FYI-0806-01507

DOW CORNING

CONTAIN NO CBI

RECEIVED
OPPT CBIC
06 AUG 17 AM 6:06

August 14, 2006

Document Control Office (7407)
TSCA Data Processing Center - CBIC
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Room 6428
1200 Pennsylvania Avenue, NW
Washington, DC 20460

FYI-06-01507

Attn: TSCA Docket Clerk

Re: For Your Information Submission:

The enclosed information is submitted on behalf of Dow Corning Corporation, Midland, Michigan, 48686-0994, on a For-Your-Information (FYI) basis as a follow-up to submissions made concerning hexamethyldisiloxane (HMDS), which chemical substance was the subject of a health and safety data rule issued under Section 8(d) of the Toxic Substances Control Act (TSCA) and with an effective date of June 14, 1993 (sunset date June 30, 1998), as codified at 40 CFR 716 (Health and Safety Data Reporting). The information presented in this submission was generated as part of our Siloxane Research Program. This program was the subject of a memorandum of understanding, dated April 9, 1996, between Dow Corning and EPA.

RECEIVED OPPT CBIC 2006 AUG 22 PM 2:02

Listed Chemical Substance:

107-46-0 Hexamethyldisiloxane (HMDS)

Final Study Report:

An Inhalation Two-Generation Reproductive Toxicity Study of Hexamethyldisiloxane (HMDS) in Rats, Including Developmental Neurotoxicity Assessment of the F2 Generation

Dow Corning Corporation
2006-I0000-56321
June 20, 2006

84060000005

Dow Corning Corporation
Midland, Michigan 48686-0994
Phone: (989) 496-4000

297989

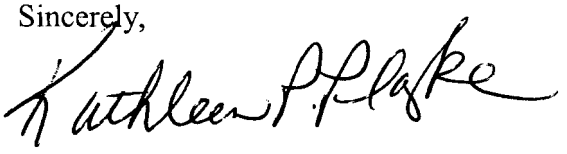
Manufacturer:

Dow Corning Corporation
PO Box 994
2200 West Salzburg Road
Midland, Michigan 48686-0994

For purposes of this TSCA For-Your-Information (FYI) submission, the general INTERNAL designation on the attached health and safety report is waived by Dow Corning.

If you require further information regarding this submission, please contact Michael Thelen, Manager of U.S. EPA Regulatory Affairs, at 989-496-4168 or at the address provided herein.

Sincerely,



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

DOW CORNING CORPORATION
HEALTH AND ENVIRONMENTAL SCIENCES
TECHNICAL REPORT

WIL Research Laboratories, LLC
1407 George Road
Ashland, Ohio 44805

Report No.:	2006-I0000-56321
Title:	An Inhalation Two-Generation Reproductive Toxicity Study of Hexamethyldisiloxane (HMDS) in Rats, Including Developmental Neurotoxicity Assessment of the F_2 Generation
Study No.:	9837-101
External Testing Facility No.:	WIL-51087
Test Article:	Hexamethyldisiloxane (HMDS)
Study Director:	Donald G. Stump, Ph.D., DABT Associate Director, Developmental and Reproductive Toxicology
Sponsor:	Dow Corning Corporation 2200 W. Salzburg Road Auburn, Michigan 48611
Sponsor Representative:	Waheed H. Siddiqui, Ph.D. Associate Toxicology Scientist
Testing Facility:	WIL Research Laboratories, LLC 1407 George Road Ashland, Ohio 44805-9281
Study Completion Date:	June 20, 2006
Security Statement:	Dow Corning Internal - This report may be reproduced and shared with any Dow Corning employee. The director of the issuing department must approve distribution outside the corporation. When this INTERNAL report is no longer needed, it must be destroyed in a manner that safeguards against unauthorized disclosure.

Volume 1 of 16

2006© Dow Corning Corporation. All rights reserved. No part of this work may be reproduced or transmitted in any form by any means, electronic or mechanical, including but not limited to photocopying or recording, or by any information storage or retrieval system without permission in writing from Dow Corning Corporation.

1. ABSTRACT

This study was conducted to evaluate the potential adverse effects of hexamethyldisiloxane (HMDS) on the reproductive capabilities, including gonadal function, estrous cyclicity, mating behavior, conception, gestation, parturition, lactation and weaning of the F_0 and F_1 generations and F_1 and F_2 neonatal survival, growth and development. One litter was produced in each generation. This study was also conducted to determine the potential of HMDS to cause functional and/or morphological changes to the nervous system of the developing rat (F_2 generation) following the exposure of the F_0 and F_1 generations.

