
Gas Chromatograph Operating Parameters
Test Substance: N, N-Dimethylacrylamide

Instrument	Varian 3700 SL039/077
Column	Alltech 0.53 mm X 30 m
Column Packing	AT-1
Temperatures	
Injector	220°C
Column	160°C
Detector	220°C
Detector	Flame Ionization Detector
Gas Flow Rates	
Nitrogen carrier	4.5-5.5 psi
Hydrogen flow	40 psi
Air Flow	40 psi
Sampling Method - Impingement with back-up	
Extraction Solvent	Acetone
Sampling Rate	1.655 Lpm
Sampling Duration	10 minutes
Volume of Chamber Air Sampled	16.55 L
Injection Volume	1.0-1.4 µL

Appendix B

ComPath Charles A. Montgomery, D.V.M.

N,N-Dimethylacrylamide/Loctite 3311 Study
Stillmeadow, Inc.

Methods Sprague-Dawley rats, ten animals per group, of equal sexes, were exposed to either N,N-dimethylacrylamide (group A) or Loctite 3311 Medical Device Adhesive (group B) by nose-only inhalation and held for 14 days for observation. Rats were necropsied, gross lesions reported, and the lungs were submitted for histopathologic interpretation. Lungs were infused at necropsy, the trachea ligated, and fixed in 10% NBF. All lobes of the lung for each rat were processed, embedded in paraffin, cut on a microtome at 4 microns, and stained with H&E. Individual animal reports are provided for each group. Details of the lung lesions observed are tabulated in Tables 1 and 2, with the frequency of lesion and average degree of severity summarized for each group. A narrative summary of the results is provided.

Results Interstitial pneumonia occurred in both groups with the same frequency (9/10) but was more severe in group B (2.9). The lesions consisted of thickening of the interstitial wall by lymphocytes and macrophages. One animal in group B also had a large focus of granulomatous inflammation in the subpleural region of the lung. Type II hyperplasia was observed in one animal in group A only. Eosinophils were seen around veins and arteries in 3/10 of group A and 5/10 of group B with the same degree of severity. Alveolar emphysema was observed in both groups, usually located at the tips of lung lobes. One animal in group B had a single subpleural mineralized microlith.

Vascular lesions and hemodynamic changes were observed in both groups but were more frequent and more severe in group B. Medial hypertrophy of arteries in the lung occurred most frequently in zones of interstitial inflammation. Those animals with alveolar hemorrhage often had foci of hemoglobin crystals in the affected area.

No significant histopathologic lesions were observed in the esophagus, trachea, or thymus.

Summary Both groups had inflammatory and hemodynamic lesions. However, the frequency and severity of lesions was greater in group B. The total number of lesions observed in group B was 40, whereas 24 were seen in group A.

Charles A. Montgomery

Charles A. Montgomery, D.V.M.
Diplomate, American College of Veterinary Pathologists
Diplomate, American College of Laboratory Animal Medicine

Appendix B (cont.)

ComPath Charles A. Montgomery, D.V.M.

Individual Animal Report
N,N-Dimethylacrylamide
Pulmonary Lesions

Rat number	*AP number*	*Lesions*
21M	8173	Cellular infiltration, eosinophils, multifocal, minimal, perivascular
22M	8173	Inflammation, chronic, multifocal, mild, interstitium
23M	8173	Inflammation, chronic, multifocal, mild, interstitium Fibrin, focal, mild, respiratory duct
24M	8173	Inflammation, chronic, multifocal, mild, interstitium Hypertrophy, focal, mild, media, arteries
25M	8173	Inflammation, chronic, multifocal, mild Emphysema, multifocal, mild
26F	8173	Inflammation, chronic, multifocal, mild, interstitium Emphysema, multifocal, mild Hemoglobin crystals, multifocal, moderate, subpleural and alveolar
27F	8173	Emphysema, multifocal, mild, lung Cellular infiltration, eosinophils, multifocal, moderate, peribronchiolar and perivascular Inflammation, chronic, multifocal, mild, interstitium Hyperplasia, focal, mild, Type II pneumocytes Hypertrophy, multifocal, mild, media, arteries
28F	8173	Inflammation, chronic, multifocal, mild, interstitium Emphysema, multifocal, mild Cellular infiltration, eosinophils, multifocal, minimal, perivascular
29F	8173	Inflammation, chronic, multifocal, mild, interstitium Emphysema, multifocal, mild Hypertrophy, focal, mild, media, arteries
30F	8173	Inflammation, chronic, multifocal, minimal Emphysema, multifocal, mild

