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May 14, 2010

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Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Attn: TSCA Section 8(e) Coordinator
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, DC 20004



Re: TSCA Section 8(e) Notification of Substantial Risk:
Supplemental Submission

Dear TSCA Section 8(e) Coordinator:

In accordance with the provisions of Section 8(e) of the Toxic Substances and Control Act (TSCA), as interpreted in the TSCA Section 8(e) Policy Statement and Guidance, Fed. Reg. 33129 (June 3, 2003) and other Agency guidance, Dow Corning submits the following information to supplement our initial TSCA Section 8(e) notification of December 23, 2008, (Document ID: 8EHQ-09-17356). The preliminary findings reported in the initial notification were confirmed in the final analysis and are reflected in the attached final report. Dow Corning has not determined whether the study findings represent any significant risk of injury to human health or the environment.

Chemical Substances

1066-42-8 Dimethylsilanediol



DCN: 89100000217

Study Title

An Acute Oral Gavage Study in Mice to Determine the Maximum Tolerated Dose and Systemic Availability of Dimethylsilanediol

Summary

Acute oral administration of dimethylsilanediol induced clinical signs of systemic toxicity which persisted less than 24 hours in males and 48 hours in females.

Dow Corning has not determined whether the study findings represent any significant risk of injury to human health or the environment. Dow Corning Corporation will notify EPA of any further relevant information that may be developed concerning these materials. Attached is the final report (Dow Corning Report Number: 2008-I0000-60042). If you have any questions concerning this submission, please contact me at (989) 496-8046, kathy.plotzke@dowcorning.com, or at the address provided herein.

Sincerely,



Kathleen P. Plotzke, Ph.D.
Director, Health and Environmental Sciences
(989) 496-8046

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

Report Number: 2008-I0000-60042

Title: An Acute Oral Gavage Study In Mice To Determine The Maximum Tolerated Dose And Systemic Availability Of Dimethylsilanediol

Study Number:

Test Article: Dimethylsilanediol

Study Director:

Sponsor: Dow Corning Corporation

HES Management: Team Leader, Toxicology
Health and Environmental Sciences

Testing Facility:

Study Completion Date: April 15, 2009

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1 ABSTRACT

The purpose of this study was to determine the Maximum Tolerated Dose (MTD) (Phase 1) of a single oral bolus dose of Dimethylsilanediol (DMSD) and to determine the systemic availability (Phase 2) of DMSD followed by a single bolus dose for a proposed in vivo genetic toxicity study.

The dosing solution was a 200 mg/mL concentration of DMSD in Milli-Q water.

This study was split into Phase 1 and Phase 2. During the Phase 1, a preliminary toxicity study was conducted using the stepwise approach described in the OECD 423 guideline to determine what dose level would induce some signs of toxicity, but not induce test article related mortality within three days of administration. A total of six female mice were used during Phase 1 and a dose of 2000 mg/kg met the criteria for MTD. In Phase 2, 21 male and 21 female mice were dosed at the 2000 mg/kg dose level. Blood was collected post dose administration from three male and three female mice each at 1, 2, 4, 6, 12, 24, and 48 hours

One animal each from Phase 1 and 2 were found dead during its experimental phase. The death of the animal from Phase 1 was not considered to test article related since a perforated esophagus was noted at necropsy. The cause of death of animal from Phase 2 was not apparent. No visible lesions were noted at necropsy. Adverse clinical observations were noted until study day 3 during Phase 1 and until the end of Phase 2 (48 hours post dose administration). Clinical signs noted included incoordinated gait, absent and decreased activity, respiratory effects (labored, shallow, slow, rapid, and irregular), fully and partially closed eye lids, bilateral and unilateral, cold to touch, muscle twitches, muscle tremors, muscle convulsions, and yellow soiling.

All surviving animals from Phase 1 had gained weight by the end of the experimental phase, however slight weight losses were noted in both groups between study day 1 and study day 4. In Phase 2, there were no remarkable body weight changes with the exception of group 7 males and females. A body weight decrease around five percent for males and around 10 percent for females in this group was noted.

Total silicon content in the plasma was used to assess the systemic availability of DMSD. The limit of quantitation was 85 µg equivalents DMSD/g plasma. The total silicon content detected in plasma was significantly above the limit of quantitation at the first five time points (1, 2, 4, 6 and 12 hours post dose administration) and decreased to near the limit of quantitation (85 µg DMSD/g plasma) 24 hours following dose administration in almost of all of the males and after 48 hours in two of the surviving females

There were no visible lesions noted at necropsy in the remaining animals assigned to Phase 1. No visible lesions were noted in the remaining animals assigned to Phase 2 with the exception of one animal. This animal was observed to be thin with no food in the stomach. No other visible lesions were note in the remaining examined tissues.

Under the conditions of this study, the dose that induced some signs of toxicity, but did not induce test article related mortality within three days after administration was determined to be 2000 mg/kg during Phase 1. During Phase 2, the test article at 2000 mg/kg was found to be systemically available in most male mice up to 24 hours post dose administration and up to 48 hours for most female mice based on total silicon content in plasma.

2 GLP COMPLIANCE STATEMENT

The study was conducted in compliance with USEPA Good Laboratory Standards 40 CFR Part 792 with the following exceptions:

Analyses to determine the composition, stability, and homogeneity of the dosing solutions were not performed.

Protocol deviations listed in Table 7.

There were no circumstances that would negatively impact or bias the results of this study.

Paul A. Neer 14 April 09
Date
Team Leader, Toxicology
Health and Environmental Sciences

Sharon L. Mudgett 15 APR 2009
Date
Study Director
Health and Environmental Sciences

3 QUALITY ASSURANCE STATEMENT

Title: An Acute Oral Gavage Study in Mice to Determine the Maximum Tolerated Dose and Systemic Availability of Dimethylsilanediol

Study Number:

This study has been audited by the Health and Environmental Sciences Quality Assurance Unit according to approved Standard Operating Procedures to assure that the raw data are accurately reflected within this final report. The following are the inspection dates and the dates inspection findings were reported.

<u>Dates of Inspection</u>	<u>Phase Inspected</u>	<u>Findings Reported to Study Director and Management</u>
24-26 May 2006	Draft Protocol Review	26 May 2006
15 June 2006	Body Weight Measurements and Dosing	15 June 2006
14 July 2006	Analytical Standards Preparation	14 July 2006
13-15 Feb. 2008	Contributing Scientist Report and Associated Raw Data	26 Feb. 2008
1-5 Dec. 2008	Draft Final Report and Associated Raw Data Review	10 Dec. 2008

Michelle A. Pravat

Quality Assurance Manager

14 April 2009

Date

4 APPROVAL SIGNATURES

The undersigned have read and approved this report:

Paul A. Sean

14 April 09

Date

Team Leader, Toxicology
Health and Environmental Sciences

Sharon J. Mudgett

15 APR 2009

Date

Study Director
Health and Environmental Sciences

5 STUDY INFORMATION

Study Initiation Date: June 14, 2006

Experimental Start Date: June 15, 2006

Experimental Termination Date: July 18, 2006

Study Completion Date: April 15, 2009

Study Director:

Study Coordinator:

Team Leader, Toxicology:

Supervisor, HES Technical Staff:

Veterinarian/Pathologist:

Contributing Scientist

Supervisor, Bioanalytical Group

6 STUDY PURPOSE

The purpose of this study was to determine the Maximum Tolerated Dose (MTD) (Phase 1) followed by a single oral bolus dose of Dimethylsilanediol (DMSD) and to determine the systemic availability (Phase 2) of DMSD followed by a single bolus dose for a proposed in vivo genetic toxicity study.

7 TEST GUIDELINES

This study was not based on a specific guideline. The study was conducted to determine the MTD which is defined as the dose that induced some signs of toxicity, but did not induce mortality within three days after dose administration. Once the desired dose level was determined further testing was conducted to determine if the test article was systemically available to the target tissues (e.g., Blood) following a single dose administration.

8 TEST ARTICLE / SUBSTANCE / ITEM

Identification:	Dimethylsilanediol
Lot Number:	20444-90
Expiration Date:	8/13/06
Source:	Dow Corning Corporation, Auburn, Michigan 48611
CAS Number:	1066-42-8
Physical Description:	Translucent white solid
Stability:	Stable if stored over dessicant
Purity:	Phase 1: 97.9 % Phase 2: 98.4%
Solubility:	Water
Storage Conditions:	Room temperature in presence of desiccant
Chemical Characterization:	
Archive:	A reserve sample will not be retained.

9 TEST SYSTEM

Species:	Albino Mice
Strain:	CD-1

Source: Charles River Laboratories, Inc.
Portage, MI

Permanent identification Transponders (BioMedic Data Systems, Inc. Seaford, DE)

Phase 1

Sex Female

Age: Approximately 8 weeks old at experimental start

Body weight range: 23.0 -28.0 grams at experimental start

Number used on study: 6 females

Number of groups: 2

Phase 2

Sex Males and Females

Age: Approximately 8 weeks at experimental start

Body weight range: Males: 26.1 – 31.2 grams at experimental start
Females: 22.0 – 26.1 grams at experimental start

Number used on study: 21 females / 21 males

Number of groups: 7

10 JUSTIFICATION FOR SELECTION OF TEST SYSTEM

This study was performed to determine the MTD and assess systemic availability of DMSD for a proposed in vivo genetic toxicity study. CD-1 mice are the strain of choice for this testing conducted for that test guideline due to availability of historical control data.

11 METHOD OF RANDOMIZATION

Animals including extras were ordered and acclimated to ensure adequate numbers for randomization into test groups. After release from quarantine/acclimation, animals were weight stratified then randomized into groups using Provantis™.v.6.5 Animals were within ± 20% of the mean body weight for the groups.

12 HOUSING AND MAINTENANCE

Animal Receipt and Quarantine/Acclimation

Upon receipt, animal resource personnel inspected each animal. Animals judged to be in good health and suitable as test animals were quarantined/acclimated for 6 days. During the quarantine period(s), animal resource personnel observed each animal at least once daily. The

attending veterinarian, or designee, examined all animals before release from quarantine/acclimation.