Groups of male and female Crl:CD®(SD)[1] rats (30/sex/group) were exposed via whole-body vapor inhalation to the test article, hexamethyldisiloxane, for 6 hours daily for at least 70 consecutive days prior to mating. Target test article concentrations were 100, 400, 1600 and 5000 parts per million (ppm) for the F_0 and F_1 generations. Mean measured exposure concentrations were 0, 103, 401, 1609 and 5020 ppm for the F_0 generation and 0, 103, 403, 1612 and 4981 ppm for the F_1 generation. A control group of identical design was exposed to clean, filtered air on a comparable regimen. F_0 animals were approximately 7 weeks of age at the beginning of exposure. The offspring selected to become the F_1 parental generation were exposed following weaning (beginning on postnatal day [PND] 22). Exposure of the F_0 and F_1 males continued throughout mating, and through the day prior to euthanasia. The F_0 and F_1 females continued to be exposed throughout mating and gestation through gestation day 20. After parturition, exposure of the F_0 and F_1 females was re-initiated on lactation day 5 and continued through the day prior to euthanasia.

All animals were observed twice daily for appearance and behavior. Clinical observations, body weights and food consumption were recorded at appropriate intervals prior to mating and during gestation and lactation. Vaginal lavages were performed daily

[1] = Prior to January 1, 2005, this strain of rat was designated the Crl:CD®(SD)IGS BR rat.

for determination of estrous cycles beginning 21 days prior to pairing. Functional observational battery (FOB) assessments were performed on F_1 females on gestation days 6 and 12, and on lactation days 10 and 21. All F_0 and F_1 females were allowed to deliver and rear their pups until weaning on lactation day 21. For both generations (F_1 and F_2), 10 pups per litter (five per sex, when possible) were selected on PND 4 to reduce the variability among the litters. Two F_1 weanlings/sex/litter were exposed to the test article from PND 22-27. From these 2 F_1 weanlings/sex/litter, 30/sex/group were selected on PND 28 to constitute the F_1 generation. Developmental landmarks (balanopreputial separation and vaginal patency) were evaluated for the selected F_1 and F_2 rats. Forty pups/sex/group from the F_2 generation were selected for evaluation of surface-righting (PND 5 to day of positive response) and air-righting (PND 13, 17, 21 and 61) reflexes; of these, 20 F_2 pups/sex/group were selected for FOB (PND 4, 11, 21, 45 and 60), auditory startle response (PND 20 and 60), locomotor activity (PND 13, 17, 21 and 61) and/or learning and memory assessment (PND 22 or 62), and 10 F_2 pups/sex/group were selected for neurobehavioral testing, neuropathology, brain weights and/or brain dimension measurements (PND 21 or 72). Nonselected F_1 pups were necropsied on PND 21 or 28, and nonselected F_2 pups were necropsied on PND 21. Selected organs were weighed from F_1 and F_2 pups (one/sex/litter) that were necropsied on PND 21. Selected F_2 rats not allocated for neuropathology and brain dimension measurements were necropsied following completion of reflex ontogeny evaluations (PND 61) or at study termination (PND 72). Each surviving F_0 and F_1 parental animal received a complete detailed gross necropsy following the completion of weaning of the F_1 and F_2 pups, respectively; selected organs were weighed. Spermatogenic endpoints (sperm motility [including progressive motility], morphology and numbers) were recorded for all F_0 and F_1 males, and ovarian primordial follicle counts were recorded for all F_1 females in the control and high-exposure groups. Designated tissues from all F_0 and F_1 parental animals, and from F_2 pups selected for neuropathological evaluation or exhibiting developmental abnormalities suggestive of an exposure-related effect, were examined microscopically.

No test article-related mortalities were observed in this study. When evaluated across two generations, reproductive performance, offspring physical condition, offspring postnatal survival (prior to weaning) and attainment of landmarks of sexual development (balanopreputial separation and vaginal patency) were unaffected by HMDS exposure. No test article-related clinical findings or effects on gestation or lactation body weight and food consumption were noted in either parental generation. No HMDS-related clinical findings, effects on body weights, or macroscopic findings were noted for F_1 or F_2 offspring selected for evaluation of organ weights on PND 21 or euthanized prior to the end of each generation (*i.e.*, not selected for the F_1 generation or F_2 neuropathological examination, *etc.*). F_1 adult females and their offspring exhibited no exposure-related effects during the FOB assessments. No test article-related effects on anogenital distance, air-righting reflex or learning and memory were noted for F_2 offspring. Brain size and weight for F_2 animals on PND 21 and 72 were unaffected by parental test article exposure; no macroscopic, histopathological or morphometric evidence of neuropathology was observed.