Table 1. N,N-Dimethylacrylamide Rats (Group A)

Histopathologic lesions in lung	*21M*	*22M*	*23M*	*24M*	*25M*	*26F*	*27F*	*28F*	*29F*	*30F*	*Incidence/ average severity*
Interstitial pneumonia	0	2	2	2	2	2	2	2	2	1	9/10 (1.9)
Granulomatous pneumonia	0	0	0	0	0	0	0	0	0	0	0/10
Perivascular eosinophils	1	0	0	0	0	0	3	1	0	0	3/10 (1.7)
Type II cell hyperplasia	0	0	0	0	0	0	2	0	0	0	1/10 (2.0)
Emphysema	0	0	0	0	2	2	2	2	2	2	6/10 (2.0)
Microlithiasis	0	0	0	0	0	0	0	0	0	0	0/10
Medial hypertrophy, pulmonary arteries	0	0	0	2	0	0	2	0	2	0	3/10 (2.0)
Acute vascular congestion	0	0	0	0	0	0	0	0	0	0	0/10
Alveolar edema	0	0	0	0	0	0	0	0	0	0	0/10
Alveolar hemorrhage, hemoglobin crystals	0	0	0	0	0	3	0	0	0	0	1/10 (3.0)
Alveolar fibrin	0	0	2	0	0	0	0	0	0	0	1/10 (2.0)

B-10

STILLMEADOW
INCORPORATED

98-11-12P12:50 RCVD

VOLUME __ OF __ OF SUBMISSION

Loctite 3311 Medical Device Adhesive, Bulk # 190381

FINAL REPORT

ACUTE INHALATION TOXICITY STUDY IN RATS

OSHA Regulation 29 CFR 1910

AUTHOR - Jerry E. Bennick

STUDY INITIATION DATE: June 9, 1998
STUDY COMPLETION DATE: November 10, 1998

CONDUCTED BY:

STILLMEADOW, Inc.
12852 Park One Drive
Sugar Land, TX 77478

LABORATORY STUDY NUMBER

4348-98

VOLUME 1 OF 1 OF STUDY

PAGE 1 OF 18

SUBMITTED TO:
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Rocky Hill, CT 06067

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QUALITY ASSURANCE STATEMENT

Study Number: 4348-98
Test Substance: Loctite 3311 Medical Device Adhesive, Bulk # 190381
Study Title: Acute Inhalation Toxicity Study in Rats

The study has been inspected and the report and data have been audited in accordance with STILLMEADOW, Inc. Standard Operating Procedures (SOP's). The findings from the inspection and audit were reported to the Study Director and Management as follows:

Phase of Study Inspected	Date Inspected	Reported to Study Director	Reported to Management
Dosing	6/30/98	6/30/98	6/30/98
Report/Data Audit	9/23/98	9/23/98	9/23/98

Lynne Magee
Lynne Magee, B.S.
Quality Assurance Unit
STILLMEADOW, Inc.

9 Nov 98
Date

SUMMARY

Loctite 3311 Medical Device Adhesive, Bulk # 190381 was evaluated for its acute inhalation toxicity potential in albino rats. Five males and five females were exposed for one hour to a vapor generated from the liquid test substance at a level of 513 ppm. There was no morality during the study. There were no clinical signs of toxicity observed during the study. Body weights were essentially unaffected by exposure. The gross necropsy revealed no observable abnormalities, except discolored, swollen lungs in one animal. As indicated by the data, the acute inhalation LC_{50} for Loctite 3311 Medical Device Adhesive, Bulk # 190381 is greater than 513 ppm.

