

Background:

In a letter dated August 10, 1990, Dow Corning submitted a Notification of Substantial Risk under TSCA Section 8(e) concerning preliminary results obtained in an acute vapor phase inhalation toxicity study of DOW CORNING® X1-6145A Additive in rats. A copy of the final report was submitted to EPA August 21, 1990. In response to an Agency request, Dow Corning provided additional follow-up to our initial notification (8EHQ-0890-1047) and has continued to submit new data on this chemical substance as such data were developed or became known to Dow Corning.

As an additional supplement to 8EHQ-0890-1047, we are providing EPA with a copy of a recent Dow Corning report on a 14-day repeated dose inhalation toxicity study of DOW CORNING® X1-6145A Additive in rats.

Summary:

A 14-day repeated dose inhalation toxicity study was conducted to investigate the inhalation toxicity of DOW CORNING® X1-6145A Additive, chemically described as hexamethyldisilylethane (HMDSE, CASRN 18406-41-2), in rats. Four groups of ten male and ten female Fischer 344 rats were exposed to target concentrations of 0, 50, 100, and 200 ppb HMDSE for six hours a day, for ten exposures over 14 days (excluding weekends). Animals were observed for treatment-related signs of toxicity, growth, and mortality. At termination of the study, rats were sacrificed and examined for changes in organ weights, gross pathology, and histopathology.

No mortality was observed in the study. Very slight to moderate rales were observed in several animals exposed to 100 and 200 ppb HMDSE. No apparent treatment-related clinical signs were observed in animals exposed to 50 ppb HMDSE. Statistically significant decreases in body weights were observed in males exposed to 200 ppb on day 8, 15, and at sacrifice. Female body weights were decreased in animals exposed to 200 ppb HMDS on day 8 only. Statistically significant increases in liver/body weight ratios were observed in males exposed to 100 and 200 ppb of the test material. Statistically significant increases in kidney/body weight ratios were observed in males exposed to 200 ppb of the test material. A statistically significant increase in the liver/body weight ratio and in the adrenal/body weight ratio was observed in females exposed to 200 ppb of the test material. There were no other statistically significant differences in organ weights between test and control animals.

There were no apparent test article-related gross pathological changes in animals exposed to HMDSE. Test article-related changes were observed microscopically in the respiratory tract of all animals exposed to the test material. The nares,

nasal cavity, and pharynx were the most common sites of test article-related changes with the larynx and trachea only infrequently affected. Squamous metaplasia and acute inflammation of the nasal cavity were the most common findings in the 200 ppb group and also occurred, with somewhat reduced incidence and severity, in many rats from the 50 and 100 ppb groups. An increased activity of mucus goblet cells of the respiratory epithelium, characterized by increased height and prominence of goblet cells with formation of microcysts, was the most common finding in all sections of the nasal cavity from the 50 and 100 ppb groups. All lesions in the lung and other organs examined microscopically were considered agonal and spontaneous and unrelated to test article exposure.

Based on these results, a No-Observable-Adverse-Effect-Level (NOAEL) was not established for the test material in Fischer 344 rats under the conditions of this study.

Actions:

Dow Corning will continue to notify EPA of any further pertinent information that may be developed concerning hexamethyldisilylethane. Dow Corning has ceased efforts to commercialize this substance and has taken actions to ensure that it is not present as an unintentional byproduct in other materials we make.

If you have any questions concerning any of the aforementioned studies, please contact me at 517-496-4057 or at the address provided herein. If you require further general information regarding this supplemental submission, please contact Dr. Rhys G. Daniels, Regulatory Compliance Specialist, Product Stewardship and Regulatory Compliance Department, at 517-496-4222 or at the address provided herein.

Sincerely,

Handwritten signature of Stephen A. Mahi, Manager Product Safety, for M.P. Hill. The signature is written in black ink and includes the name "Stephen A. Mahi" followed by a comma and the title "Manager Product Safety" and "for M.P. Hill".

Michael P. Hill
Americas Vice-President and Corporate Director
Health and Environmental Sciences
(517)496-4057

**DOW CORNING CORPORATION
HEALTH & ENVIRONMENTAL SCIENCES
TECHNICAL REPORT**

REPORT NO.: 1996-10000-41496

Title: A 14-Day Repeated Dose Inhalation Toxicity Study of
Dow Corning® X1-6145A Additive in Albino Rats

Study No: 7758

Test Article: DOW CORNING® X1-6145A Additive

Study Director: Waheed H. Siddiqui, Ph.D.

Author(s): Waheed H. Siddiqui, Ph.D.
Gary B. Kolesar, M.S., M.P.H., DABT
Leland W. Dochterman, D.V.M., DACVP
Sharon L. Mudgett, B.S.

Sponsor: Dow Corning Corporation

Sponsor
Representative: Patrick W. Langvardt

Testing Facility: Dow Corning Corporation
Health and Environmental Sciences
2200 W. Salzburg Rd.
Midland, Michigan 48686-0994

Study Completion
Date: August 19, 1997

Security Classification
Statement:

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ABSTRACT

A 14-day repeated dose inhalation toxicity study was conducted to investigate the inhalation toxicity of DOW CORNING® X1-6145A Additive* in rats. Four groups of ten male and ten female Fischer 344 rats each were exposed to target concentrations of 0, 50, 100, and 200 ppb of DOW CORNING® X1-6145A Additive for six hours a day, for ten exposures over 14 days (excluding weekends). Animals were observed for treatment-related signs of toxicity, growth, and mortality. At the termination of the study, rats were sacrificed and examined for changes in organ weights, gross pathology, and histopathology.

The mean daily exposure concentrations of DOW CORNING® X1-6145A Additive ranged from 43.4-52.7 ppb for the 50 ppb exposure group, 89.9-109.7 ppb for the 100 ppb exposure group, and 183.1-218.4 ppb for the 200 ppb exposure group. No mortality was observed during the study. Very slight to moderate rales were observed in several animals exposed to 100 and 200 ppb of DOW CORNING® X1-6145A Additive. No apparent treatment-related clinical signs were observed in animals exposed to 50 ppb of the test material. Statistically significant decrease in body weights were observed in males exposed to 200 ppb of DOW CORNING® X1-6145A Additive on day 8, 15 and at sacrifice. Female body weights were decreased in animals exposed to 200 ppb on day 8 only. Statistically significant increase in liver/body weight ratios were observed in males exposed to 100 and 200 ppb of the test material. Statistically significant increase in kidney/body weight ratios were observed in males exposed to 200 ppb of the test material. In addition, a statistically significant increase was observed in the liver/body weight and adrenal/body weight ratios of females exposed to 200 ppb of DOW CORNING® X1-6145A Additive. There were no other statistically significant differences in organ weights between test and control animals. There were no apparent test article-related gross pathological changes in animals exposed to DOW CORNING® X1-6145A Additive. Test article-related changes were observed microscopically in the respiratory tract of all animals exposed to DOW CORNING® X1-6145A Additive. The nares, nasal cavity, and pharynx were the most common sites of test article-related changes with the trachea and larynx only infrequently affected. Squamous metaplasia and acute inflammation of the nasal cavity were the most common findings in the 200 ppb group and also occurred, with somewhat reduced incidence and severity, in many rats from the 50 and 100 ppb groups. An increased activity of mucus goblet cells of the respiratory epithelium, characterized by increased height and prominence of goblet cells with formation of microcysts, was the most common finding in all sections of the nasal cavity of rats from the 50 and 100 ppb groups. All lesions in the lung and other organs examined microscopically were considered agonal or spontaneous and unrelated to test article exposure. Based on these results, a No-Observable-Adverse-Effect-Level (NOEL) was not established for DOW CORNING® X1-6145A Additive in Fischer 344 rats under the conditions of this study.