Animal Housing

Animals were housed two/three per cage in suspended wire-mesh cages elevated above fecal pans containing Bed-O'Cobs® litter, during quarantine/acclimation period. Animals were individually housed in the same type of caging during the in-life phase of the study. The cages and litter/fecal pans were routinely cleaned consistent with good husbandry practices.

Environmental Enrichment

Animals were given plastic tunnels for environmental enrichment.

Environmental Conditions

Animals for Phase 1 and 2 were housed in environmentally controlled animal rooms with a (12-hour fluorescent-light/dark cycle during the in life phase of the study. For Phase 1 the temperature ranged from 20.19 °C to 22.86 °C, the humidity ranged from 27.00 % to 64.00 % and the actual air changes per hour were 15.8 and were verified by Inc. personnel on January 8, 2006. For Phase 2 the temperature ranged from 21.33°C to 22.48°C, the humidity ranged from 49.00 % to 57.00 % and the actual air changes per hour were 9.0 and were verified by Inc. personnel on January 8, 2006. Temperature and humidity were monitored continuously, recorded every 15 minutes using a HOBO® Data Logger and manually recorded twice daily on weekdays and at least once per day during weekends and holidays.

Basal Diet

Lab Diet 5002, Certified Rodent Diet was provided *ad libitum* during the quarantine/acclimation period and throughout the study. The Study Director reviewed the results of the analyses of certified food which are maintained on file at the testing facility. The food was found to be free of heavy metals, pesticides and other contaminants capable of interfering with the study.

Drinking Water

Municipal water, further purified by reverse osmosis was available *ad libitum* via an automatic watering system. Water was monitored routinely and also analyzed on a semi-annual basis. The Study Director reviewed the most recent water analysis results maintained on file at the testing facility. The water was found to be free of contaminants capable of interfering with the study.

13 ANIMAL WELFARE ACT COMPLIANCE

This study complied with all applicable sections of the final rule of the Animal Welfare Act regulations (9 CFR, Part 1, 2, and 3).

14 EXPERIMENTAL DESIGN

Data Acquisition System

Test system observations, body weights, documentation of dosing, and morphologic pathology data were collected using Provantis™ v6.5

Timeline of Study Events**Phase 1: Determination of MTD**

Event	
Acclimation:	6 days
Dosing:	Study Day 1
Body weights:	Prior to dosing, 24 hours post-dose, 72 hours post-dose and weekly thereafter
Clinical Observations:	Two times within four hours post dosing (once within (30 ± 10) minutes of dosing) and daily thereafter
Termination:	14 days post dose following body weight collection

Phase 2: Systemic Bioavailability Determination

Event	
Acclimation:	6 days
Single dose:	Study Day 1
Body weights:	Prior to dosing for all animals assigned to the study and also prior to blood collection for all animals assigned to Groups 6 and 7.
Clinical Observations:	(30 ± 10) minutes, 4, 24, and 48 hours post dose
Blood Collection:	1, 2, 4, 6, 12, 24, or 48 hours post dose (± 10 minutes for each time point)
Necropsy:	Immediately following blood collection
Experimental Termination:	Following the blood collection and necropsy for the surviving group 7 animals.

Route and Rationale of Test Article Administration**Route**

Test article was administered by oral gavage.

Rationale

Animals were dosed by oral gavage for Phase 1 and 2. Oral gavage is the acceptable route of administration for the proposed studies with this test article. During both Phase 1 and 2, the animals received the test article as a single administration.

Dosing Solution Preparation and Analysis**Preparation of Test Article (Phase 1 and 2)**

The dosing solution of DMSD in Milli-Q water with a concentration of 200 mg/mL was prepared for both Phase 1 and 2.

Analysis

Dosing solutions were not analyzed.

Storage conditions

The dosing solutions were prepared fresh on each day of dosing.

Organization of Test Groups and Treatment Regimen

A preliminary toxicity study based on stepwise approach described in the OECD 423 guideline was conducted to determine the MTD during Phase 1 of study. The first group dosed (group 8) was administered 2000 mg/kg based on the toxicity of the test article. A second group (group 9) was also administered 2000 mg/kg based on the lack of test article related deaths in group 8.

The dose level selected for Phase 2 was 2000 mg/kg bodyweight based on the MTD established in Phase 1.

The dose volume did not exceed 20 mL/kg body weight.

Group Assignments

Group	Length of Experimental Phase	Number of animals Males/Females	Dose Level (mg/kg)
Phase 1			
8	14 days	0/3	2000
9	14 days	0/3	2000
Phase 2			
1	1 hour	3/3	2000
2	2 hour	3/3	2000
3	4 hour	3/3	2000
4	6 hour	3/3	2000
5	12 hour	3/3	2000
6	24 hour	3/3	2000
7	48 hour	3/3	2000

Test System Observations

Mortality/Morbidity/Moribundity

All animals were observed at least twice daily and once daily on weekends in their cages for mortality, morbidity, and moribundity by study personnel throughout the completion of the in-life phase of the study. Animals found dead were placed in a refrigerator for preservation until appropriate personnel were available for necropsy. The Study Director and Attending Veterinarian (or designees) were notified when animals were found sick, moribund, or dead.

Clinical Observations

All surviving animals were observed for clinical abnormalities 30 ± 10 minutes post-dose, within four hours post dose and daily thereafter. The health condition of the animals was recorded.

Disposition

Scheduled

Fourteen days after treatment, all surviving Phase 1 animals were euthanized by carbon dioxide asphyxiation and subjected to a gross necropsy. All surviving Phase 2 animals were anesthetized with isoflurane at time points specified in the Timeline of Study Events and blood was drawn for analysis via cardiac puncture. Following blood collection, all Phase 2 animals were subjected to a gross necropsy.

PARAMETERS MEASURED

Individual Body Weights

For Phase 1 Individual body weights were determined prior to randomization, prior to dosing, 24 hours post dose, 72 hours post dose and weekly thereafter, including the day of necropsy.

For Phase 2 Individual body weights were determined prior to randomization, prior to dosing, and prior to blood collection.

Blood Collection

For blood collection, the animals were anesthetized with isoflurane. Blood was collected via open cardiac puncture and placed in tubes containing EDTA.

Macroscopic Examination

At the scheduled intervals, all animals were subjected to a complete gross necropsy which included examination of the external surface and all orifices of the body, the cranial, thoracic and abdominal cavities and their contents.

15 RESULTS AND DISCUSSION

Phase 1

Mortality and Morbidity

One animal from group 8 was found dead on Study Day 3. The remaining animals from the groups assigned to Phase 1 survived until the experimental phase.

Clinical Signs

Clinical signs for Phase 1 are summarized in Table 1. Individual clinical signs are tabulated in Appendix A. In group 8, no abnormalities were noted 30 minutes after dosing, however at the four hour observation activity and reactivity were decreased in two of the three animals in the group. Two animals had eye lids, partially closed (bilateral). One animal had labored respiration. One animal not affected on study day 1 had eye lids, partially closed (bilateral), crouched posture, labored respiration, and hair standing up on study day 2. One of the two affected animals from study day 1 had increased reactivity on study day 2 and the other animal had incoordinated gait and yellow soiling on the general abdomen, general urogenital, hind paws (bilateral), and hind limb (bilateral). On study day 3, no abnormalities were noted in the two surviving animals for the rest of the experimental phase. Based on these results, another three females (Group 9) were dosed at the same dose level as Group 8. No abnormalities were noted 30 minutes after dosing, however by the four hour observations, effects were noted in two out of the three animals. Both animals had labored respiration and decreased activity with one also having slow respiration and absent reactivity. One animal also had eye lids, fully closed (bilateral), incoordinated gait, cold to touch, and general muscle twitches at this time point. The other animal had eye lids partially closed (bilateral) and crouched posture. On study day 2, effects were still apparent in these two animals. The effects included decreased activity, cold to touch, continuous muscle tremors, crouched posture, and yellow soiling on general chest, abdomen, and urogenital regions. One animal also had eye lids, partially closed (bilateral) and yellow soiling on forepaws (bilateral), forelimbs (bilateral), hindpaw (bilateral), and hindlimb (bilateral). On study day 3 and through the end of the experimental phase, no abnormalities were noted.

Body Weights

The individual body weight data and means and standard deviations for Phase 1 are reported in Table 2. Body weight changes are reported in Table 3. All surviving animals had gained weight by the end of the experimental phase, however slight weight losses were noted in both groups between study day 1 and study day 4.

Gross Pathology Observations

Gross pathology observations are summarized in Table 4. Individual gross pathology observations are tabulated in Appendix B. A perforation was noted in the esophagus of the animals that was found dead. This was believed to be due a gavage accident. No visible lesions were noted in the surviving animals in group 8 and animals in group 9.

Phase 2

Mortality and Morbidity

One animal from group 6 was found dead approximately 24 hours after dose administration. The cause of death was not apparent at necropsy. The remaining animals survived until their blood collection time point.

Clinical Signs

Clinical signs for Phase 2 are summarized in Table 5. Individual clinical signs are tabulated in Appendix C.

Approximately thirty minutes following dose administration, males in all the groups had incoordinated gait. Over half the males had crouched posture; and three-quarters of the males had decreased activity. Five males had general muscle twitches; and one male was dragging its hindquarters. During this same time point, all but one of the females had incoordinated gait. Three-quarters of the females had decreased activities; and one female had absent activity. All but three females had crouched posture; and one female had splayed hind limbs. Three females had labored respiration; and one female had an irregular respiration rate. One female had partially closed eye lids, bilateral. Six females had general muscle twitches; and one female had muscle convulsions, tonic/clonic.

Approximately four hours following dose administration, two of the remaining males (groups 3, 4, 5, 6, and 7) had no abnormalities detected. Approximately one-third of the remaining males had decreased or absent activity. Approximately one-third had partially closed eye lids, bilateral; and two had fully closed eye lids, bilateral. Almost half had shallow respiration with one having rapid respiration and three having slow respiration. Almost half had crouched posture and incoordinated gait. Four had general muscle twitches. Two had yellow soiling general abdomen. Almost three-quarters of the remaining females absent activity; and two had decreased activity. Three had an incoordinated gait; and three had crouched posture. Over half had fully closed eye lids, bilateral; and three had partially closed eye lids. Two had muscle convulsion, tonic/clonic; one had an absent muscle tremor, and four had general muscle twitches. Six females had shallow and slow respirations; one had slow respiration with an irregular rate; and one had just slow respirations. One had labored and rapid respirations; and one had rapid and shallow respirations. The only respiratory effect in two animals was rapid respiration.