INTRODUCTION

The objective of this study was to determine the acute inhalation toxicity potential of the test substance in accordance with US OSHA Regulation: 29 CFR 1910.1200. This study was conducted for Loctite Corporation, according to the approved protocol and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. The original protocol, raw data, and this report are kept on file in the STILLMEADOW, Inc. archives. The the animals were exposed as follows:

Beginning of 1 Hour Exposure					Termination of In-Life Observations	
Dose (ppm)	Males		Females		Date	
	Date	Time	Date	Time	Males	Females
513	6/30/98	11:05	6/30/98	11:05	7/14/98	7/14/98

TEST SUBSTANCE

Identification:	Loctite 3311 Medical Device Adhesive Part No. 19737 Batch 8CP263A
Date and Quantity Received:	June 8, 1998; 2 x 1 liter
Physical Description:	Pale yellow liquid
Storage:	Room temperature
Purity and Composition:	Certificate of Analysis not provided by sponsor
Stability:	March, 1999 (label claim)

Records pertaining to stability, characterization, and verification of test substance identity are the responsibility of the sponsor.

TEST SYSTEM

Experimental Animals

Species and Strain:	Rat; HSD:Sprague-Dawley
Justification of Species:	The rat is a representative rodent species preferred by various regulatory agencies for use in acute inhalation toxicity studies.
Source:	Harlan Sprague Dawley, Inc., Indianapolis, IN
Quarantine Period:	Five days
Date Received:	June 25, 1998
Quantity and Sex:	5 males and 5 females (nulliparous and non-pregnant)
Animal Identification:	Ear punch and cage cards
Weight When Tested:	Males (230-246 g); Females (194-209 g)
Date of Birth:	May 1, 1998

Animal Husbandry

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	One per cage
Environmental Controls Set to Maintain:	•Temperature Range: 22°C ± 3° •Humidity Range: 30-80% •12-hour light/dark cycle •10-12 air changes/hour
Food:	PMI™ Lab Diet Formula #5008, available *ad libitum* except during the exposure period
Water Type:	Municipal water supply from automatic water system, available *ad libitum* except during the exposure period

Animal husbandry and housing at STILLMEADOW, Inc. comply with Animal Welfare Act Regulations. No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

PROCEDURES

Exposure Chamber

A 15.5L nose-only stainless steel, dynamic flow inhalation chamber was utilized in this experiment. The body of the chamber has 16 ports in 3 rows. Polycarbonate tubes are inserted into 10 designated individual ports. The test substance is introduced through the opening in the top of the chamber. The bottom section has a corresponding air outlet and a drain valve for cleaning the chamber. The individual polycarbonate tubes are tapered at one end to fit the shape of the animal's head and the back portion is sealed with a polycarbonate cap. The tubes containing the animals fit tightly into the ports, and are sealed with "O" rings.

PROCEDURES (cont.)

Generation of Test Atmosphere

The vapor was generated by bubbling air through a 500 mL Erlenmeyer flask containing 200 mL of the test substance. The vapor was pulled from the flasks through the exposure chamber. Air flow into the chamber was maintained through the use of a calibrated orifice plate at a rate of 21.9 air changes per hour. Air flow was recorded just prior to and after the exposure period, and was sufficient to ensure an oxygen content of at least 19% of the exposure atmosphere. Temperature and humidity were recorded prior to and after the exposure period from a Solomat hygrometer located in the exposure chamber.

Test Substance Administration

Healthy albino rats were released from quarantine, and five males and five females were selected for testing. The animals were exposed to a vapor generated from the liquid test substance for a period of one hour. A visible coating was observed on the inside of the sample delivery flask, sample delivery line and inhalation chamber. When 99% concentration (t-99) was attained, the animals which were individually housed in polycarbonate exposure tubes were inserted into a 15.5L stainless steel nose-only inhalation chamber for the specified exposure period. At the termination of the exposure period, the animals were washed and returned to their stock laboratory cages.

Determination of Concentration

The concentration of test substance in the exposure atmosphere (taken from the breathing zone of the animals) was determined analytically twice during the exposure. The analytical determination was made using a Tracor Model 560 gas chromatograph (Appendix A). The nominal concentration was determined by dividing the loss in weight of the test substance after the exposure by the total volume of air which passed through the chamber.

In-life Observations

Observations for mortality and signs of pharmacologic and/or toxicologic effects were made frequently on the day of exposure and at least once daily thereafter for 14 days (Day 0 is day of exposure). Observations include skin, fur, eyes, mucous membranes, somatomotor activity and behavior pattern, with particular attention to convulsions, coma, diarrhea, lethargy, sleep, salivation and tremors. Individual body weights were recorded just prior to the inhalation exposure and on Days 7 and 14.

PROCEDURES (cont.)