* 1,2-Bis(trimethoxysilyl)ethane; "Hexabis"

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

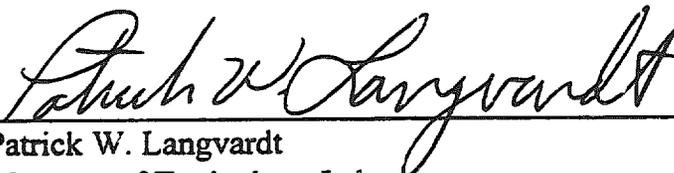
Following is the study compliance statement for Dow Corning's report for Study Number 7758, "A 14-Day Repeated Dose Inhalation Toxicity Study of Dow Corning® X1-6154A Additive in Albino Rats." The Study Director for the above study confirms that the study with the exception of the activities associated with histopathological slide preparation¹, in-life phase quality assurance audit, test substance use tracking, and test article characterization was conducted in compliance with current Environmental Protection Agency, Toxic Substances Control Act; Good Laboratory Practice Standards, 40 CFR 792 adopted Thursday, August 17, 1989.



Waheed H. Siddiqui, Ph.D.
Study Director
Health and Environmental Sciences

8/19/97

Date



Patrick W. Langvardt
Manager of Toxicology Laboratory
Health and Environmental Sciences

19 AUG 97

Date

¹ The histologist, Marco A. Bejarano, for this study acknowledged fraudulent activities documented in an affidavit dated June 28, 1994 on file in the corporate legal department. Based on this finding, Experimental Pathology Laboratories (EPL), Inc. was asked to review the study. EPL conducted a study validation review and performed a wet tissue and slide block inspection. Five slide block mismatches (~0.3% of slides) and some quality control issues (~4.1% of slides) were identified. With the help of Leland W. Dochterman, DVM, DACVP, and Jane M. Regan corrective action was taken.

SUMMARY OF PROTOCOL DEVIATIONS

1. Lot number BN099001, of Dow Corning® X1-6145A Additive was archived for studies 7491 and 7486. This study had the same lot number; however, a sample specific to this study was not taken.
2. Chamber humidities below the acceptable limits specified in Section 6.2.I.A. of the protocol (i.e., humd14, 20-Sep-93 from 8:17 to 8:37; humd14, 24-Sep-93 from 8:11 to 8:21; humd15, 24-Sep-93 from 8:11 to 8:21, etc.).
3. Animal room temperatures and humidities were below the acceptable limits specified in Section 10 of the protocol.

The above mentioned deviations did not affect the quality or integrity of the study.

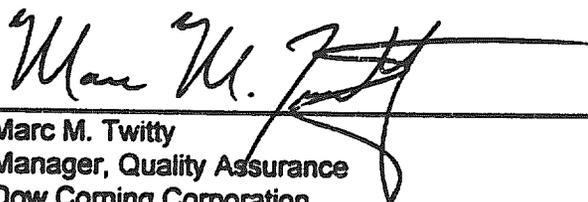
QUALITY ASSURANCE STATEMENT

Study Number: 7758

Title: A 14-Day Repeated Dose Inhalation Toxicity Study of Dow Corning® X1-6145A Additive in Albino Rats

The above study has been audited by the Dow Corning Corporation Health and Environmental Sciences Quality Assurance Unit. The following are the inspection dates and the dates inspection findings were reported.

<u>Dates of Inspection</u>	<u>Findings Reported to Study Director</u>	<u>Findings Reported to Management</u>
14 July 1993	14 July 1993	14 July 1993
09 November 1995 *	09 November 1995	09 November 1995
27-31 January 1997	14 February 1997	22 July 1997
16 May 1997	16 May 1997	04 June 1997
29 May 1997	29 May 1997	05 June 1997
09 July 1997	11 July 1997	17 July 1997



Marc M. Twitty
 Manager, Quality Assurance
 Dow Corning Corporation
 Health & Environmental Sciences

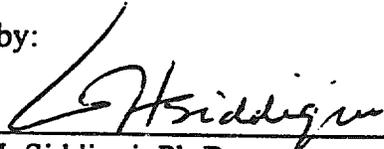
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 Date

* Conducted by Experimental Pathology Laboratories (EPL), Inc.

APPROVAL SIGNATURES

This report consists of pages 1 through 234 including Figures 1 through 2, Tables I through VI, and Appendices A through G.

Prepared by:

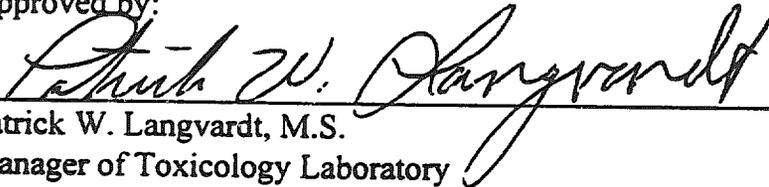


8/19/97

Waheed H. Siddiqui, Ph.D.
Study Director

Date

Approved by:



19 AUG 97

Patrick W. Langvardt, M.S.
Manager of Toxicology Laboratory
Health and Environmental Sciences

Date

STUDY INFORMATION

Testing Facility: Dow Corning Corporation
Health and Environmental Sciences
2200 W. Salzburg Road
Midland, Michigan 48686-0994

Study Initiation Date: September 14, 1993

Experimental Start Date: September 16, 1993

Experimental Termination Date: March 21, 1997

Study Completion Date: August 19, 1997

Study Director: Waheed Siddiqui, Ph.D.

Study Sponsor: Dow Corning Corporation
2200 W. Salzburg Road
Midland, Michigan 48686-0994

Sponsor Representative: Patrick W. Langvardt

Study Personnel: Janet E. Allen
Marco A. Bejarano
Steven D. Crofoot, M.S.
Leland W. Dochterman, D.V.M., DACVP
Mark G. Evans, D.V.M., DACVP, Ph.D.
Richard D. Hoffman, B.S.
Kristen L. Jezewski, A.S.
Gary B. Kolesar, M.S., M.P.H., DABT
Virgil V. Kowalski, B.S.
Joan McMahan
Bonnie J. Miller, LATG
Sharon L. Mudgett, B.S.
Jane M. Regan, MLT/HT (ASCP)
Earnestine Stanton, B.A.

OBJECTIVE

A previously conducted inhalation toxicity study with DOW CORNING® X1-6145A Additive was terminated, because the target exposure concentrations were too high and caused morbidity in rats (Crofoot, et. al., 1993). The purpose of this study was to assess the repeated dose inhalation toxicity of DOW CORNING® X1-6145A Additive and to determine the No-Observable-Adverse-Effect-Level (NOAEL) in rats. This study was conducted in accordance with the EPA Toxic Substances Control Act, Good Laboratory Practices Regulations, 40 CFR, Part 792, adopted Thursday, August 17, 1989.

MATERIALS AND METHODS

A. Test Material

Test material was characterized by Dow Corning's Analytical department using best available technology.

Identification:	DOW CORNING® X1-6145A Additive (1,2-Bis(trimethoxysilyl)ethane)
Lot Number:	BN099001
Purity:	Approximately 94%
CAS No.:	018406412
Physical Description:	Water white liquid
Stability:	Stable
Storage conditions:	Container was closed and kept away from water and moisture.
Reserve sample:	A retention sample was collected for lot number BN099001 in the Archive at HES Dow Corning Corporation; however, it is not specific to this study.
Supplier:	Dow Corning Corporation, Midland, MI

B. Route of Exposure

The route of exposure was whole body inhalation. This is an anticipated route of human exposure.

C. Test System

Male and female Fischer 344 rats weighing approximately 100-185 g and 5 to 8 weeks of age, were purchased from Charles River Laboratories, Kingston, New York. Upon arrival, all rats were quarantined for one week. Approved rats were weighed and randomized into control and test groups (10/sex/group) using the Xybion® PATHTOX ASLECT program. After randomization, test animals were uniquely identified with monel metal eartags and color coded tags placed on the outside of each cage listing the study number, group number, exposure level, ear tag number, and sex.

D. Animal Maintenance

The rats were housed individually in suspended stainless steel, wire mesh bottom cages. Before each exposure, the animals were transferred into cages that were designed to be

placed within the exposure chambers. After each exposure, the animals were returned to their original housing. The rats were fed certified Purina[®] Rodent Chow and water via the automatic watering system ad libitum except during exposures. The sponsor or study director was not aware of any potential contaminants likely to be present in the diet or drinking water that would interfere with the results of this study. The rats were housed during non-exposure periods in a room maintained at 68-75°F, 40-70 percent relative humidity and light cycles of alternating 12 hours light and 12 hours dark. Temperature and humidity were monitored continuously with a chart recorder. Animal room conditions were checked twice a day on weekdays and once a day on weekends.