Approximately 24 hours following dose administration, five of the remaining males (groups 6 and 7) had no abnormalities detected. The remaining animal had absent activity, partially closed eye lids, bilateral, was cold to touch, and had shallow and slow respirations. Four animals had absent activity. One of the females was found dead around this time point. Two of the remaining females had no abnormalities detected. Four had absent activity. Two had fully closed eye lids, bilateral. One animal had partially closed eyelids, bilateral. One animal had each a partially and fully closed eyelid. Four animals were cold to touch. One had general muscle twitches. Three animals had shallow and slow respirations; and one had only rapid respirations. One animal had yellow soiling on general abdomen and urogenital regions and hindlimb, unilateral.

Approximately 48 hours following dose administration, all of the remaining males (group 7) had no abnormalities detected. Two of the remaining females had no abnormalities detected. The other female had decreased activity, eye lids fully closed, bilateral, continuous muscle tremor, and yellow soiling on the general urogenital region.

Body Weights

The individual body weight data and individual body weight changes and means and standard deviations for Phase 2 are reported in Table 6. There was no remarkable body weight changes with the exception of group 7 males and females noted during the experimental phase. A body weight decrease around five percent for males and around 10 percent for females was noted.

Gross Pathology Observations

Gross pathology observations are summarized in Table 8. Individual gross pathology observations are tabulated in Appendix D. No visible lesions were noted in the remaining animals assigned to Phase 2 with the exception of animal number 3315. This animal was observed to be thin with no food in the stomach. No other visible lesions were noted in the remaining examined tissues.

Quantitation of Total Silicon

The contributing scientist report for the total silicon quantitation in the plasma can be found in Appendix E. Total silicon content in the plasma was used to assess the systemic availability of DMSD. The limit of quantitation was 85 µg equivalents DMSD/g plasma. The total silicon content detected in plasma was significantly above the limit of quantitation at the first five time points (1, 2, 4, 6 and 12 hours post dose administration) and decreased to near the limit of quantitation (85 µg equivalents DMSD/g plasma) 24 hours following dose administration in almost all of the males and after 48 hours in two of the surviving females.

16 CONCLUSIONS

Under the conditions of this study, the dose that induced some signs of toxicity, but did not induce test article related mortality within three days after administration was determined to be 2000 mg/kg during Phase 1. During Phase 2, the test article at 2000 mg/kg was found to be systemically available in most male mice up to 24 hours post dose administration and up to 48 hours for most female mice based on total silicon content in plasma.

17 PROTOCOL DEVIATIONS

Protocol deviations for this study are listed in Table 7.

These deviations had no impact on the study.

18 ARCHIVE

Protocol, amendments and deviations, study authorization documentation, raw data, correspondence, and final report are retained in the HES Archives,

19 REFERENCES

1. Organization for Economic Cooperation and Development. OECD Guideline for Testing of Chemicals. Section 4, No. 423: Acute Oral Toxicity, (2001).
2. U.S. Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.1100. Acute Oral Toxicity, (1998).
3. U.S. Environmental Protection Agency, Good Laboratory Practices, 40 CFR Part 792.
- 4.

Figure 1

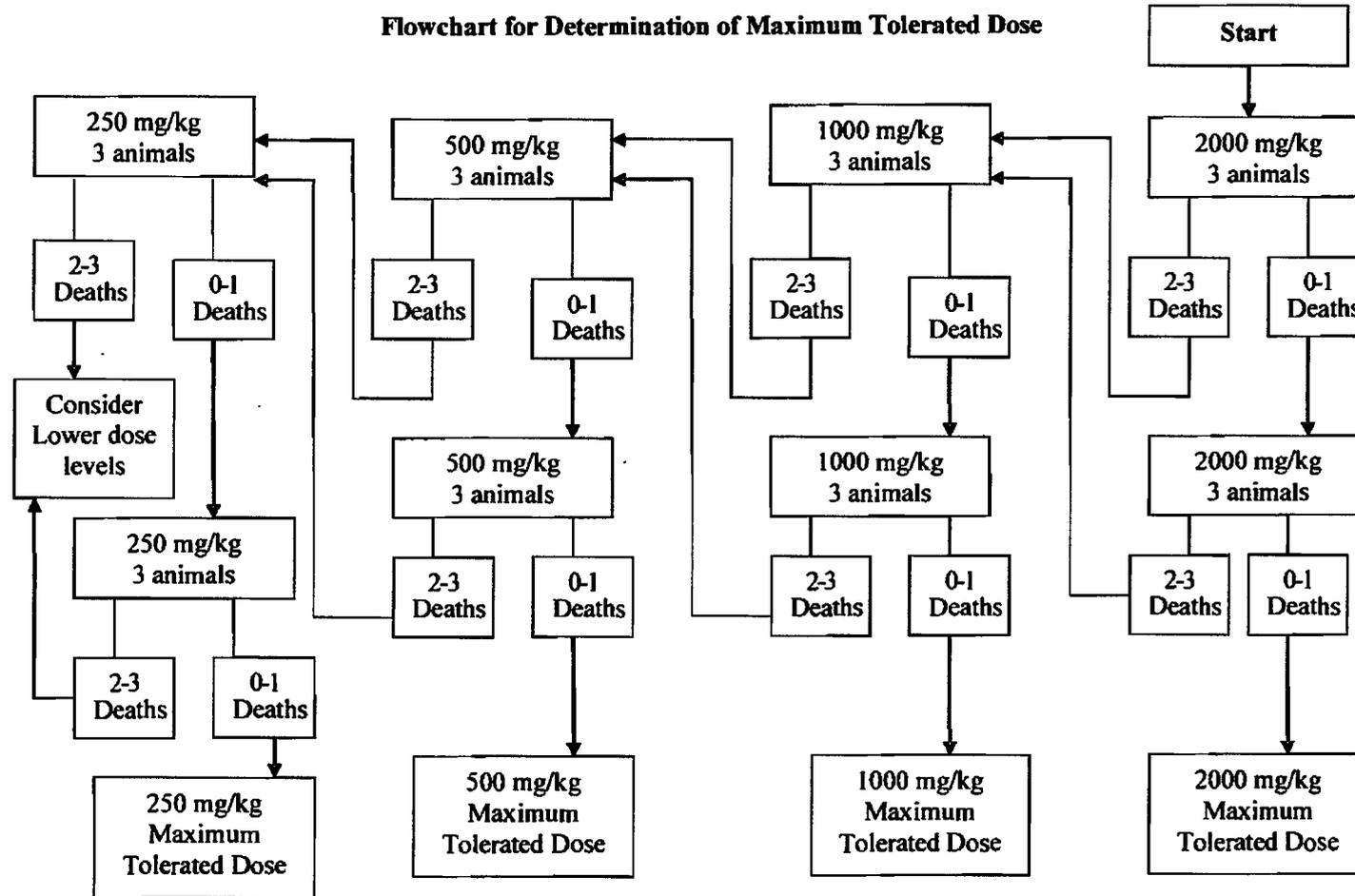


TABLE 1
Phase 1 - Summary of Clinical Observations

Group Number	Sex		Day on Study																	
			1 ^a	1 ^b	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
8	F	No Abnormalities Detected	3/3	1/3	0/3	2/3	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2	
		Behavior, Activity																		
		- Decreased	0/3	2/3	1/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		Behavior, Reactivity																		
		- Decreased	0/3	2/3	0/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		- Increased	0/3	0/3	1/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		Eye, Lid(s) partially closed																		
		- Bilateral	0/3	2/3	1/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		Gait, Incoordinated	0/3	0/3	1/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		Posture, Crouched	0/3	0/3	1/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		Respiration, Labored	0/3	1/3	1/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		Skin, Hair Standing Up	0/3	0/3	1/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		Soiling, Yellow																		
		- Abdomen, General	0/3	0/3	1/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		- Urogenital, General	0/3	0/3	1/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		- Hindpaw, Bilateral	0/3	0/3	1/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		- Hindlimb, Bilateral	0/3	0/3	1/3	0/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		Spontaneous Death	0/3	0/3	0/3	1/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2

		9	F	No Abnormalities Detected	2/3	1/3	1/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
Behavior, Activity																				
- Absent	0/3			1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	
- Decreased	1/3			1/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	
Behavior, Reactivity																				
- Absent	0/3			1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	
- Decreased	0/3			0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	
- Increased	0/3			0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	

^a30 minutes post dose administration

^b4 hours post dose administration

TABLE 1 (Continued)
Phase 1 - Summary of Clinical Observations

Group Number	Sex		Day on Study																
			1 ^a	1 ^b	2	3	4	5	6	7	8	9	0	1	1	1	1	1	1
9	F	Eye, Lid(s) fully closed																	
		- Bilateral	0/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		Eye, Lid(s) partially closed																	
		- Bilateral	0/3	1/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		Gait, Incoordinated	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		Misc. Cold to Touch	0/3	1/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		Muscle, Tremor																	
		- Continuous	0/3	0/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		Muscle, Twitches																	
		- General	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		Posture, Crouched	0/3	1/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		Respiration																	
		- Labored	0/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		- Slow	0/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		Soiling, Yellow																	
		- Chest, General	0/3	0/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		- Abdomen, General	0/3	0/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		- Urogenital, General	0/3	0/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		- Forepaw, Bilateral	0/3	0/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		- Forelimb																	
		- Bilateral	0/3	0/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		- Unilateral	0/3	0/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		- Hindpaw, Bilateral	0/3	0/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
		- Hindlimb, Bilateral	0/3	0/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3

^a30 minutes post dose administration

^b4 hours post dose administration

TABLE 2
Phase I - Individual Body Weight (g) and Individual Body Weight (g) Change Data and Means and Standard Deviations