Postmortem Observations

At study termination, each animal was euthanized by an intraperitoneal injection of Fatal Plus® (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy, and all abnormalities were recorded. Gross necropsy includes observations of external surfaces and orifices; thoracic, abdominal and pelvic cavities, and major organs. The lungs were preserved and submitted for histopathological interpretation.

Statistical Analysis

In order to calculate a mean exposure, the Mean Value Theorem of Calculus was used to properly weight the concentration, since the concentrations could not be measured continuously (see Table 4). This method weights concentrations based on the time span of each concentration. A concentration can be calculated for each minute, which better represents the exposure concentration received by each animal.

RESULTS AND DISCUSSION

Mortality/Estimated LC_{50} Values

There was no mortality during the study. As indicated by the data, the acute inhalation LC_{50} for Loctite 3311 Medical Device Adhesive, Bulk # 190381 is greater than 513 ppm.

Body Weights

Individual body weights are presented in Table 1. Body weight gain was largely unaffected by the administration of the test substance. One female exhibited slight weight loss between Days 0 and 7.

Clinical Signs

Clinical signs are presented in Table 2. All animals appeared normal for the duration of the study.

Necropsy Findings

Individual necropsy findings are presented in Table 1. The gross necropsy conducted on each animal at termination of the study revealed no observable abnormalities, except for blotchy red and swollen lungs in one male. Histopathological results are presented in Appendix B.

RESULTS AND DISCUSSION (cont.)

Inhalation Chamber Conditions

Chamber operating parameters are presented in Table 3. Concentration determinations and calculations are presented in Table 4.

CONCLUSION

Loctite 3311 Medical Device Adhesive, Bulk # 190381 was evaluated for its acute inhalation toxicity potential in albino rats. As indicated by the data, the acute inhalation LC_{50} for Loctite 3311 Medical Device Adhesive, Bulk # 190381 is greater than 513 ppm in males and females.

Jerry E. Benick
Study Director
STILLMEADOW, Inc.

10 Nov 98
Date

STUDY PERSONNEL

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Table 1
ACUTE INHALATION TOXICITY STUDY IN RATS
Body Weights, Time of Death, and Gross Necropsy
Test Substance: Loctite 3311 Medical Device Adhesive, Bulk # 190381
Exposure Concentration: 513 ppm

Animal Number	Body Weights (g)			Time of Death*	Gross Necropsy Findings
	Day 0	Day 7	Final		
41-M	230	273	335	Day 14	NOA
42-M	239	279	331	Day 14	Lungs slightly swollen, with dark red blotches throughout.
43-M	234	269	325	Day 14	NOA
44-M	236	284	329	Day 14	NOA
45-M	246	283	341	Day 14	NOA
46-F	194	197	209	Day 14	NOA
47-F	197	203	210	Day 14	NOA
48-F	199	193	204	Day 14	NOA
49-F	209	212	217	Day 14	NOA
50-F	195	218	224	Day 14	NOA

* - Day of dosing considered Day 0; Day 14 is terminal sacrifice.
M - Male; F - Female; NOA - No Observable Abnormalities

Table 2
ACUTE INHALATION TOXICITY STUDY IN RATS
Pharmacologic and/or Toxicologic Signs
Test Substance: Loctite 3311 Medical Device Adhesive, Bulk # 190381
Exposure Concentration: 513 ppm
Sex: Males and Females

	Time After Exposure Begins																		
	HOURS					DAYS													
Reaction and Severity	0.5	1.0	2.5	4.5	5.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Males																			
Fur coated with feces/urine	0	5	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Females																			
Fur coated with feces/urine	0	5	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

v - very slight; s - slight; m - moderate; e - extreme
Note: Digits indicate number of animals exhibiting reaction.

Table 3
ACUTE INHALATION TOXICITY STUDY IN RATS
Chamber Operating Parameters
Test Substance: Loctite 3311 Medical Device Adhesive, Bulk # 190381

Exposure Concentration: 513 ppm

Time (Hour)	Temp. (°F)	RH (%)	Air Flow (Lpm)
Pre-exposure	64	77	5.66
Post-exposure	64	75	5.66
Mean:	64	76	5.66

t-99 Determination

Initial Chamber Air Flow	5.66 Lpm
Exposure Chamber Size	15.5 L
Baffling Chamber	Not used
t-99 Value	13 min