E. Experimental Design

Animal Groups: A structural outline of the experimental design is given below and the protocol with alteration is included in Appendix A:

Group Number	Number of		Test Material	Target Exposure Concentration (ppb)
	Male	Female		
1	10	10	Filtered Room Air	N.A.
2	10	10	DOW CORNING [®] X1-6145A Additive	50
3	10	10	DOW CORNING [®] X1-6145A Additive	100
4	10	10	DOW CORNING [®] X1-6145A Additive	200

The exposure levels (50, 100, and 200 ppb) were selected on the basis of results obtained in a previously conducted study (Crofoot, et al., 1993). The animals were exposed for six hours per day, for ten exposures over 14 days (excluding weekends).

F. Exposure Methods and Generating Equipment

Exposures were conducted in 2m³ stainless steel whole body exposure chambers (Figure 1). The chambers were operated under dynamic conditions where chamber air was room air, which had been filtered (HEPA and charcoal filters). Airflow through the chambers were kept at approximately 10-15 air changes per hour. Chamber temperature, humidity, and airflow were monitored continuously and were recorded every five minutes by the validated Camile[®] Data Acquisition System. The test material for the 100 and 200 ppb groups was introduced into the chambers through special designed glass J-tubes designed by Miller et al., 1980 (Figure 2). The test material was metered into the heated J-tubes with Harvard Apparatus syringe pumps. Instrument air which was filtered, flowed through the J-tubes at a controlled rate. The air/vapor mixture passed into the inlet port at the top of the chambers. Test material generation for the 50 ppb group was performed by preparing bag standards

which were metered into the dilution air stream to produce the desired chamber concentration. During the exposure periods, attempts were made to keep the actual concentrations of the test material in the chambers as constant as possible.

The duration of each exposure period was six hours after equilibration of the chamber concentration. The equilibration time, which is a function of chamber airflow, was approximately 25 minutes (Silver, 1946). The amount of test material used during the exposure period was determined by pre- and post-measuring the weight of the test material in each syringe. The exposure duration (exposure period and equilibration time), test material used, and airflows through the chambers were then used to calculate nominal concentrations for the 100 and 200 ppb groups. The actual chamber concentration was measured using an Analect® Diamond FT-IR spectrometer equipped with a fixed 22 meter path length cell. The spectrometer was calibrated before the study with standards prepared in Tedlar® gas sampling bags.

G. Observations

Animals were observed daily during the week following each exposure for test article-related signs of toxicity and mortality/morbidity. Signs evaluated included, but were not limited to, any evidence of respiratory, dermal, behavioral, nasal, and/or ocular changes. Animals were observed for signs of mortality/morbidity once a day on weekends by Animal Resources personnel.

H. Body Weight Measurements

Individual body weights were collected for randomization purposes prior to exposure. Also, body weights were recorded on days 1, 8, 15, and prior to terminal necropsy.

I. Gross Pathology and Organ Weight Assessment

A gross pathologic examination was conducted on all rats on Study Day 15. The heart, brain, kidneys, lungs, liver, spleen, adrenals, and ovaries or testes were dissected free of fat and weighed. The lungs were removed intact, weighed, and distended to their approximate normal inspiratory volume by tracheal infusion with 10% neutral buffered formalin.

J. Histopathology

Samples of organs and tissues listed below for all groups with the exception of the eyes were preserved in 10% neutral buffered formalin. Eyes were preserved in Davidson's fixative. Hematoxylin and eosin stained paraffin sections of the organs and tissues were prepared using standard histologic methods.

Adrenal (2)	Trachea (multiple levels, cervical and bifurcation)
Nasal Cavity (4 levels)	Ovaries (2)
Brain (3 levels)	Pharynx
Eyes (2)	Spleen
Heart	Testes (2)
Kidneys (2)	Thymus
Larynx	Nares
Liver (3 lobes)	Selected Gross Lesions
Lymph Nodes (Mandibular, Mediastinal)	
Lungs (5 lobes)	

Histopathological examination was performed on the tissues specified from all rats from the control and 200 ppb exposure groups by consulting pathologist, Robert G. Geil, D.V.M., DACVP. Lesions were observed in the nasal tissue, trachea, and, larynx, therefore, as instructed by the protocol in section 14.2, histopathological examinations were performed on these tissues from the rats in the 50 and 100 ppb exposure group. The histologist, Marco A. Bejarano, for this study acknowledged fraudulent activities documented in an affidavit dated June 28, 1994 on file in the corporate legal department. Based on this finding, Experimental Pathology Laboratories (EPL), Inc. was asked to review the study. EPL conducted a study validation review and performed a wet tissue and slide block inspection. Five slide block mismatches (~0.3% of slides) and some quality control issues (~4.1% of slides) were identified. With the help of Leland W. Dochterman, DVM, DACVP, and Jane M. Regan corrective action was taken.

K. Statistics

Statistical analysis of body weights, organ weights, and organ weight ratios were conducted. Originally, the data was analyzed by a two-sided Welch Trend test, however during a data review, it was noted that Animal no. C4363 had two significantly different body weights for Study Day 15 and terminal sacrifice. Both of these body weights were taken on the same day. When this error was discovered the study director elected to reanalyze the data. Because the software package with this procedure was no longer being supported, the data could not be reanalyzed with the two-sided Welch Trend test. Therefore, Dr. Robert Gallavan, biostatistician elected to analyze the data as an one-way analysis of variance using proc GLM, SAS® V. 6.12.

When the overall F test indicated significant treatment-related effects, mean responses in exposed animals were compared to control using a two-tailed Dunnett's test for multiple comparisons. The probability of Type I error was set at 5% ($p < 0.05$).

RESULTS AND DISCUSSION

Mean chamber conditions for the entire study are presented in Table I and daily exposure period data are reported in Appendix B. The range of mean daily chamber temperatures, relative

humidity, and airflow for the entire study were 23.4-24.0°C, 37.6-40.8 %, and 356.7-358.7 LPM, respectively. Mean daily actual and nominal chamber concentration data are also presented in Table I and daily exposure data are reported in Appendix C. The mean daily exposure concentrations of DOW CORNING® X1-6145A Additive ranged from 43.4-52.7 ppb for the 50 ppb exposure group, 89.9-109.7 ppb for the 100 ppb exposure group, and 183.1-218.4 ppb for the 200 ppb exposure group.

Mean body weight data for male and female rats are reported in Table II. Individual body weight values are reported in Appendix D. Statistically significant decrease in body weights were observed in males exposed to 200 ppb of DOW CORNING® X1-6145A Additive on day 8, 15 and at sacrifice. Female body weights were decreased in animals exposed to 200 ppb on day 8. No significant differences between test and control body weights were observed in females on day 15.

No mortality was observed during the study. Summary of group incidence of clinical signs are included in Table III and individual data are presented in Appendix E. Very slight to moderate rales were observed in several animals exposed to 100 and 200 ppb of DOW CORNING® X1-6145A Additive during the first week of exposure. At the termination of the study, no apparent treatment-related clinical signs were observed in any of the animals exposed to 100 and 200 ppb of DOW CORNING® X1-6145A Additive. No apparent treatment-related clinical signs were observed in animals exposed to 50 ppb of the test material during the study.