Group Number	Animal Number	Body Weight Day 1	Body Weight Day 2	Body Weight Change Day 1 to 2	Body Weight Day 4	Body Weight Change Day 2 to 4	Body Weight Day 8	Body Weight Change Day 4 to 8	Body Weight Day 15	Body Weight Change Day 8 to 15
8	3318	22.5	22.3	-0.2	24.1	1.8	24.3	0.2	24.9	0.6
	3319	26.1	24.4	-1.7						
	3320	24.6	24.4	-0.2	25.6	1.2	27.2	1.6	26.9	-0.3
	Mean	24.40	23.70	-0.70	24.85	1.50	25.75	0.90	25.90	0.15
	Standard Deviation	1.808	1.212	0.866	1.061	0.424	2.051	0.990	1.414	0.636
9	3321	26.4	25.8	-0.6	24.9	-0.9	27.1	2.2	28	0.9
	3322	26.3	24.5	-1.8	23.7	-0.8	24.2	0.5	25.3	1.1
	3323	28.4	28.5	0.1	28.5	0	28.3	-0.2	29.3	1
	Mean	27.03	26.27	-0.77	25.70	-0.57	26.53	0.83	27.53	1.00
	Standard Deviation	1.185	2.040	0.961	2.498	0.493	2.108	1.234	2.040	0.100

Group 8 - MTD 2000 mg/kg Group 9 - MTD-2 2000 mg/kg

TABLE 3
Phase 1 - Summary of Gross Findings

	----- FEMALES -----		
	Group Number:	8	9
	Dose Level (mg/kg):	2000	2000
	Number of Animals on Study :	3	3
	Number of Animals Completed:	(2)	(3)
ESOPHAGUS;			
Submitted.....		(1)	(0)
No Visible Lesions.....		0	0
Perforation		1	0
WHOLE BODY;			
Submitted.....		(2)	(3)
No Visible Lesions.....		2	3

TABLE 4
Phase 2 - Summary of Clinical Observations

	Males			
	30 Min	Four hours	24 Hours	48 Hours
No abnormalities detected	0/21	2/15	5/6	3/3
Behavior, activity, decreased	11/21	5/15	0/6	0/3
Behavior, activity, absent	0/21	6/15	1/6	0/3
Eye, Lid(s) partially closed, bilateral	0/21	6/15	1/6	0/3
Eye, Lid(s) fully closed, bilateral	0/21	2/15	0/6	0/3
Respiration, Labored	1/21	0/15	0/6	0/3
Respiration, Shallow	0/21	7/15	1/6	0/3
Respiration, Rapid	0/21	1/15	0/6	0/3
Respiration, Slow	0/21	3/15	1/6	0/3
Posture, Crouched	16/21	7/15	0/6	0/3
Posture, Hind limbs splayed	1/21	0/15	0/6	0/3
Gait, Incoordinated	21/21	6/15	0/6	0/3
Gait, Dragging Hindquarters	1/21	0/15	0/6	0/3
Misc. Cold to Touch	0/21	0/15	1/6	0/3
Muscle Convulsion, Tonic/Clonic	1/21	0/15	0/6	0/3
Muscle, Twitches, General	5/21	4/15	0/6	0/3
Yellow soiling, abdomen, General	0/21	2/15	0/6	0/3

TABLE 4 (Continued)
Phase 2 - Summary of Clinical Observations

	30 Min	Four hours	24 Hours	48 Hours
No Abnormalities Detected	0/21	0/15	1/6	2/3
Behavior, Activity, Decreased	16/21	2/15	0/6	1/3
Behavior, Activity, Absent	1/21	11/15	4/6	0/3
Gait, Incoordinated	20/21	3/15	0/6	0/3
Posture, Crouches	18/21	3/15	0/6	0/3
Posture, Hind Limbs Splayed	1/21	0/15	0/6	0/3
Eye, Lid(s) fully closed, Bilateral	0/21	8/15	1/6	1/3
Eye, Lid(s) fully closed, Unilateral	0/21	0/15	1/6	0/3
Eye, Lid(s) partially closed, Bilateral	1/21	3/15	2/6	0/3
Eye, Lid(s) partially closed, Unilateral	0/21	0/15	1/6	0/3
Misc Cold To Touch	0/21	0/15	4/6	0/3
Muscle Convulsion, Tonic/Clonic	1/21	2/15	0/6	0/3
Muscle, Tremor, Associated with movement	0/21	1/15	0/6	0/3
Muscle, Tremor, Continuous	0/21	0/15	0/6	1/3
Muscle, Twitches, General	6/21	4/15	1/6	0/3
Respiration, Irregular rate	1/21	1/15	0/6	0/3
Respiration, Labored	3/21	1/15	0/6	0/3
Respiration, Rapid	0/21	4/15	1/6	0/3
Respiration, Shallow	0/21	7/15	3/6	0/3
Respiration, Slow	0/21	8/15	3/6	0/3
Yellow soiling, abdomen, General	0/21	0/15	1/6	0/3
Yellow soiling, urogenital, General	0/21	0/15	1/6	1/3
Yellow soiling, hindlimb, Unilateral	0/21	0/15	1/6	0/3
Spontaneous Death	0/21	0/15	1/6	0/3

TABLE 5
Phase 2 (Males) - Individual Body Weight (g) and Individual Body Weight (g) Change Data
and Means and Standard Deviations

		Initial Body Weight (g)	Final Body Weight (g)	Body Weight Change (g)
1M	3276	27.5	27.2	-0.3
	3277	28.9	28.7	-0.2
	3278	29.4	29.8	0.4
	Mean	28.6	28.6	0.0
	S.D.	0.98	1.31	0.38
2M	3279	28.1	27.1	-1.0
	3280	27.5	27.4	-0.1
	3281	30.2	29.8	-0.4
	Mean	28.6	28.1	-0.5
	S.D.	1.42	1.48	0.46
3M	3282	26.1	26.7	0.6
	3283	29.4	28.9	-0.5
	3284	28.5	28.3	-0.2
	Mean	28.0	28.0	0.0
	S.D.	1.71	1.14	0.57
4M	3285	26.8	27.1	0.3
	3286	29.7	29.5	-0.2
	3287	29.5	29.2	-0.3
	Mean	28.7	28.6	-0.1
	S.D.	1.62	1.31	0.32
5M	3288	28.2	27.9	-0.3
	3289	28.0	27.1	-0.9
	3290	31.2	30.8	-0.4
	Mean	29.1	28.6	-0.5
	S.D.	1.79	1.95	0.32
6M	3291	27.2	26.6	-0.6
	3292	30.1	29.5	-0.6
	3293	28.8	28.4	-0.4
	Mean	28.7	28.2	-0.5
	S.D.	1.45	1.46	0.12
7M	3294	30.3	29.7	-0.6
	3295	28.7	28.3	-0.4
	3296	27.0	25.3	-1.7
	Mean	28.7	27.8	-0.9
	S.D.	1.65	2.25	0.70

TABLE 5 (Continued)
Phase 2 (Females) - Individual Body Weight (g) and Individual Body Weight (g) Change Data
and Means and Standard Deviations

		Initial Body Weight (g)	Final Body Weight (g)	Body Weight Change (g)
1F	3297	23.5	22.6	-0.9
	3298	23.6	24.3	0.7
	3299	23.5	23.6	0.1
		23.5	23.5	0.0
		0.06	0.85	0.81
2F	3300	23.1	22.8	-0.3
	3301	24.7	24.6	-0.1
	3302	23.9	23.8	-0.1
		23.9	23.7	-0.2
		0.80	0.90	0.12
3F	3303	24.1	23.9	-0.2
	3304	23.5	23.5	0.0
	3305	23.7	23.7	0.0
		23.8	23.7	-0.1
		0.31	0.20	0.12
4F	3306	23.8	24.0	0.2
	3307	23.5	23.1	-0.4
	3308	24.8	24.4	-0.4
		24.0	23.8	-0.2
		0.68	0.67	0.35
5F	3309	23.5	23.9	0.4
	3310	25.1	24.5	-0.6
	3311	22.0	22.4	0.4
		23.5	23.6	0.1
		1.55	1.08	0.58
6F	3312	24.8	24.5	-0.3
	3313	24.7	24.2	-0.5
	3314	23.4	22.9	-0.5
		24.3	23.9	-0.4
		0.78	0.85	0.12
7F	3315	24.8	24.0	-0.8
	3316	26.1	23.3	-2.8
	3317	23.8	22.1	-1.7
		24.9	23.1	-1.8
		1.15	0.96	1.00

TABLE 6
Phase 2 - Summary of Gross Findings

		----- MALES -----						
		1 hr	2 hr	4 hr	6 hr	12 hr	24 hr	48 hr
		2000	2000	2000	2000	2000	2000	2000
Number of Animals on Study :		3	3	3	3	3	3	3
Number of Animals Completed:		(3)	(3)	(3)	(3)	(3)	(3)	(3)
-----		-----						
WHOLE BODY;								
Submitted.....		(3)	(3)	(3)	(3)	(3)	(3)	(3)
No Visible Lesions.....		3	3	3	3	3	3	3
-----		-----						
		----- FEMALES -----						
		1 hr	2 hr	4 hr	6 hr	12 hr	24 hr	48 hr
		2000	2000	2000	2000	2000	2000	2000
Number of Animals on Study :		3	3	3	3	3	3	3
Number of Animals Completed:		(3)	(3)	(3)	(3)	(3)	(2)	(2)
-----		-----						
WHOLE BODY;								
Submitted.....		(3)	(3)	(3)	(3)	(3)	(3)	(3)
No Visible Lesions.....		3	3	3	3	3	3	2
WHOLE BODY the animal is thin and there is no food in the stomach								
No visible lesions were noted in the remaining tissues.....		0	0	0	0	0	0	1

TABLE 7
Phase 1 and 2 - Protocol Deviations

Protocol Section	Protocol Requirement	Deviation	Impact
10 HOUSING AND MAINTENANCE	Animals will be housed in an environmentally controlled animal room (12-hour fluorescent-light/dark cycle, 19-25°C, 30-70% relative humidity...	The relative humidity fell to 27%.	None. It was not that far out of the acceptable range.
13 PARAMETERS MEASURED	Phase 1 All surviving animals will be observed for clinical abnormalities at the following time points post dosing: two times within four hours post dose...	The four observations were recorded between 4 hours and 6 minutes and 4 hours and 14 minutes post dose administration.	None. The times were not that far out of range.