Table 4
ACUTE INHALATION TOXICITY STUDY IN RATS
Analytical Concentration Calculations
Test Substance: Loctite 3311 Medical Device Adhesive, Bulk # 190381

Standard Curve

Standard	Conc. (mg/mL)	Area
A	3.120	217680
B	1.560	102538
C	1.040	66734
D	0.520	34173

Corr (r) = 0.999472 y intercept = -5710.07 slope = 71148.3

Calculation for 513 ppm Conc

Sample Number	Peak Area	Conc. (mg/mL)	Multi. Factor*	Chamber Conc. (ppm)
1	99100	1.47313 x	1.50	543
2	88466	1.32306 x	1.50	488

* - Multiplication factor (mL/L) calculated from figures in Appendix A using following formula:

$$\frac{\text{Solvent volume}}{(\text{Duration})(\text{Sample rate})} = \text{Multifactor}$$

Table 4 (cont.)
ACUTE INHALATION TOXICITY STUDY IN RATS
Analytical Concentration Determination
Test Substance: Loctite 3311 Medical Device Adhesive, Bulk # 190381

	Dose Level: 513 ppm	
Event*	Time Period	Concentration
Start-up	10:52	
t-99 (begin exposure)	11:05	
Extrapolation calculated	11:05-11:15	543 ppm
Sample 1 taken	11:15-11:25	543 ppm
Interpolation calculated	11:25-11:40	516 ppm
Sample 2 taken	11:40-11:50	488 ppm
Extrapolation calculated	11:50-12:05	488 ppm
End exposure	12:05	
MEAN EXPOSURE CONC.		513 ppm
Nominal Concentration		796 ppm

* - Sample # taken is the concentration measured during the sampling period.
Extrapolation is the measured concentration of the adjacent event period carried over to the present event period.
Interpolation is the concentration calculated as the average of the measured concentration before and after the present event period.
Mean exposure concentration is the sum of the actual time weighted concentrations divided by the sum of elapsed times and represents the mean value of the exposure concentration.

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Appendix A
ACUTE INHALATION TOXICITY STUDY IN RATS
Gas Chromatograph Operating Parameters
Test Substance: Loctite 3311 Medical Device Adhesive, Bulk # 190381

Instrument	Tracor 560
Column	Alltech
Column Packing	AT-1
Sampling Method - Impingement with back-up	
Extraction Solvent	Acetone
Sampling Rate	1.665 Lpm
Sampling Duration	10 minutes
Volume of Chamber Air Sampled	16.65 L
Injection Volume	25 mL

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Appendix B

ComPath Charles A. Montgomery, D.V.M.

N,N-Dimethylacrylamide/Loctite 3311 Study
Stillmeadow, Inc.

Methods Sprague-Dawley rats, ten animals per group, of equal sexes, were exposed to either N,N-dimethylacrylamide (group A) or Loctite 3311 Medical Device Adhesive (group B) by nose-only inhalation and held for 14 days for observation. Rats were necropsied, gross lesions reported, and the lungs were submitted for histopathologic interpretation. Lungs were infused at necropsy, the trachea ligated, and fixed in 10% NBF. All lobes of the lung for each rat were processed, embedded in paraffin, cut on a microtome at 4 microns, and stained with H&E. Individual animal reports are provided for each group. Details of the lung lesions observed are tabulated in Tables 1 and 2, with the frequency of lesion and average degree of severity summarized for each group. A narrative summary of the results is provided.

Results Interstitial pneumonia occurred in both groups with the same frequency (9/10) but was more severe in group B (2.9). The lesions consisted of thickening of the interstitial wall by lymphocytes and macrophages. One animal in group B also had a large focus of granulomatous inflammation in the subpleural region of the lung. Type II hyperplasia was observed in one animal in group A only. Eosinophils were seen around veins and arteries in 3/10 of group A and 5/10 of group B with the same degree of severity. Alveolar emphysema was observed in both groups, usually located at the tips of lung lobes. One animal in group B had a single subpleural mineralized microlith.

Vascular lesions and hemodynamic changes were observed in both groups but were more frequent and more severe in group B. Medial hypertrophy of arteries in the lung occurred most frequently in zones of interstitial inflammation. Those animals with alveolar hemorrhage often had foci of hemoglobin crystals in the affected area.

No significant histopathologic lesions were observed in the esophagus, trachea, or thymus.