Group mean absolute and relative organ weights are presented in Table IV and the individual data is given in Appendix F. Statistically significant increase in liver/body weight ratios were observed in males exposed to 100 and 200 ppb of the test material. Statistically significant increase in kidney/body weight ratios were observed in males exposed to 200 ppb of the test material. In addition, a statistically significant increase was observed in the liver/body weight and adrenal/body weight ratios of females exposed to 200 ppb of DOW CORNING® X1-6145A Additive. The biological significance of these results are questionable because of the depression of body weights in animals exposed to 200 ppb of test article and the lack of correlation between the organ weight increases and microscopic finding. There were no other significant organ weight differences between test and control animals

Incidence of necropsy findings for male and female rats are given in Table V. There were no significant test article-related gross changes in the treated groups. A summary of microscopic findings for male and female rats is given in Table VI and the individual data can be found in Appendix G. Test article related changes were limited to the respiratory tract organs and occurred in all rats exposed to 50, 100, and 200 ppb of DOW CORNING® X1-6145A Additive. The nares, nasal cavity, and pharynx were the most common sites of test article related changes with the trachea and larynx only infrequently affected. The most severe lesions in each treated rat were found in the Nasal Cavity #1 section with decreasing incidence of changes occurring in the upper levels of the nasal cavity. Squamous metaplasia and acute inflammation of the nasal cavity were the most common findings in animals exposed to 200 ppb and also occurred, with somewhat reduced incidence and severity, in many rats exposed to 50 and 100 ppb of the test

article. An increased activity of mucus goblet cells of the respiratory epithelium, characterized by increased heights and prominence of goblet cells with formation of microcysts, was the most common findings in all sections of the nasal cavity of rats exposed to 50 and 100 ppb of the test article. This was also seen in animals exposed to 200 ppb of the test article at nasal levels 2, 3, and 4. Mucous goblet cell hyperactivity also occurred in sections of pharynx in all treatment groups. Incidence and severity of nasal cavity and pharyngeal changes generally had a positive dose response relationship. Other test article related changes in the nasal cavity included erosions and ulcers of the epithelium, suppurative exudate in the lumen, chronic inflammation and hemorrhage. Test article related changes in the larynx and trachea were infrequently seen. These included laryngeal ulcers in two rats exposed to 200 ppb and one exposed to 50 ppb, suppurative laryngeal exudate in one animal exposed to 200 ppb, and chronic tracheitis in one animal exposed to 200 ppb of the test article. Epithelial desquamation, of varying severity, occurred in the nasal cavity, pharynx and trachea in similar numbers of rats exposed to 0, 50, 100, and 200 ppb of the test article. Where desquamation was unaccompanied by inflammation, as was the case in most instances, it was considered an artifact which was probably induced by handling at necropsy. All lesions in the lung and other organs examined microscopically were considered agonal or spontaneous and unrelated to test article exposure.

CONCLUSIONS

Test article related changes were observed microscopically in the respiratory tract of all animals exposed to DOW CORNING® X1-6145A Additive. All lesions in the lung and other organs examined microscopically were considered agonal or spontaneous unrelated to test article exposure. Based on these results, a No-Observable-Adverse-Effect-Level (NOEL) was not established for DOW CORNING® X1-6145A Additive in Fischer 344 rats under the conditions of this study.

ARCHIVES

All records concerning the daily observations, body weights, exposure data, gross examinations, and all other information relevant to the quality and integrity of the study are located at Dow Corning Corporation, Health and Environmental Sciences, Midland, Michigan, 48686-0994.

REFERENCES

1. Crofoot, S.D., Kolesar, G.B., and Evans, M. G. (1993). An Acute and 14-Day Repeated Dose Inhalation Toxicity Study of Dow Corning® X1-6154A Additive in Albino Rats. Dow Corning Internal Report. 1993-I0000-38352.
2. Miller, R.R., Letts, R.L., Potts, W.J., and Mckenna, M.J. (1980). Improved Methodology for Generating Controlled Test Atmospheres. *Am. Ind. Hyg. Assoc. J.* 41, 844-846.
3. Silver, S.D., (1946). Constant Flow Gassing Chambers: Principles Influencing Design and Operation. *The Journal of Laboratory and Clinical Medicine.* 31, 1153-1161.