APPENDIX A
Phase 1 – Individual Clinical Observations

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date										
					1	1	2	2	3	4	5	6	7		
					30 min	4 Hr		24 Hr							
8	f	3318	No Abnormalities Detected		X	X	X	X	X	X	
			Behavior, Activity		.	D
			Behavior, Reactivity		.	D	.	I
				Eye, Lid(s) partially closed	Bilateral	.	X
		3319	No Abnormalities Detected		X	X
			Behavior, Activity		D
				Eye, Lid(s) partially closed	Bilateral	.	.	.	X	
				Posture, Crouched		.	.	.	X	
				Respiration, Labored		.	.	.	X	
				Skin, Hair Standing Up		.	.	.	X	
	3320			Spontaneous Death		X	
		No Abnormalities Detected		X	X	X	X	X	X	
		Behavior, Activity		.	D	
		Behavior, Reactivity		.	D	
				Eye, Lid(s) partially closed	Bilateral	.	X	
				Gait, Incoordinated		.	.	.	X	
				Respiration, Labored		.	X	
				Soiling	Abdomen, General	.	.	.	Y	
			Soiling	Urogenital, General	.	.	.	Y		
		Soiling	Hindpaw, Bilateral	.	.	.	Y			
		Soiling	Hindlimb, Bilateral	.	.	.	Y			

Severity Codes: X = Present; . = Not Present; D = Decreased; I = Increased; Y = Yellow
 Group 8 - MYD 2000 mg/kg

APPENDIX A (Continued)
Phase 1 – Individual Clinical Observations

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date									
					8	9	10	11	12	13	14	15		
8	f	3318	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	
			Behavior, Activity	
			Behavior, Reactivity	
					Eye, Lid(s) partially closed	Bilateral
		3319	No Abnormalities Detected	
			Behavior, Activity	
			Eye, Lid(s) partially closed	Bilateral
			Posture, Crouched	
			Respiration, Labored	
			Skin, Hair Standing Up	
					Spontaneous Death	
		3320	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X
			Behavior, Activity	
			Behavior, Reactivity	
			Eye, Lid(s) partially closed	Bilateral
Gait, Incoordinated				
Respiration, Labored				
Soiling	Abdomen, General			
Soiling	Urogenital, General			
Soiling	Hindpaw, Bilateral			
Soiling	Hindlimb, Bilateral			

-----Severity
 Codes: X = Present; . = Not Present
 Group 8 - MTD 2000 mg/kg

APPENDIX A (Continued)
Phase 1 – Individual Clinical Observations

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date											
					1 30 min	1 4 Hr	2 24 Hr	2	3	4	5	6	7			
9	f	3321	No Abnormalities Detected		X	X	X	X	X			
			Behavior, Activity		D	A	D		
			Behavior, Reactivity		.	A	
			Eye, Lid(s) fully closed	Bilateral	.	X	
			Eye, Lid(s) partially closed	Bilateral	.	.	X	
			Gait, Incoordinated		X	
			Misc. Cold to Touch		.	X	X	
			Muscle, Tremor		.	.	C	
			Muscle, Twitches	General	X	
			Posture, Crouched		.	.	X	
			Respiration, Labored		.	X	
			Respiration, Slow		.	X	
			Soiling	Chest, General	.	.	Y	
			Soiling	Abdomen, General	.	.	Y	
			Soiling	Urogenital, General	.	.	Y	
		Soiling	Forepaw, Bilateral	.	.	Y		
		Soiling	Forelimb, Bilateral	.	.	Y		
		Soiling	Hindpaw, Bilateral	.	.	Y		
		Soiling	Hindlimb, Bilateral	.	.	Y		
		3322		3322	No Abnormalities Detected		X	.	.	.	X	X	X	X	X	
					Behavior, Activity		.	D	D
					Eye, Lid(s) partially closed	Bilateral	.	X
					Misc. Cold to Touch		.	.	X
					Muscle, Tremor		.	.	C
					Posture, Crouched		.	X	X
					Respiration, Labored		.	X
					Soiling	Chest, General	.	.	Y
Soiling	Abdomen, General				.	.	Y		
Soiling	Urogenital, General				.	.	Y		
Soiling	Forelimb, Left				.	.	Y		
Soiling	Hindlimb, Bilateral				.	.	Y		
3323		3323	No Abnormalities Detected		X	X	X	.	X	X	X	X	X			

Severity Codes: X = Present; . = Not Present; A = Absent; D = Decreased; C = Continuous; Y = Yellow
 Group 9 - MTD-2 2000 mg/kg

APPENDIX A(Continued)
Phase I - Individual Clinical Observations

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date								
					8	9	10	11	12	13	14	15	
9	f	3321	No Abnormalities Detected		X	X	X	X	X	X	X	X	X
			Behavior, Activity	
			Behavior, Reactivity	
			Eye, Lid(s) fully closed	Bilateral
			Eye, Lid(s) partially closed	Bilateral
			Gait, Incoordinated	
			Misc. Cold to Touch	
			Muscle, Tremor	
			Muscle, Twitches	General
			Posture, Crouched	
			Respiration, Labored	
			Respiration, Slow	
			Soiling	Chest, General
			Soiling	Abdomen, General
			Soiling	Urogenital, General
			Soiling	Forepaw, Bilateral
			Soiling	Forelimb, Bilateral
			Soiling	Hindpaw, Bilateral
			Soiling	Hindlimb, Bilateral
		3322	No Abnormalities Detected		X	X	X	X	X	X	X	X	X
			Behavior, Activity	
			Eye, Lid(s) partially closed	Bilateral
			Misc. Cold to Touch	
			Muscle, Tremor	
			Posture, Crouched	
			Respiration, Labored	
			Soiling	Chest, General
			Soiling	Abdomen, General
			Soiling	Urogenital, General
			Soiling	Forelimb, Left
			Soiling	Hindlimb, Bilateral
		3323	No Abnormalities Detected		X	X	X	X	X	X	X	X	X

 Severity Codes: X = Present; . = Not Present

Group 9 - MTD-2 2000 mg/ kg

APPENDIX B
Phase I - Individual Gross Pathology Observations

Animal Ref.	Mode Of Death	Death Day (Week)	Observation(s)
Group: 8			
3318	Scheduled Necropsy - CO2	15 (3)	No Visible Lesions
3319	Found Dead	3 (1)	ESOPHAGUS: Possible gavage accident: ESOPHAGUS; Perforation Any remaining protocol required tissues, which have been examined, have no visible lesions
3320	Scheduled Necropsy - CO2	15 (3)	No Visible Lesions
Group: 9			
3321	Scheduled Necropsy - CO2	15 (3)	No Visible Lesions
3322	Scheduled Necropsy - CO2	15 (3)	No Visible Lesions
3323	Scheduled Necropsy - CO2	15 (3)	No Visible Lesions
Group 8 - MTD 2000 mg/kg		Group 9 - MTD- 2000 mg/kg	

APPENDIX C
Phase 2 (Males) – Individual Clinical Observations

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date	
					1 30 min	1 4 Hr
1	m	3276	Gait, Incoordinated		X	
			Behavior, Activity		D	
		3278	Gait, Dragging Hindquarters		F	
			Gait, Incoordinated		X	
			Behavior, Activity		D	
			Gait, Incoordinated		X	
2	m	3279	Posture, Crouched		X	
			Behavior, Activity		D	
		3280	Gait, Incoordinated		X	
			Posture, Crouched		X	
			Behavior, Activity		D	
			Gait, Incoordinated		X	
3	m	3281	Posture, Crouched		X	
			Gait, Incoordinated		X	
		3282	Muscle, Twitches	General	X	
			Behavior, Activity		D	A
			Eye, Lid(s) partially closed	Bilateral	.	X
			Gait, Incoordinated		X	.
			Muscle, Twitches	General	X	.
			Posture, Crouched		X	.
3283	Respiration, Shallow		.	X		
	No Abnormalities Detected		.	X		
3284	Gait, Incoordinated		X	.		
	Behavior, Activity		-	D		
	Eye, Lid(s) partially closed	Bilateral	.	X		
	Gait, Incoordinated		X	X		
	Posture, Crouched		X	X		
		Respiration, Shallow		.	X	

Severity Codes: X = Present; . = Not Present; A = Absent; D = Decreased; F = Limbs Flaccid;
Group 1 - 1 hr 2000 mg/kg Group 2 - 2 hr 2000 mg/kg Group 3 - 4 hr 2000 mg/kg

APPENDIX C (Continued)
Phase 2 (Males) - Individual Clinical Observations

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date	
					1 30 min	1 4 Hr
4	m	3285	Behavior, Activity		D	A
			Eye, Lid(s) fully closed	Bilateral	.	X
			Gait, Incoordinated		X	.
			Muscle, Twitches	General	X	X
			Posture, Crouched		X	.
			Respiration, Shallow		.	X
		3286	Behavior, Activity		D	D
			Eye, Lid(s) partially closed	Bilateral	.	X
			Gait, Incoordinated		X	X
			Muscle, Twitches	General	X	X
			Posture, Crouched		X	X
			Soiling	Abdomen, General	.	Y
3287	Behavior, Activity		D	D		
	Gait, Incoordinated		X	X		
	Posture, Crouched		X	X		
5	m	3288	Behavior, Activity		.	A
			Eye, Lid(s) partially closed	Bilateral	.	X
			Gait, Incoordinated		X	.
			Muscle, Twitches	General	.	X
			Posture, Crouched		X	.
			Respiration, Shallow		.	X
		3289	Respiration, Slow		.	X
			No Abnormalities Detected		.	X
			Gait, Incoordinated		X	.
		3290	Muscle, Twitches	General	X	.
			Posture, Crouched		X	.
			Behavior, Activity		D	A
			Eye, Lid(s) fully closed	Bilateral	.	X
			Gait, Incoordinated		X	.
			Muscle, Convulsion		T	.
			Muscle, Twitches	General	.	X
			Posture, Crouched		X	.
			Posture, Hind Limbs Splayed		X	.
3290	Respiration, Labored		X	.		
	Respiration, Shallow		.	X		
	Respiration, Slow		.	X		

Severity Codes: X = Present; . = Not Present; A = Absent; D = Decreased; T = Tonic/Clonic
 Group 4 - 6 hr 2000 mg/kg Group 5 - 12 hr 2000 mg/kg

APPENDIX C (Continued)

Phase 2 (Males) – Individual Clinical Observations

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date				
					1 30 min	1 4 Hr	2	3	
6	m	3291	No Abnormalities Detected		.	.	X		
			Behavior, Activity		D	.	.		
			Gait, Incoordinated		X	.	.		
			Posture, Crouched		X	X	.		
			Soiling	Abdomen, General	.	Y	.		
		3292	No Abnormalities Detected		.	.	X		
			Gait, Incoordinated		X	X	.		
			Posture, Crouched		X	X	.		
		3293		No Abnormalities Detected		.	.	X	
				Behavior, Activity		.	D	.	
				Eye, Lid(s) partially closed	Bilateral	.	X	.	
Gait, Incoordinated				X	X	.			
Posture, Crouched				.	X	.			
7	m	3294	No Abnormalities Detected		.	.	X	X	
			Behavior, Activity		.	A	.	.	
			Gait, Incoordinated		X	.	.	.	
			Posture, Crouched		X	.	.	.	
			Respiration, Rapid		.	X	.	.	
			Respiration, Shallow		.	X	.	.	
		3295		No Abnormalities Detected		.	.	X	X
				Behavior, Activity		.	D	.	.
				Gait, Incoordinated		X	X	.	.
				Posture, Crouched		X	X	.	.