Summary Both groups had inflammatory and hemodynamic lesions. However, the frequency and severity of lesions was greater in group B. The total number of lesions observed in group B was 40, whereas 24 were seen in group A.

Charles A. Montgomery

Charles A. Montgomery, D.V.M.
Diplomate, American College of Veterinary Pathologists
Diplomate, American College of Laboratory Animal Medicine

Appendix B (cont.)

ComPath Charles A. Montgomery, D.V.M.

Individual Animal Report
Loctite 3311 Medical Device Adhesive
Pulmonary Lesions

Rat number	*AP number*	*Lesions*
41M	8174	Inflammation, chronic, diffuse, moderate, interstitium Cellular infiltration, eosinophils, focal, minimal, perivascular
42M	8174	Vascular congestion, acute, diffuse, moderate Edema, diffuse, mild, alveoli Hemorrhage, acute, with hemoglobin crystals, multifocal, moderate, alveoli Hypertrophy, multifocal, mild, media, arteries
43M	8174	Inflammation, chronic, diffuse, moderate, interstitium Emphysema, focal, minimal
44M	8174	Inflammation, chronic, multifocal, mild, interstitium Emphysema, multifocal, minimal Hypertrophy, multifocal, mild, media, arteries Vascular congestion, acute, focal, mild
45M	8174	Inflammation, chronic, diffuse, moderate, interstitium Cellular infiltration, eosinophils, multifocal, mild, perivascular Hypertrophy, multifocal, mild, media, arteries Emphysema, multifocal, mild
46F	8174	Inflammation, chronic, diffuse, moderate, interstitium Emphysema, multifocal, mild Vascular congestions, acute, multifocal, mild
47F	8174	Inflammation, chronic, diffuse, moderate, interstitium Vascular congestion, acute, multifocal, mild Emphysema, multifocal, minimal Cellular infiltration, eosinophils, focal, minimal, perivascular

Individual Animal Report
Loctite 3311 Medical Device Adhesive
Pulmonary Lesions

Rat number	*AP number*	*Lesions*
48M	8174	Inflammation, chronic, diffuse, moderate, interstitium Emphysema, multifocal, mild Inflammation, granulomatous, focal, moderate, subpleural Cellular infiltration, eosinophils, multifocal, mild, perivascular Hypertrophy, multifocal, moderate, media, arteries Vascular congestion, acute, multifocal, mild, subpleural Hemorrhage, with hemoglobin crystals, focal, moderate
49M	8174	Inflammation, chronic, diffuse, moderate, interstitium Vascular congestion, acute, multifocal, mild Emphysema, focal, minimal Cellular infiltration, eosinophils, multifocal, mild, perivascular Microlith, focal, mild, alveoli, subpleural
50M	8174	Inflammation, chronic, multifocal, moderate, interstitium Vascular congestion, acute, multifocal, mild Hemorrhage, focal, mild, alveoli Emphysema, multifocal, mild Hypertrophy, multifocal, mild, media, arteries

Table 2. Loctite 3311 Medical Device Adhesive Rats (Group B)

Histopathologic lesions in lung	*41M*	*42M*	*43M*	*44M*	*45M*	*46F*	*47F*	*48F*	*49F*	*50F*	*Incidence/ average severity*
Interstitial pneumonia	3	0	3	2	3	3	3	3	3	3	9/10 (2.9)
Granulomatous pneumonia	0	0	0	0	0	0	0	3	0	0	1/10 (3.0)
Perivascular eosinophils	1	0	0	0	2	0	1	2	2	0	5/10 (1.6)
Type II cell hyperplasia	0	0	0	0	0	0	0	0	0	0	0/10
Emphysema	0	0	1	1	2	2	1	2	1	2	8/10 (1.5)
Microlithiasis	0	0	0	0	0	0	0	0	2	0	1/10 (2.0)
Medial hypertrophy, pulmonary arteries	0	2	0	2	2	0	0	3	0	2	5/10 (2.2)
Acute vascular congestion	0	3	0	2	0	2	2	2	2	2	7/10 (2.1)
Alveolar edema	0	2	0	0	0	0	0	0	0	0	1/10 (2.0)
Alveolar hemorrhage, hemoglobin crystals	0	3	0	0	0	0	0	3	0	2	3/10 (2.7)
Alveolar fibrin	0	0	0	0	0	0	0	0	0	0	0/10