FIGURE 1

Diagram of Exposure Chamber and Sampling System

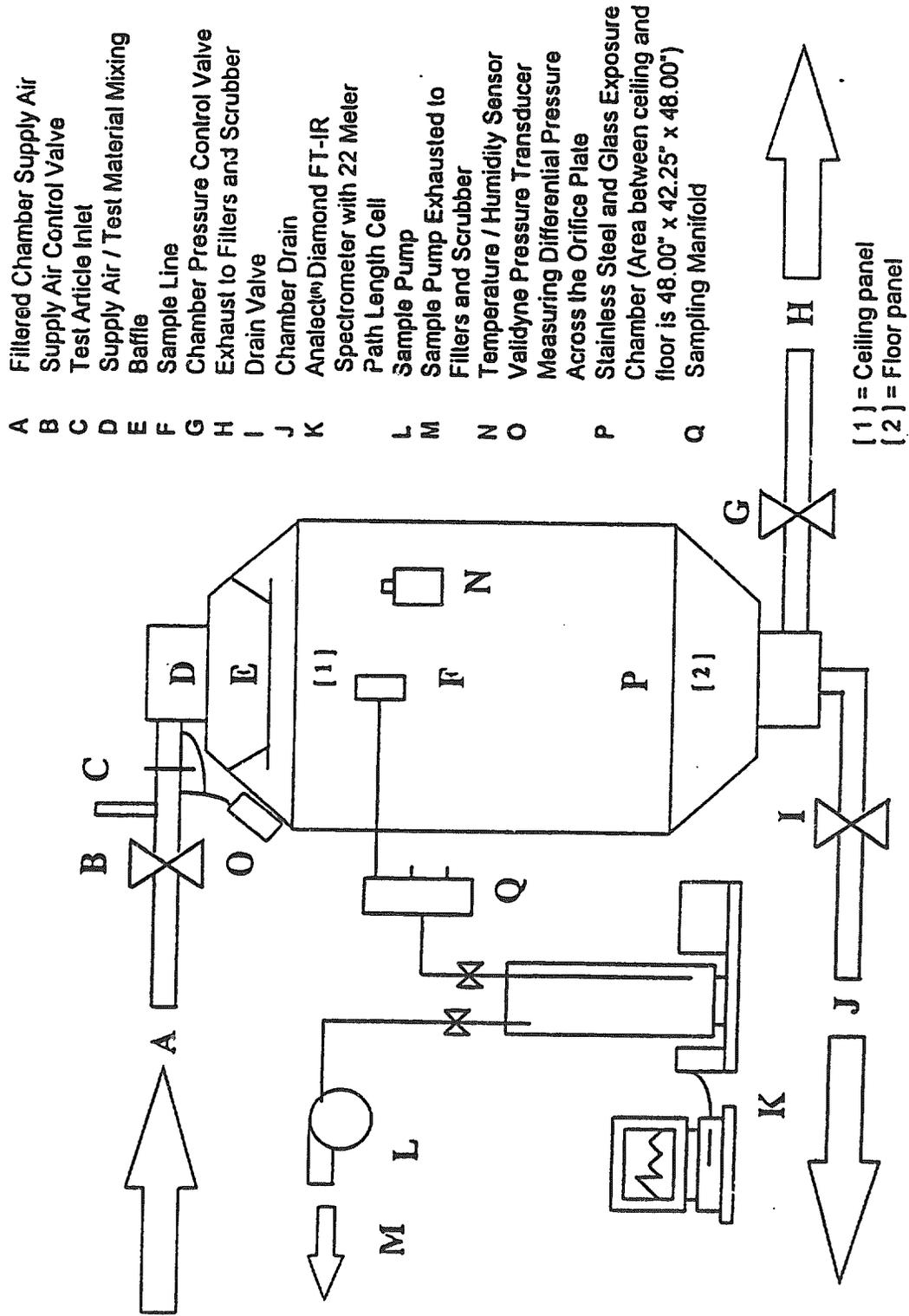


FIGURE 2

Diagram of Vapor Generation System

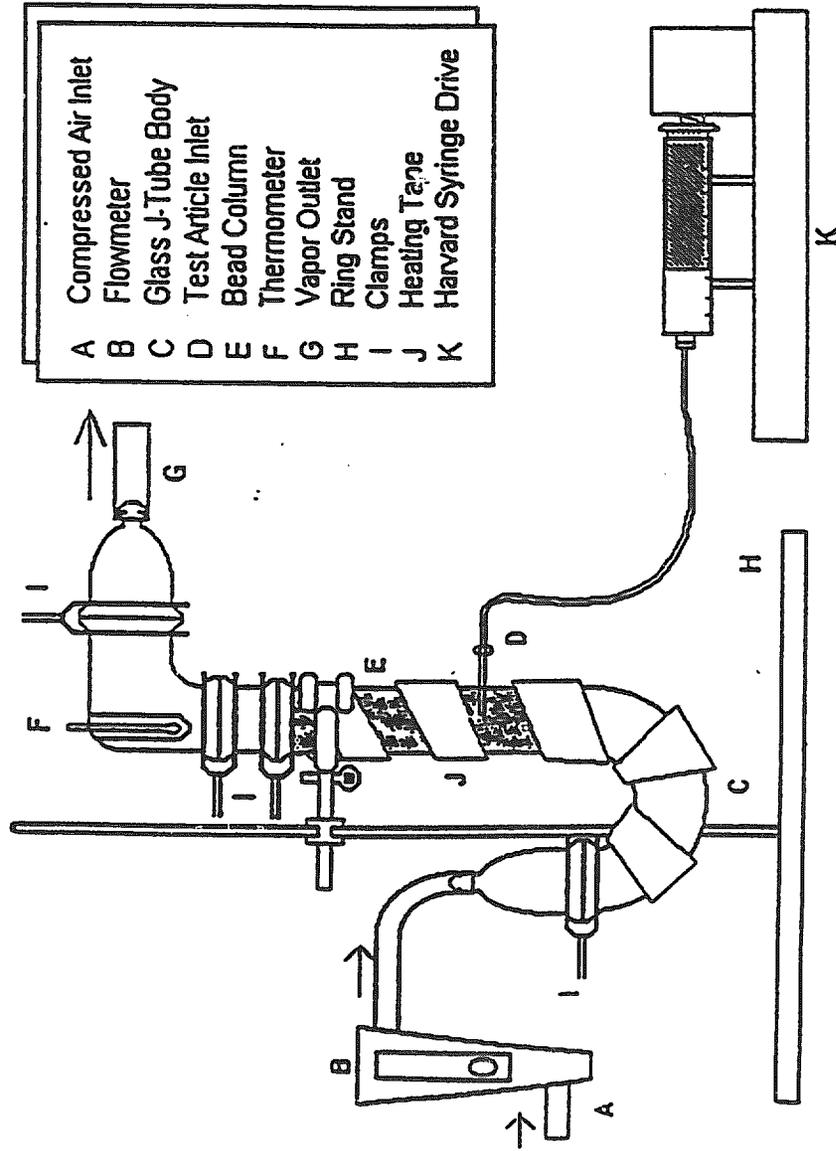


TABLE I

Summary of Daily Mean Chamber Conditions (Mean \pm S.D.)

Group No. 1

Target Exposure - 0 ppb

Study Day		Temperature (°C)	% Relative Humidity	Air Flow (LPM)	Actual Conc. (ppb)	Nominal Conc. (ppb)
1	Mean	23.9	40.5	359.1	N.A.	N.A.
	S.D.	0.4	3.0	2.10	N.A.	N.A.
2	Mean	23.7	36.7	354.0	N.A.	N.A.
	S.D.	0.2	2.5	2.67	N.A.	N.A.
5	Mean	23.6	40.3	355.8	N.A.	N.A.
	S.D.	0.4	2.4	2.9	N.A.	N.A.
6	Mean	23.8	36.5	361.4	N.A.	N.A.
	S.D.	0.3	0.4	2.1	N.A.	N.A.
7	Mean	23.8	37.9	358.9	N.A.	N.A.
	S.D.	0.3	0.4	3.2	N.A.	N.A.
8	Mean	23.8	36.1	361.5	N.A.	N.A.
	S.D.	0.3	2.1	1.9	N.A.	N.A.
9	Mean	23.8	38.5	360.6	N.A.	N.A.
	S.D.	0.3	2.6	2.4	N.A.	N.A.
12	Mean	23.8	36.2	356.7	N.A.	N.A.
	S.D.	0.3	1.2	2.7	N.A.	N.A.
13	Mean	23.9	41.2	357.6	N.A.	N.A.
	S.D.	0.4	3.2	3.7	N.A.	N.A.
14	Mean	23.9	40.7	361.5	N.A.	N.A.
	S.D.	0.4	2.5	1.8	N.A.	N.A.

N.A. = Not Applicable

TABLE I (Continued)

Summary of Daily Mean Chamber Conditions (Mean \pm S.D.)

Group No. 2

Target Exposure - 50 ppb

Study Day		Temperature (°C)	% Relative Humidity	Air Flow (LPM)	Actual Conc. (ppb)	Nominal Conc. (ppb)
1	Mean	23.6	43.2	359.2	48.9	N.C.
	S.D.	0.3	3.5	5.49	10.62	N.A.
2	Mean	23.7	38.8	358.3	47.1	N.C.
	S.D.	0.2	2.7	5.48	9.26	N.A.
5	Mean	23.5	42.6	358.4	43.4	N.C.
	S.D.	0.4	2.6	4.5	7.60	N.A.
6	Mean	23.5	39.0	356.7	45.5	N.C.
	S.D.	0.2	0.3	5.1	8.69	N.A.
7	Mean	23.6	40.1	361.8	46.4	N.C.
	S.D.	0.3	0.6	5.1	9.94	N.A.
8	Mean	23.7	38.2	357.3	51.0	N.C.
	S.D.	0.3	2.0	4.9	7.00	N.A.
9	Mean	23.6	40.9	358.8	46.8	N.C.
	S.D.	0.2	2.7	4.7	5.04	N.A.
12	Mean	23.7	38.4	356.4	42.9	N.C.
	S.D.	0.2	1.5	4.5	6.07	N.A.
13	Mean	23.6	43.8	357.9	52.7	N.C.
	S.D.	0.3	3.7	5.1	5.87	N.A.
14	Mean	23.6	43.1	358.6	52.1	N.C.
	S.D.	0.3	3.0	4.5	6.83	N.A.

N.C. = Not Calculated. Material metered from Tedlar[®] gas bags

N.A. = Not Applicable

TABLE I (Continued)**Summary of Daily Mean Chamber Conditions (Mean \pm S.D.)****Group No. 3****Target Exposure - 100 ppb**

Study Day		Temperature (°C)	% Relative Humidity	Air Flow (LPM)	Actual Conc. (ppb)	Nominal Conc. (ppb)
1	Mean	23.5	40.4	356.8	109.7	99.0
	S.D.	0.4	2.5	3.87	12.74	N.A.
2	Mean	23.4	36.9	356.0	90.8	92.4
	S.D.	0.3	2.2	4.29	37.97	N.A.
5	Mean	23.3	39.8	354.0	96.7	79.2
	S.D.	0.5	2.0	4.4	13.93	N.A.
6	Mean	23.4	36.8	360.4	90.4	87.0
	S.D.	0.3	0.4	3.3	24.01	N.A.
7	Mean	23.5	37.9	361.0	89.9	77.7
	S.D.	0.4	0.4	3.7	25.23	N.A.
8	Mean	23.5	36.3	359.9	95.9	74.8
	S.D.	0.4	2.0	3.1	18.25	N.A.
9	Mean	23.4	38.4	356.3	106.4	92.3
	S.D.	0.4	2.2	4.3	11.54	N.A.
12	Mean	23.4	36.7	360.4	95.5	87.6
	S.D.	0.4	1.0	4.3	11.25	N.A.
13	Mean	23.5	40.9	358.0	97.2	85.1
	S.D.	0.4	2.8	4.7	25.56	N.A.
14	Mean	23.4	40.8	358.8	91.0	129.8
	S.D.	0.4	2.3	4.0	35.98	N.A.