Severity Codes: X = Present; . = Not Present; A = Absent; D = Decreased; F = Limbs Flaccid;
Y = Yellow

Group 6 - 24 hr 2000 mg/kg Group 7 - 48 hr 2000 mg/kg

APPENDIX C (Continued)
Phase 2 (Males) – Individual Clinical Observations

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date			
					1 30 min	1 4 Hr	2	3
7	♂	3296	No Abnormalities Detected		.	.	.	X
			Behavior, Activity		D	A	A	.
			Eye, Lid(s) partially closed	Bilateral	.	X	X	.
			Gait, Incoordinated		X	.	.	.
			Misc. Cold to Touch		.	.	X	.
			Posture, Crouched		X	.	.	.
			Respiration, Shallow		.	X	X	.
			Respiration, Slow		.	X	X	.

Severity Codes: X = Present; . = Not Present; A = Absent; O = Decreased
Group 7 - 48 hr 2000 mg/kg

APPENDIX C (Continued)
Phase 2 (Females) – Individual Clinical Observation

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date	
					1 30 min	1 4 Hr
1	f	3297	Behavior, Activity		D	
			Gait, Incoordinated		X	
			Muscle, Twitches	General	X	
		3298	Posture, Crouched		X	
			Respiration, Labored		X	
			Behavior, Activity		D	
		3299	Gait, Incoordinated		X	
			Muscle, Twitches	General	X	
			Posture, Crouched		X	
2	f	3300	Behavior, Activity		D	
			Gait, Incoordinated		X	
			Muscle, Twitches		X	
		3301	Posture, Crouched		X	
			Behavior, Activity		A	
			Eye, Lid(s) partially closed	Bilateral	X	
		3302	Muscle, Convulsion		T	
			Respiration, Labored		X	
			Gait, Incoordinated		X	X
3	f	3303	Posture, Crouched		.	X
			Behavior, Activity		D	A
			Eye, Lid(s) fully closed	Bilateral	.	X
		3304	Gait, Incoordinated		X	.
			Posture, Crouched		X	.
			Respiration, Irregular Rate		X	.
		3305	Respiration, Slow		.	X
			Behavior, Activity		D	A
			Eye, Lid(s) fully closed	Bilateral	.	X
3305	Gait, Incoordinated		X	.		
	Muscle, Twitches	General	.	X		

Severity Codes: X = Present; . = Not Present; A = Absent; D = Decreased; T = Tonic/Clonic
 Group 1 - 1 hr 2000 mg/kg Group 2 - 2 hr 2000 mg/kg Group 3 - 4 hr 2000 mg/kg

APPENDIX C (Continued)
Phase 2 (Females) – Individual Clinical Observation

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date		
					1 30 min	1 4 Hr	
3	f	3305	Posture, Crouched		X	.	
			Respiration, Shallow		.	X	
			Respiration, Slow		.	X	
4	f	3306	Behavior, Activity		.	A	
			Eye, Lid(s) partially closed	Bilateral	.	X	
			Gait, Incoordinated		X	.	
			Muscle, Twitches	General	X	X	
			Posture, Crouched		X	.	
			Respiration, Irregular Rate		.	X	
			Respiration, Slow		.	X	
			3307	Behavior, Activity		D	D
				Gait, Incoordinated		X	X
				Muscle, Tremor		.	A'
			3308	Behavior, Activity		D	.
Gait, Incoordinated		X		X			
Posture, Crouched		X		.			
5	f	3309	Behavior, Activity		D	A	
			Eye, Lid(s) fully closed	Bilateral	.	X	
			Gait, Incoordinated		X	.	
			Posture, Crouched		X	.	
			Respiration, Shallow		.	X	
			Respiration, Slow		.	X	
			3310	Behavior, Activity		D	D
				Gait, Incoordinated		X	.
				Posture, Crouched		X	X
			3311	Respiration, Labored		.	X
				Respiration, Rapid		.	X
Behavior, Activity		D		A			
Eye, Lid(s) fully closed	Bilateral	.		X			
Gait, Incoordinated		X		.			

Severity Codes: X = Present; . = Not Present A = Absent; D = Decreased;
A' = Associated with Movement

Group 3 - 4 hr 2000 mg/kg Group 4 - 6 hr 2000 mg/kg Group 5 - 12 hr 2000 mg/kg

APPENDIX C (Continued)
Phase 2 (Females) – Individual Clinical Observation

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date		
					1 30 min	1 4 Hr	2
5	f	3311	Posture, Crouched		X	.	.
			Respiration, Shallow		.	X	.
			Respiration, Slow		.	X	.
6	f	3312	Behavior, Activity		D	A	.
			Eye, Lid(s) fully closed	Bilateral	.	X	.
			Gait, Incoordinated		X	.	.
			Muscle, Convulsion		.	T	.
			Posture, Crouched		X	.	.
			Respiration, Rapid		.	X	.
			Respiration, Shallow		.	X	.
		Spontaneous Death		.	.	X	
		3313	Behavior, Activity		D	A	A
			Eye, Lid(s) fully closed	Right	.	.	X
			Eye, Lid(s) partially closed	Left	.	.	X
			Eye, Lid(s) partially closed	Bilateral	.	X	.
			Gait, Incoordinated		X	.	.
			Misc. Cold to Touch		.	.	X
			Muscle, Twitches	General	.	X	.
		3314	Posture, Crouched		X	.	.
			Respiration, Shallow		.	X	X
			Respiration, Slow		.	X	X
			Behavior, Activity		D	A	A
			Eye, Lid(s) fully closed	Bilateral	.	X	.
			Eye, Lid(s) partially closed	Bilateral	.	.	X
Gait, Incoordinated			X	.	.		
Misc. Cold to Touch		.	.	X			
	Posture, Crouched		X	.	.		
	Respiration, Shallow		.	X	X		
	Respiration, Slow		.	X	X		

Severity Codes: X = Present; . = Not Present; A = Absent; D = Decreased; T = Tonic/Clonic
Group 5 - 12 hr 2000 µg/kg Group 6 - 24 hr 2000 µg/kg

APPENDIX C (Continued)

Phase 2 (Females) – Individual Clinical Observation

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date			
					1 30 min	1 4 Hr	2	3
6	f	3314	Soiling	Abdomen, General	.	.	Y	.
			Soiling	Urogenital, General	.	.	Y	.
			Soiling	Hindlimb, Left	.	.	Y	.
7	f	3315	Behavior, Activity		D	A	A	D
			Eye, Lid(s) fully closed	Bilateral	.	X	X	X
			Gait, Incoordinated		X	.	.	.
		Misc. Cold to Touch		.	.	X	.	
		Muscle, Tremor		.	.	.	C	
		Muscle, Twitches	General	X	X	X	.	
		Posture, Crouched		X	.	.	.	
		Respiration, Rapid		.	X	X	.	
		Soiling	Urogenital, General	.	.	.	Y	
		3316	No Abnormalities Detected		.	.	.	X
			Behavior, Activity		D	A	A	.
			Eye, Lid(s) partially closed	Bilateral	.	X	X	.
			Gait, Incoordinated		X	.	.	.
			Misc. Cold to Touch		.	.	X	.
			Muscle, Convulsion		.	T	.	.
			Posture, Crouched		X	.	.	.
			Posture, Hind Limbs Splayed		X	.	.	.
Respiration, Labored			X	.	.	.		
Respiration, Shallow			.	X	X	.		
Respiration, Slow		.	X	X	.			
3317	No Abnormalities Detected		.	.	X	X		
	Behavior, Activity		D	A	.	.		
	Eye, Lid(s) fully closed	Bilateral	.	X	.	.		
	Gait, Incoordinated		X	.	.	.		
	Muscle, Twitches	General	X	.	.	.		
	Posture, Crouched		X	.	.	.		
Respiration, Rapid		.	X	.	.			