N.A. = Not Applicable

TABLE I (Continued)**Summary of Daily Mean Chamber Conditions (Mean \pm S.D.)****Group No. 4****Target Exposure - 200 ppb**

Study Day		Temperature (°C)	% Relative Humidity	Air Flow (LPM)	Actual Conc. (ppb)	Nominal Conc. (ppb)
1	Mean	24.1	40.1	354.2	218.4	183.2
	S.D.	0.4	3.4	3.96	5.30	N.A.
2	Mean	24.0	35.6	356.7	211.6	176.4
	S.D.	0.3	2.9	3.96	18.72	N.A.
5	Mean	23.8	39.5	353.3	204.9	156.8
	S.D.	0.5	2.8	4.2	13.25	N.A.
6	Mean	23.9	35.4	358.9	190.0	162.4
	S.D.	0.3	0.4	3.3	33.37	N.A.
7	Mean	24.0	36.7	358.8	199.7	175.3
	S.D.	0.4	0.5	3.7	28.19	N.A.
8	Mean	24.0	34.9	360.2	212.6	N.A.*
	S.D.	0.3	2.3	2.7	21.01	N.A.
9	Mean	24.0	37.8	358.0	206.9	173.9
	S.D.	0.3	2.9	3.5	18.54	N.A.
12	Mean	24.0	35.0	356.6	197.7	182.0
	S.D.	0.3	1.2	3.5	17.11	N.A.
13	Mean	24.1	40.9	355.8	183.1	155.7
	S.D.	0.4	3.5	4.1	64.94	N.A.
14	Mean	24.1	40.4	354.7	210.0	175.5
	S.D.	0.4	2.8	3.1	23.11	N.A.

* One measurement not collected

N.A. = Not Applicable

N.C. = Not Calculated. Material metered from Tedlar® gas bags

TABLE II
Summary of Mean Body Weights (g)
Males

Target Exposure Conc. (ppb)		STUDY DAY		
		1	8	15
0 ppb	Mean	185	201	216
	Std Error	1.3	2.2	2.6
	N	10	10	10
50 ppb	Mean	186	205	221
	Std Error	1.6	2.4	2.7
	N	10	10	10
100 ppb	Mean	185	195	215
	Std Error	1.4	2.1	2.6
	N	10	10	10
200 ppb	Mean	186	175	206
	Std Error	1.8	2.3	2.3
	N	10	10	10
p value ¹		0.986	0.000 ²	0.002 ²

¹The p value reported is that associated with the overall F-test for exposure effect. Subsequent comparisons of means were carried out using Dunnett's test at $p < 0.05$.

²Animals exposed at target concentrations of 200 ppb had significantly lower body weights than control animals ($p < 0.05$).

TABLE II (Continued)

Summary of Mean Body Weights (g)
Females

Target Exposure Conc. (ppb)		STUDY DAY		
		1	8	15
0 ppb	Mean	152	157	158
	Std Error	1.4	1.3	1.4
	N	10	10	10
50 ppb	Mean	152	159	162
	Std Error	1.2	1.6	2.1
	N	9 ³	9 ³	9 ³
100 ppb	Mean	152	156	161
	Std Error	1.2	1.9	2.0
	N	10	10	10
200 ppb	Mean	152	147	157
	Std Error	1.4	1.6	1.7
	N	10	10	10
p value ¹		1.000	0.000 ²	0.226

¹The p value reported is that associated with the overall F-test for exposure effect. Subsequent comparisons of means were carried out using Dunnett's test at $p < 0.05$.

²Animals exposed at target concentrations of 200 ppb had significantly lower body weights than control animals ($p < 0.05$).

³Observations for animal no. C4363 were excluded.

TABLE III
Incidence of Clinical Signs Males & Females

Clinical Sign	Concentration (ppb)	Study Day													
		1	2	5	6	7	8	9	12	13	14				
Normal/no visible abnormalities	0.0	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
	50.0	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
	100.0	10/10	10/10	2/10	8/10	9/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
	200.0	10/10	10/10	0/10	0/10	0/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Labored Breathing	0.0	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
	50.0	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
	100.0	10/10	10/10	8/10	9/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
	200.0	10/10	10/10	0/10	1/10	4/10	9/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Rales, dry	0.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	50.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	100.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	200.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Rales, wet	0.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	50.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	100.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	200.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10

TABLE IV
Summary of Mean Organ Weights
Males

Target Exposure Conc. (ppb)	Body Wt. (g)	Brain g	Brain/Bw g/100	Heart g	Hrt/Bw g/100	Liver g	Liv/Bw g/100	Kidneys g	Kid/Bw g	Spleen g	Sp/Bw g/100	Lungs g
0	Mean	1.693	0.794	0.662	0.310	7.940	3.717	1.578	0.740	0.466	0.218	0.966
	Std. Error	0.019	0.013	0.012	0.005	0.168	0.051	0.016	0.005	0.013	0.006	0.018
	N	10	10	10	10	10	10	10	10	10	10	10
50	Mean	1.705	0.782	0.691	0.316	8.311	3.804	1.610	0.737	0.464	0.222	1.007
	Std. Error	0.028	0.018	0.013	0.004	0.136	0.034	0.024	0.007	0.011	0.012	0.012
	N	10	10	10	10	10	10	10	10	10	10	10
100	Mean	1.691	0.799	0.671	0.317	8.195	3.868	1.610	0.760	0.449	0.212	0.953
	Std. Error	0.023	0.013	0.014	0.006	0.177	0.049	0.029	0.009	0.016	0.007	0.014
	N	10	10	10	10	10	10	10	10	10	10	10
200	Mean	1.673	0.824	0.648	0.319	8.141	4.003	1.562	0.768	0.447	0.220	0.963
	Std. Error	0.016	0.012	0.008	0.003	0.132	0.031	0.026	0.010	0.008	0.004	0.024
	N	10	10	10	10	10	10	10	10	10	10	10
p value ¹	0.002 ²	0.788	0.194	0.093	0.573	0.402	0.000 ³	0.417	0.019 ⁴	0.589	0.817	0.153

¹The p value reported is that associated with the overall F-test for exposure effect. Subsequent comparisons of means were carried out using Dunnett's test at $p < 0.05$.

²Animals exposed at target concentrations of 200 ppb had significantly lower body weights than control animals ($p < 0.05$).

³Liver/Body weight (Liv/Bw) was significantly greater than control in 100 and 200 ppb groups.

⁴Kidney/Body weight (Kid/Bw) was significantly greater than control in 200 ppb groups.

Brm=Brain Hrt=Heart Liv=Liver Kid=Kidneys Spl=Spleen Bw=Body weight

TABLE IV (Continued)

Summary of Mean Organ Weights
Males (Continued)

Target Exposure Conc. (ppb)	Lun/Bw		Adrenals		Adr/BW		Testes		Tes/Bw	
		g/100		g		g/100 g		g		g/100
0	Mean	0.453	0.048		0.022		2.689		1.261	
	Std. Error	0.010	0.004		0.002		0.036		0.019	
	N	10	10		10		10		10	
50	Mean	0.461	0.042		0.019		2.704		1.239	
	Std. Error	0.008	0.003		0.001		0.023		0.016	
	N	10	10		10		10		10	
100	Mean	0.450	0.047		0.022		2.658		1.257	
	Std. Error	0.004	0.004		0.002		0.029		0.021	
	N	10	10		10		10		10	
200	Mean	0.474	0.052		0.026		2.633		1.296	
	Std. Error	0.012	0.003		0.001		0.038		0.016	
	N	10	10		10		10		10	
p value ¹			0.271		0.307		0.099		0.423	

¹The p value reported is that associated with the overall F-test for exposure effect. Subsequent comparisons of means were carried out using Dunnett's test at p < 0.05.

Lun=Lungs Bw=Body weights Adr=Adrenals Tes=Testes

TABLE IV (Continued)

Summary of Mean Organ Weights
Females

Target Exposure Conc. (ppb)	Body		Brain	Brn/Bw	Heart	Hrt/Bw	Liver	Liv/Bw	Kidneys	Kid/Bw	Spleen	Sp/Bw	Lungs
	Wt. (g)	g	g	g/100	g	g/100	g	g/100	g	g	g	g/100	g
0	Mean	154.3	1.698	1.102	0.521	0.338	4.571	2.962	1.117	0.724	0.410	0.265	0.870
	Std. Error	1.7	0.016	0.017	0.007	0.004	0.119	0.067	0.025	0.015	0.009	0.005	0.017
	N	10	10	10	10	10	10	10	10	10	10	10	10
50	Mean	158.2	1.685	1.065	0.548	0.346	4.929	3.113	1.183	0.747	0.443	0.280	0.869
	Std. Error	1.948	0.021	0.011	0.011	0.004	0.166	0.088	0.023	0.011	0.020	0.013	0.027
	N	9 ²	9 ²	9 ²	9 ²	9 ²	9 ²	9 ²	9 ²				
100	Mean	156.7	1.662	1.064	0.540	0.346	4.714	3.006	1.118	0.714	0.406	0.259	0.856
	Std. Error	2.5	0.025	0.025	0.005	0.004	0.124	0.058	0.015	0.009	0.008	0.003	0.017
	N	10	10	10	10	10	10	10	10	10	10	10	10
200	Mean	152.0	1.677	1.104	0.521	0.342	4.950	3.254	1.123	0.738	0.398	0.262	0.841
	Std. Error	1.2	0.021	0.019	0.009	0.004	0.142	0.084	0.018	0.009	0.011	0.007	0.017
	N	10	10	10	10	10	10	10	10	10	10	10	10
p value ¹	0.119	0.678	0.258	0.416	0.174	0.038 ⁴	0.095	0.182	0.074	0.223	0.688		

¹The p value reported is that associated with the overall F-test for exposure effect. Subsequent comparisons of means were carried out using Dunnett's test at $p < 0.05$.

²Animal no. C4363 was excluded from the statistical analysis.

³Although the global F-test for heart weight was significant, no treatment groups were significantly different from control.

⁴Liver/Body weight (Liv/Bw) was significantly greater than control in 200 ppb group.

Brn=Brain Bw=Body weight Hrt=Heart Liv=Liver Kid=Kidney Spl=Spleen

TABLE IV (Continued)

Summary of Mean Organ Weights
Females (Continued)

Target Exposure Conc. (ppb)	Lun/Bw g/100	Adrenals g	Adr/BW g/100 g	Ovaries g	Ovr/Bw g/100
0	Mean	0.564	0.033	0.060	0.039
	Std. Error	0.009	0.002	0.002	0.002
	N	10	10	10	10
50	Mean	0.549	0.034	0.063	0.040
	Std. Error	0.013	0.002	0.003	0.001
	N	9 ²	9 ²	9 ²	9 ²
100	Mean	0.547	0.033	0.060	0.038
	Std. Error	0.014	0.001	0.003	0.002
	N	10	10	10	10
200	Mean	0.551	0.038	0.059	0.039
	Std. Error	0.010	0.002	0.002	0.001
	N	10	10	10	10
p value ¹	0.730	0.096	0.034 ³	0.819	0.961

¹The p value reported is that associated with the overall F-test for exposure effect. Subsequent comparisons of means were carried out using Dunnett's test at $p < 0.05$.

²Animal no. C4363 was excluded from the statistical analysis.

³Adrenal/Body weight (ADR/BW) was significantly greater than control in the 200 ppb group.

Lun=Lungs Bw=Body weight Adr=Adrenals Ovr=Ovaries

TABLE V

Incidence of Macroscopic Findings
Males and Females

Tissue/Diagnosis	0 ppb		50 ppb		100 ppb		200 ppb	
	M	F	M	F	M	F	M	F
All Tissues Within normal limits	10	8	8	8	10	10	9	9
Adrenal Small, unilateral			1	1				
Lymph Node (mandibular) Enlarged, bilateral, mild							1	
Skin Erosion, focal, nose			1					
Stomach Discolored, red, diffuse, glandular mucosa								1
Uterus Distended, lumen, bilateral, horns Thickened wall, bilateral, horns, diffuse		2		1				

TABLE VI
Incidence of Histopathologic Findings
Males and Females

Tissue/Diagnosis/Modifier(s)	0 ppb		50 ppb		100 ppb		200 ppb	
	M	F	M	F	M	F	M	F
Adrenal	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)
Within normal limits	10	10	0	0	0	0	10	10
Brain	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)
Within normal limits	10	10	0	0	0	0	10	10
Eye	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)
Within normal limits	10	7	0	0	0	0	8	9
Mineralized epithelial foci, limbus	0	3	0	0	0	0	0	1
Necrosis, epithelium minimal	0	0	0	0	0	0	2	0
Heart	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)
Within normal limits	10	9	0	0	0	0	9	9
Myocarditis, chronic minimal	0	1	0	0	0	0	1	1
	0	1	0	0	0	0	1	1
Kidney	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)
Within normal limits	0	5	0	0	0	0	0	3
Alpha 2 u globulin inclusions, tubules	10	0	0	0	0	0	10	0
Mild	3	0	0	0	0	0	4	0
Moderate	7	0	0	0	0	0	6	0
Basophilic tubules, cortex	1	0	0	0	0	0	0	0
Mild	1	0	0	0	0	0	0	0
Mineralization	6	5	0	0	0	0	3	7
Minimal	6	5	0	0	0	0	3	7
Larynx	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within normal limits	10	10	9	8	9	10	9	8
Desquamation, epithelium	0	0	1	1	1	0	0	0
Mild	0	0	1	1	1	0	0	0
Exudate, suppurative	0	0	0	0	0	0	1	0
Minimal	0	0	0	0	0	0	1	0
Ulcer	0	0	0	1	0	0	0	2
Minimal	0	0	0	0	0	0	0	1
Mild	0	0	0	1	0	0	0	0
Moderate	0	0	0	0	0	0	0	1
Liver	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)
Within normal limits	10	8	0	0	0	0	10	8
Mononuclear cell foci, parenchyma	0	1	0	0	0	0	0	0
Minimal	0	1	0	0	0	0	0	0
Portal mononuclear cell infiltrate	0	2	0	0	0	0	0	2
minimal	0	2	0	0	0	0	0	2

() = Number of Animals Examined For This Tissue

TABLE VI (Continued)

Incidence of Histopathologic Findings
Males and Females

Tissue/Diagnosis/Modifier(s)	0 ppb		50 ppb		100 ppb		200 ppb	
	M	F	M	F	M	F	M	F
Lung	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)
Within normal limits	7	9	0	0	0	0	9	8
Alveolar macrophage	0	0	0	0	0	0	0	1
Minimal	0	0	0	0	0	0	0	1
Hemorrhage	0	1	0	0	0	0	0	0
Minimal	0	1	0	0	0	0	0	0
Perivascular mononuclear infiltrate	0	0	0	0	0	0	0	1
Minimal	0	0	0	0	0	0	0	1
Pneumonia, interstitial, chronic	2	0	0	0	0	0	0	0
Minimal	2	0	0	0	0	0	0	0
Vascular mineralization	1	0	0	0	0	0	1	1
Minimal	1	0	0	0	0	0	1	1
Lymph Node (mandibular)	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)
Within normal limits	7	8	0	0	0	0	5	9
Hemorrhage	3	2	0	0	0	0	2	1
Minimal	3	2	0	0	0	0	2	1
Hyperplasia	0	0	0	0	0	0	3	0
Mild	0	0	0	0	0	0	1	0
Moderate	0	0	0	0	0	0	2	0
Lymph Node (mediastinal)	(9)	(9)	(0)	(0)	(0)	(0)	(9)	(8)
Within normal limits	8	6	0	0	0	0	9	8
Hemorrhage	1	3	0	0	0	0	0	0
Minimal	0	3	0	0	0	0	0	0
Mild	1	0	0	0	0	0	0	0
Nares	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within normal limits	10	10	4	1	4	3	1	2
Erosion	0	0	6	4	0	0	0	1
Minimal	0	0	1	1	0	0	0	1
Mild	0	0	4	1	0	0	0	0
Moderate	0	0	1	2	0	0	0	0
Exudate, suppurative	0	0	0	0	0	0	1	1
Minimal	0	0	0	0	0	0	1	1
Hemorrhage	0	0	0	0	0	0	0	1
Minimal	0	0	0	0	0	0	0	1
Inflammation, acute, epithelium	0	0	1	1	3	5	2	3
Minimal	0	0	1	1	1	3	2	1
Mild	0	0	0	0	2	2	0	1
Moderate	0	0	0	0	0	0	0	1
Inflammation, chronic	0	0	2	7	3	1	5	3
Minimal	0	0	1	4	3	1	3	3
Mild	0	0	1	3	0	0	2	0

() = Number of Animals Examined For This Tissue

TABLE VI (Continued)