Severity Codes: X = Present; . = Not Present; A = Absent; D = Decreased; T = Tonic/Clonic;
C = Continuous; Y = Yellow

Group 6 - 24 hr 2000 mg/kg Group 7 - 48 hr 2000 mg/kg

APPENDIX D
Phase 2 (Males) – Individual Gross Pathology Observations

Animal Ref.	Mode Of Death	Death Day (Week)	Observation(s)
Group: 1 Dose: 1 hr 2000			
3276	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3277	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3278	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
Group: 2 Dose: 2 hr 2000			
3279	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3280	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3281	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
Group: 3 Dose: 4 hr 2000			
3282	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3283	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3284	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
Group: 4 Dose: 6 hr 2000			
3285	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3286	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3287	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
Group: 5 Dose: 12 hr 2000			
3288	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3289	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3290	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
Group: 6 Dose: 24 hr 2000			
3291	Scheduled Necropsy - Iso/Exsanguination	2 (1)	No Visible Lesions
3292	Scheduled Necropsy - Iso/Exsanguination	2 (1)	No Visible Lesions
3293	Scheduled Necropsy - Iso/Exsanguination	2 (1)	No Visible Lesions
Group: 7 Dose: 48 hr 2000			
3294	Scheduled Necropsy - Iso/Exsanguination	3 (1)	No Visible Lesions
3295	Scheduled Necropsy - Iso/Exsanguination	3 (1)	No Visible Lesions
3296	Scheduled Necropsy - Iso/Exsanguination	3 (1)	No Visible Lesions

Group 1 - 1 hr 2000 mg/kg	Group 2 - 2 hr 2000 mg/kg	Group 3 - 4 hr 2000 mg/kg	
Group 4 - 6 hr 2000 mg/kg	Group 5 - 12 hr 2000 mg/kg	Group 6 - 24 hr 2000 mg/kg	
Group 7 - 48 hr 2000 mg/kg			

APPENDIX D (Continued)
Phase 2 (Females) -- Individual Gross Pathology Observations

Animal Ref.	Mode Of Death	Death Day (Week)	Observation(s)
Group: 1 Dose: 1 hr 2000 Sex: Female			
3297	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3298	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3299	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
Group: 2 Dose: 2 hr 2000 Sex: Female			
3300	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3301	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3302	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
Group: 3 Dose: 4 hr 2000 Sex: Female			
3303	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3304	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3305	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
Group: 4 Dose: 6 hr 2000 Sex: Female			
3306	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3307	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3308	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
Group: 5 Dose: 12 hr 2000 Sex: Female			
3309	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3310	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
3311	Scheduled Necropsy - Iso/Exsanguination	1 (1)	No Visible Lesions
Group: 6 Dose: 24 hr 2000 Sex: Female			
3312	Found Dead	2 (1)	No Visible Lesions
3313	Scheduled Necropsy - Iso/Exsanguination	2 (1)	No Visible Lesions
3314	Scheduled Necropsy - Iso/Exsanguination	2 (1)	No Visible Lesions
Group: 7 Dose: 48 hr 2000 Sex: Female			
3315	Scheduled Necropsy - Iso/Exsanguination	3 (1)	WHOLE BODY:the animal is thin and there is no food in the stomach. Any remaining protocol required tissues, which have been examined, have no visible lesions
3316	Scheduled Necropsy - Iso/Exsanguination	3 (1)	No Visible Lesions
3317	Scheduled Necropsy - Iso/Exsanguination	3 (1)	No Visible Lesions

Group 1 - 1 hr 2000 mg/kg	Group 2 - 2 hr 2000 mg/kg	Group 3 - 4 hr 2000 mg/kg	
Group 4 - 6 hr 2000 mg/kg	Group 5 - 12 hr 2000 mg/kg	Group 6 - 24 hr 2000 mg/kg	
Group 7 - 48 hr 2000 mg/kg			

APPENDIX E
Contributing Scientist Report – Quantitation of Total Silicon

**DOW CORNING CORPORATION
HEALTH & ENVIRONMENTAL SCIENCES
CONTRIBUTING SCIENTIST REPORT**

Report Title: Quantitation of Total Silicon in Mice Plasma
Following Oral Dosing of Dimethylsilanediol

HES Study Number:

Test Article: Dimethylsilanediol

Contributing Scientist:

Sponsor: Dow Corning Corporation

HES Group Manager:

Testing Facility:

Analysis Start Date: 06-15-2006

Analysis End Date: 07-18-2006

Dow Corning INTERNAL

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APPROVAL SIGNATURES

Approved by:

 4-7-09

Associate Analytical Specialist
Contributing Scientist



Bioanalytical Supervisor
Health and Environmental Sciences

OBJECTIVE

The purpose of this analysis was to determine the concentration of total silicon in mouse plasma using inductively coupled plasma-optical emission spectroscopy (ICP-OES).

EXPERIMENTAL

Stability:

A method was developed for the dilution and analysis of mouse plasma for the quantitation of total silicon. The method was based upon the principle of calibrating an ICP-OES using dimethylsilanediol (DMSD) spiked standards of 5% plasma in deionized water, and then analyzing matrix matched mouse plasma samples against this calibration curve. The ICP-OES instrument is not a specific analytical technique in that it can measure the total amount of silicon in a sample, but it cannot distinguish between the molecular or atomic form that the silicon is in. As a result, if the mice dosed with DMSD in this study metabolized the DMSD in any way, this analysis cannot assess the identity or extent of any metabolic species, only the amount of silicon as compared to a standard of DMSD. Since the standards were prepared with DMSD, the amount of silicon in the unknown samples were quantified according to the standards, and thus measured as microgram (μg) equivalents of DMSD / gram (g) of plasma.

The plasma utilized for the dilution of the calibration standards was from mice which were not exposed to DMSD. The limit of quantitation (LOQ) was set at the lowest calibration standard prepared for the quantitation procedure. The target analytical range was from $\sim 6 \mu\text{g}$ to $\sim 180 \mu\text{g}$ equivalents of DMSD per gram of plasma ($\mu\text{g/g}$). The sampling intervals required that the method be proved to be stable over an extended period of time to allow for analysis of all sample time points under one calibration curve for quantitation. Calibration standards were prepared on both day 0 and day 4. Two samples within the range of the curve were prepared on day 0 and analyzed on both days to observe the difference and determine the stability of the material. With each set analyzed, a linear regression analysis was performed relating the concentration of the calibration standards to the counts per second (cps) intensity reported by the ICP-OES. Quantitation of total silicon (μg equivalents of DMSD per gram of plasma ($\mu\text{g equiv./g}$)) was accomplished by quantitating the amount of silicon in the $\sim 5\%$ plasma solution analyzed via ICP-OES and then applying the exact dilution factor to that sample to obtain a $\mu\text{g equiv. DMSD per gram of plasma}$ quantity. For clarity, all data presented in this report are in terms of $\mu\text{g equiv. DMSD/g plasma}$. These calculations are presented in the Data Analysis section of this report.

Study Conduct:

Blood samples were collected at 1, 2, 4, 6, 12, 24, and 48 hours after dosing of the mice. The blood was centrifuged and the plasma portion was diluted with in-house produced Milli-Q water to a plasma concentration of approximately 5%. This solution was then analyzed via ICP-OES and quantitated against a calibration curve prepared from non-treated mice plasma spiked with a known amount of DMSD. Past work with other silicon

containing materials demonstrated that a representative sample of whole blood can be obtained by separating the plasma portion for analysis. The diluted plasma samples were analyzed via inductively coupled plasma-optical emission spectroscopy (ICP-OES). A total of 6 treated mice were processed for total silicon analysis at each time point.

The standard curves covered the range of approximately 60 μg to 5000 μg equiv. of DMSD per gram of plasma. Due to lack of feasibility data, the calibration range was not assured of encompassing the results of the samples until the day of the analysis. The initial calibration curve was set to be from approximately 6 μg to 180 μg equiv. DMSD per gram of plasma, this was to match the target concentrations of the calibration curve from the stability determination. After the analysis of 1 hour plasma samples it was apparent that the initial calibration range would not be sufficient to properly bracket the concentration of the plasma samples being analyzed. Enough control plasma remained to prepare 2 additional standards which allowed for the quantitation of all the plasma samples. These calibration standards were prepared to a target concentration of 900 and 5000 μg equiv. DMSD/g plasma. These standards were analyzed as part of another complete analysis of the entire calibration curve that occurred after all samples were analyzed. All sample data were quantitated against this curve for processing. Although the stability determination portion of this quantitation determined a LOQ of approximately 6-7 μg equiv. DMSD/g plasma, adding the standards with the target concentrations of 900 and 5000 μg equiv. DMSD/g plasma caused the refits of the target 6 and 20 $\mu\text{g/g}$ to vary outside of the acceptable range due to the calibration curve covering such a wide range of sample concentrations. The LOQ for this study was obtained by using the target 60 μg equiv. DMSD/g plasma which had a prepared concentration of 58.75 μg equiv. DMSD/g plasma.

Animal ID's 3292 and 3313 both initially did not have enough plasma drawn to dilute for sample analysis. After inspection of the initial data, a discussion took place between the analytical chemist and the study director and the option to further dilute these samples in water was determined to be acceptable and the samples and calibration standards were diluted with water to allow for a matrix matched analysis. The data and refits for the standards analyzed for this calibration curve are summarized in Table VII. Due to only the three highest concentration calibration standards refits meeting the criteria of +/- of actual concentration, they were the only points used for the quantitating the data. The LOQ of the samples determined in this fashion was set at the concentration of the lowest concentration calibration standard which was 85.0 μg equiv. DMSD/g plasma. The data obtained for these 2 samples is also outside of the previously determined stability of the samples. Stability of silicon as μg equiv. DMSD in plasma of up to 4 days was demonstrated prior to animal dosing. The samples from animals 3292 and 3313 were 5 days old at the point of analysis.

No data was obtained for animals 3312, 3299, and 3311. Animal 3312 died prior to necropsy, and an insufficient amount of sample was obtained for the analysis for 3299 and 3311.

Table I: ICP-OES System Components used for Analyses

A. System Components

ICP Spectrophotometer

Perkin-Elmer® Optima 3100XL ICP Spectrometer

Model: Optima 3100XL

Serial Number: 069N7101002

Part Number: N069-0032

Autosampler

Perkin-Elmer® AS-91 Autosampler with Controller Unit

Model: AS-91

Serial Number: 3675

Part Number: 507910

Peristaltic Pump

Perkin-Elmer® 3-Channel Peristaltic Pump

Serial Number: 7100116

Part Number: N069-0166

Recirculating Chiller

Neslab CFT-33 Recirculating Chiller

Model: CFT-33

Serial Number: 197282154

Software

Windows XP Operating System

Perkin Elmer WinLab 32 for ICP, Version 3.1.0.0107

DATA ANALYSIS

Verification of the test article concentration was performed by comparing the target concentration of the test substance to the mean observed test substance concentration by refitting the peak areas to the standard curve.

Statistical methods including mean, standard deviation, relative standard deviation and linear regression analyses were performed using Microsoft Excel ® 2003.