Histopathologic Findings
Males and Females

Tissue/Diagnosis/Modifier(s)	0 ppb		50 ppb		100 ppb		200 ppb	
	M	F	M	F	M	F	M	F
Nares (continued)								
Ulcer	0	0	0	0	0	3	2	1
Minimal	0	0	0	0	0	0	0	1
Mild	0	0	0	0	0	3	2	0
Nasal Cavity I	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within normal limits	10	10	0	0	0	0	0	0
Erosion	0	0	1	0	0	2	0	0
Minimal	0	0	1	0	0	0	0	0
Mild	0	0	0	0	0	2	0	0
Exudate, suppurative	0	0	0	0	0	0	2	3
Minimal	0	0	0	0	0	0	1	1
Mild	0	0	0	0	0	0	1	2
Hemorrhage	0	0	2	0	0	0	0	0
Minimal	0	0	2	0	0	0	0	0
Hyperactivity, mucus goblet cells	0	0	10	10	10	10	0	3
Minimal	0	0	0	1	0	0	0	3
Mild	0	0	2	3	3	1	0	0
Moderate	0	0	8	6	7	9	0	0
Inflammation, acute, epithelium	0	0	0	0	5	5	10	10
Minimal	0	0	0	0	0	0	1	0
Mild	0	0	0	0	5	5	4	7
Moderate	0	0	0	0	0	0	5	3
Inflammation, chronic	0	0	7	5	2	0	0	0
Minimal	0	0	1	4	1	0	0	0
Mild	0	0	6	1	1	0	0	0
Metaplasia, squamous	0	0	5	2	9	10	5	10
Minimal	0	0	1	0	0	0	0	0
Mild	0	0	4	2	9	9	1	2
Moderate	0	0	0	0	0	1	4	8
Ulcer	0	0	0	0	0	0	9	10
Mild	0	0	0	0	0	0	6	7
Moderate	0	0	0	0	0	0	3	3
Nasal Cavity II	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within normal limits	10	10	0	3	0	0	0	0
Desquamation, epithelium	0	0	0	0	2	0	0	1
Mild	0	0	0	0	2	0	0	1
Erosion	0	0	0	0	0	1	0	0
Mild	0	0	0	0	0	1	0	0
Exudate, fibrinopurulent	0	0	0	0	0	0	2	0
Minimal	0	0	0	0	0	0	2	0
Exudate, suppurative	0	0	0	0	0	0	2	0
Minimal	0	0	0	0	0	0	2	0

() = Number of Animals Examined For This Tissue

TABLE VI (Continued)

Histopathologic Findings
Males and Females

Tissue/Diagnosis/Modifier(s)	0 ppb		50 ppb		100 ppb		200 ppb	
	M	F	M	F	M	F	M	F
Nasal Cavity II (continued)								
Hyperactivity, mucus goblet cells	0	0	10	7	10	10	9	10
Minimal	0	0	2	5	1	1	2	3
Mild	0	0	8	2	8	8	6	6
Moderate	0	0	0	0	1	1	1	1
Inflammation, acute, epithelium	0	0	0	0	1	1	4	4
Minimal	0	0	0	0	0	0	2	2
Mild	0	0	0	0	1	1	2	1
Moderate	0	0	0	0	0	0	0	1
Inflammation, chronic, epithelium	0	0	0	0	0	0	2	0
Mild	0	0	0	0	0	0	2	0
Metaplasia, squamous	0	0	0	0	5	9	5	10
Minimal	0	0	0	0	1	2	1	0
Mild	0	0	0	0	4	7	4	6
Moderate	0	0	0	0	0	0	0	4
Ulcer	0	0	0	0	0	0	8	6
Minimal	0	0	0	0	0	0	3	3
Mild	0	0	0	0	0	0	5	3
Nasal Cavity III	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within normal limits	10	9	3	6	0	0	0	0
Desquamation, epithelium	0	1	0	0	0	2	0	0
Minimal	0	1	0	0	0	0	0	0
Mild	0	0	0	0	0	1	0	0
Moderate	0	0	0	0	0	1	0	0
Hyperactivity, mucus goblet cells	0	0	7	4	10	10	8	10
Minimal	0	0	2	4	0	0	1	0
Mild	0	0	5	0	9	10	5	6
Moderate	0	0	0	0	1	0	2	4
Inflammation, acute, epithelium	0	0	0	0	1	0	2	1
Minimal	0	0	0	0	0	0	1	0
Mild	0	0	0	0	1	0	1	1
Inflammation, chronic	0	0	0	1	0	0	2	0
Mild	0	0	0	1	0	0	1	0
Moderate	0	0	0	0	0	0	1	0
Metaplasia, squamous	0	0	0	0	3	1	9	10
Minimal	0	0	0	0	1	0	2	0
Mild	0	0	0	0	2	1	6	7
Moderate	0	0	0	0	0	0	1	3

() = Number of Animals Examined For This Tissue

TABLE VI (Continued)

Histopathologic Findings
Males and Females

Tissue/Diagnosis/Modifier(s)	0 ppb		50 ppb		100 ppb		200 ppb	
	M	F	M	F	M	F	M	F
Nasal Cavity III (Continued)								
Ulcer	0	0	0	0	0	0	6	7
Minimal	0	0	0	0	0	0	3	2
Mild	0	0	0	0	0	0	1	2
Moderate	0	0	0	0	0	0	2	3
Nasal Cavity IV	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within normal limits	10	10	1	7	0	0	0	0
Desquamation, epithelium	0	0	0	1	2	5	2	2
Minimal	0	0	0	1	0	1	0	0
Mild	0	0	0	0	2	4	2	1
Marked	0	0	0	0	0	0	0	1
Hyperactivity, mucus goblet cells	0	0	9	2	10	10	10	10
Minimal	0	0	2	0	0	8	0	0
Mild	0	0	7	2	7	2	4	0
Moderate	0	0	0	0	3	0	6	10
Inflammation, chronic	0	0	0	0	0	0	1	0
Mild	0	0	0	0	0	0	1	0
Metaplasia, squamous	0	0	0	0	0	0	8	6
Minimal	0	0	0	0	0	0	3	2
Mild	0	0	0	0	0	0	5	3
Moderate	0	0	0	0	0	0	0	1
Ulcer	0	0	0	0	0	0	1	1
Minimal	0	0	0	0	0	0	1	0
Mild	0	0	0	0	0	0	0	1
Ovary	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)
Within normal limits	0	10	0	0	0	0	0	10
Pharynx	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
Within normal limits	7	7	4	7	2	3	2	1
Desquamation, epithelium	3	3	3	2	6	4	6	3
Minimal	2	1	1	1	1	1	2	1
Mild	1	1	2	1	5	3	3	2
Moderate	0	1	0	0	0	0	1	0
Hyperactivity, mucus goblet cells	0	0	6	1	5	4	7	7
Minimal	0	0	2	0	4	4	2	2
Mild	0	0	4	1	1	0	5	4
Moderate	0	0	0	0	0	0	0	1
Spleen	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)
Within normal limits	10	10	0	0	0	0	10	10
Testis	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)
Within normal limits	10	0	0	0	0	0	10	0

() = Number of Animals Examined For This Tissue

TABLE VI (Continued)

Histopathologic Findings
Males and Females

Tissue/Diagnosis/Modifier(s)	0 ppb		50 ppb		100 ppb		200 ppb	
	M	F	M	F	M	F	M	F
Thymus	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)
Within normal limits	6	8	0	0	0	0	7	9
Hemorrhage	4	2	0	0	0	0	3	1
Minimal	4	2	0	0	0	0	3	0
Mild	0	0	0	0	0	0	0	1
Trachea	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within normal limits	10	5	1	3	4	3	2	4
Desquamation, epithelium	0	5	9	7	6	7	8	6
Minimal	0	1	2	2	1	2	1	1
Mild	0	4	6	5	4	5	6	5
Moderate	0	0	1	0	1	0	1	0
Tracheitis, chronic	0	0	0	0	0	0	0	1
Mild	0	0	0	0	0	0	0	1
Uterus	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
Dilatation, uterine horn(s)	0	2	0	0	0	0	0	0
Moderate	0	1	0	0	0	0	0	0
Marked	0	1	0	0	0	0	0	0

() = Number of Animals Examined For This Tissue

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