Calculation of µg equiv./g DMSD concentration in solution-This calculation was only used for determination of the concentration of the calibration standards

$$\frac{[\text{spiked DSMD solution (g)}]}{[\text{plasma (g)} + \text{water (g)} + \text{spiked DMSD solution (g)}]} \times \text{spiked DMSD concentration (µg/g)}$$

Calculation of $\mu\text{g equiv./g}$ DMSD concentration in plasma-This calculation was applied to all samples. For unknown samples the concentration of the solution was calculated first by linear regression, the following equation was then applied to account for the dilution factor of the plasma in the solution

$$\text{DMSD solution concentration } (\mu\text{g equiv./g}) \times [(\text{plasma (g)} + \text{water (g)}) / \text{plasma (g)}]$$

DEVIATIONS

There were no circumstances that negatively impacted this study.

RESULTS AND DISCUSSION

Stability:

The results of the stability are listed in Table II and were deemed to be acceptable both in terms of deviation from actual value as well as "sample drift" from day 4 to day 0.

Table II: Stability of Silieon Dimethylsilanediol Equivalents

Calculated Silicon concentration ($\mu\text{g equiv./g}$) in plasma	Observed Silicon concentration ($\mu\text{g equiv./g}$) in plasma Day 0	Deviation from Calculated Value-Day 0	Observed Silicon concentration ($\mu\text{g equiv./g}$) in plasma Day 4	Deviation from Calculated Value-Day 4	Deviation from Day 4 to Day 0
16.4	17.1	4.0%	14.6	11.5%	14.9%
67.6	64.0	5.4%	67.9	0.4%	6.2%

The data from the calibration curve generation for the stability determination is presented in Table III and Table IV. The R-squared values were 1.00 and 0.993 for Day 0 and Day 4, respectively. As stated in the Experimental portion of this report, for clarity, all data are presented in $\mu\text{g equiv. DMSD per g plasma}$, however, the calibration curve is reflective of the concentration of $\mu\text{g equiv. DMSD per g}$ of diluted plasma solution. The exact dilution factor was then applied to the data to obtain a $\mu\text{g equiv. DMSD per gram}$ of plasma quantity.

Table III: Calibration Curve Data for Silicon Stability Determination- Day 0

Study 10219-101- Analysis of Silicon- Stability Day 0				
Target DMSD Level (μg equiv./g)	Average Counts per Second	Observed Concentration (μg equiv./g) from Calibration Curve	Calculated Concentration (μg equiv./g)	Percent of Calculated Concentration
0	926.8	1.3	0.0	NA
6	3231.2	7.2	6.5	109.5%
20	9196.2	22.9	22.4	101.9%
60	25197.2	64.8	68.1	95.0%
180	79827.8	226.0	224.9	100.5%

Linear Regression: $y = 7876.6x + 445.5$

Table IV: Calibration Curve Data for Silicon Stability Determination- Day 4

Study 10219-101- Analysis of Silicon- Stability Day 4				
Target DMSD Level (μg equiv./g)	Average Counts per Second	Observed Concentration (μg equiv./g) from Calibration Curve	Calculated Concentration (μg equiv./g)	Percent of Calculated Concentration
0	932.6	-3.17	0.00	NA
6	4327.1	6.08	6.73	90.3%
20	9294.4	18.97	21.45	88.5%
60	29916.9	73.34	64.49	113.7%
180	75237.1	205.22	208.00	98.7%

Linear Regression: $y = 7413.8x + 2095.4$

Study Conduct:

The individual animal results of the total silicon in mouse plasma are presented in Table V below with group means presented in Table VI. A graphical depiction of the group means for male and female mice plasma total silicon concentrations as a function of the collection time is displayed in Figure I. The calibration curve data for the calculation of study samples are located in Tables VII and VIII.

Table V: Total Silicon (DMSD $\mu\text{g equiv./g}$) Observed in Mouse Plasma

Element: Si 251.611

Animal ID	Group #	Time Point (HR)	Silicon concentration ($\mu\text{g equiv/g}$) in plasma
Males			
3276	1	1	1876.3
3277	1	1	2389.5
3278	1	1	2007.4
3279	2	2	1891.0
3280	2	2	1704.7
3281	2	2	1349.9
3282	3	4	2092.3
3283	3	4	862.1
3284	3	4	1612.6
3285	4	6	2181.0
3286	4	6	989.1
3287	4	6	730.2
3288	5	12	1501.0
3289	5	12	109.8
3290	5	12	1795.1
3291	6	24	84.1
3292	6	24	-1.7 b
3293	6	24	57.3
3294	7	48	6.7
3295	7	48	6.1
3296	7	48	114.7
Females			
3297	1	1	2246.1
3298	1	1	1691.5
3299	1	1	-
3300	2	2	1381.2
3301	2	2	1560.3
3302	2	2	2247.1
3303	3	4	1102.1
3304	3	4	2162.5
3305	3	4	1938.8
3306	4	6	1762.7
3307	4	6	1088.4
3308	4	6	387.0
3309	5	12	1934.9
3310	5	12	1337.5
3311	5	12	-
3312	6	24	a
3313	6	24	2311.7 b
3314	6	24	2036.8
3315	7	48	2378.6
3316	7	48	21.4
3317	7	48	0.6

* = Insufficient sample volume was obtained

a = Animal died prior to scheduled necropsy

b=sample analyzed on later date at higher dilution factor

Table VI: Group Mean Results of Total Silicon Analysis (DMSD $\mu\text{g equiv./g}$) Observed in Mouse Plasma

Group #	Time Point (hr)	Males		Females	
		Average Si Concentration ($\mu\text{g equiv./g}$)	Standard error of the mean	Average Si Concentration ($\mu\text{g equiv./g}$)	Standard error of the mean
1	1	2091.1	± 153.9	1968.8	± 277.3
2	2	1648.5	± 158.7	1729.6	± 263.9
3	4	1522.3	± 358.0	1734.5	± 322.7
4	6	1303.4	± 450.0	1079.4	± 397.1
5	12	1135.3	± 519.7	1636.2	± 298.7
6	24	46.6	± 25.3	2174.2	± 137.5
7	48	42.5	± 36.1	800.2	± 789.2

Table VII: Calibration Curve Data for Study Conduct

Study 10219-101- Analysis of Silicon- Study Conduct				
Target DMSD Level ($\mu\text{g equiv./g}$)	Average Counts per Second	Observed Concentration ($\mu\text{g equiv./g}$) from Calibration Curve	Calculated Concentration ($\mu\text{g equiv./g}$)	Percent of Calculated Concentration
0	3790.4	-5.8	0.0	NA
60	23612.6	52.0	58.7	88.5%
180	65267.1	168.2	170.9	98.4%
900	339706	1015.0	995.6	101.9%
5000	1816831	5191.2	5194.3	99.9%

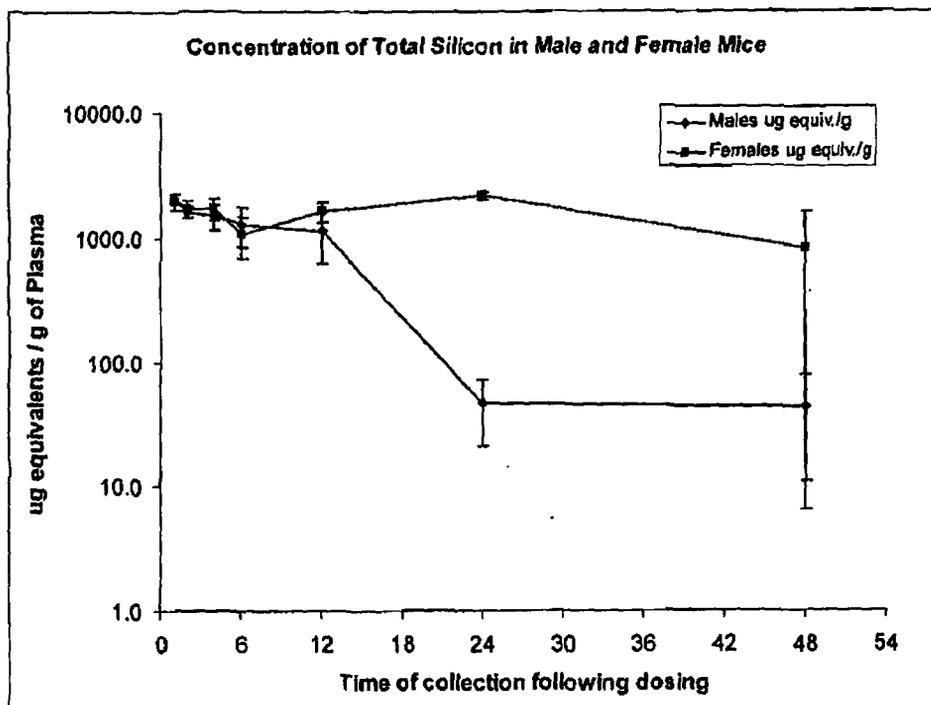
Linear Regression: $y = 6902.6 x + 5796.9$

Table VIII: Calibration Curve Data for Study Conduct-2nd Day

Study - Analysis of Silicon- Study Conduct- 2nd Day				
Target DMSD Level (µg equiv./g)	Average Counts per Second	Observed Concentration (µg equiv./g) from Calibration Curve	Calculated Concentration (µg equiv./g)	Percent of Calculated Concentration
0	1490.2	-9.8	0.0	NA
90	34772.7	78.5	85.9	91.4%
450	188571.4	521.5	499.6	104.4%
2500	970102	2586.4	2589.9	99.9%

Linear Regression: $y = 7382.2 x + 5095.1$

Figure I: Concentration of Total Silicon in Male and Female Mice



CONCLUSIONS

An ICP-OES method was utilized to determine the concentration of total silicon in mouse plasma. The samples were deemed to be stable over the course of 4 days.

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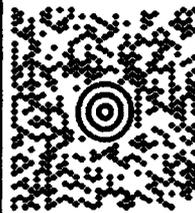
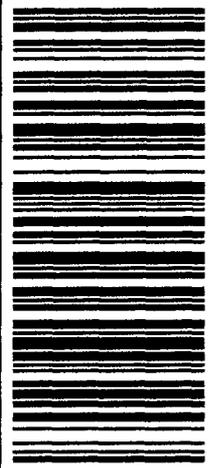
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