Lower weekly body weight gains were noted for F_0 males and females in the 1600 and 5000 ppm groups and F_1 males in the 5000 ppm group. Mean body weights in the 1600 ppm group for both the F_0 and F_1 generations were generally similar to control group values, while those in the 5000 ppm group were reduced throughout the majority of both the F_0 and F_1 generations; food consumption was lower for the 5000 ppm group males during the premating period (F_0) and throughout the entire generation (F_1). Food consumption for F_1 females in the 5000 ppm group was reduced during the first week following weaning (week 17-18) only. Offspring body weight gains were decreased for F_1 pups in the 5000 ppm group from PND 4-21 and F_2 pups in the 1600 and 5000 ppm groups from PND 4-14. In the 5000 ppm group, these reduced body weight gains resulted in substantially lower mean body weights on PND 14 and 21 in both generations (approximately 6% to 7% lower by PND 21); lower body weights continued to be observed for the F_2 males and females through PND 56 and PND 35, respectively. In the F_2 pups in the 1600 ppm group, the lower body weight gain during PND 4-14 resulted in

significantly lower mean body weights on PND 14 (approximately 7% and 5% for male and female pups, respectively); lower body weights were also observed for the F_2 males and females in this group through PND 49 and 35, respectively.

The only test article-related effect on attainment of developmental landmarks noted for F_2 pups was a slight delay in attainment of the surface-righting response for females in the 5000 ppm group. On PND 21, decreased thymus weights were noted for F_2 male pups in the 1600 and 5000 ppm groups and F_2 female pups in the 5000 ppm group only.

Effects on developmental neurobehavioral endpoints consisted of increased motor activity for F_2 females in the 5000 ppm group on PND 13 and 21. The higher total activity counts on PND 21 were the result of an attenuated habituation. By PND 61, a normal pattern of habituation was observed for these females. No effects on motor activity were observed for F_2 males at any exposure level. Decreases in the average and peak responses to the acoustic startle response stimulus (V_{AVE} and V_{MAX}, respectively) were observed on PND 20 for F_2 males and females at 5000 ppm. However, no effects on the time from latency to peak response to the acoustic startle response stimulus (T_{MAX}) were observed.

Test article-related higher kidney weights were noted for F_0 and F_1 males in the 1600 and 5000 ppm groups. Corresponding histopathological effects of HMDS in this study were similar to those previously reported (Cassidy *et al.*, 2001) in rats following long-term inhalation exposure at 593 and 5012 ppm. These findings included hyaline droplets (F_0 and F_1 males at 5000 ppm) and increased incidence and severity of basophilic tubules in the kidneys (F_0 males, F_1 males and F_1 females at 5000 ppm). Male rat-specific hyaline droplet (consistent with α-2 urinary globulin) nephropathy was associated with the increase in basophilic tubules. Other test article-related microscopic findings, including golden-brown pigment in the periportal areas of the liver for F_0 males in the 5000 ppm group and F_1 males and females in the 1600 and 5000 ppm groups. This pigment was accompanied by infiltration of primarily mononuclear inflammatory cells and/or bile duct hyperplasia in the liver in the F_0 and F_1 5000 ppm groups, and

corresponded to higher mean relative liver weights for the F_1 males in the 1600 and 5000 ppm groups. The golden-brown pigment demonstrated bright red birefringence with a central dark Maltese cross under polarized light, characteristic of porphyrin (Churukian, 2002). In the 5000 ppm group F_1 males and females, golden-brown pigment was also noted in the medullary macrophages of the mesenteric lymph nodes and alveolar macrophage aggregates were noted for F_0 and F_1 males and females in the 5000 ppm group.

Based on the results of this study, an exposure level of 5000 ppm was considered to be the NOAEL (no-observed-adverse-effect level) for parental reproductive toxicity of hexamethyldisiloxane (HMDS) when administered via whole-body inhalation exposure to rats. The NOAEL for neonatal toxicity was considered to be 1600 ppm due to decreased offspring weights at 5000 ppm, and the NOAEL for developmental neurobehavioral endpoints was considered to be 1600 ppm due to the lack of habituation exhibited in the locomotor activity assessments and delayed attainment of the surface righting response in the 5000 ppm group F_2 females, and decreases in average and peak acoustic startle response on PND 20 in the 5000 ppm group F_2 males and females. The NOAEL for neuropathologic endpoints was considered to be 5000 ppm.

2. GLP COMPLIANCE STATEMENT

This study, designated WIL-51087, was conducted in compliance with the Good Laboratory Practice Regulations for Nonclinical Laboratory Studies of the United States Food and Drug Administration (21 CFR Part 58), October 5, 1987, and Environmental Protection Agency (40 CFR Parts 160 and 792), October 16 and September 18, 1989, respectively; the Principles of Good Laboratory Practice [C (97) 186/Final] of the Organisation for Economic Cooperation and Development, November 26, 1997; the standard operating procedures of WIL Research Laboratories, LLC and the protocol as approved by the sponsor, with the exception of the following GLP deviation. The initial test article purity analysis was conducted on December 3, 2003, which was six days prior to the GLP-defined study initiation date (date of protocol signature by the study director). This GLP deviation did not negatively impact the study or the data interpretation.

The protocol was designed to be in general accordance with the United States Environmental Protection Agency OPPTS Health Effects Test Guidelines [870.3800, Reproduction and Fertility Effects, August, 1998, and 870.6300, Developmental Neurotoxicity Study, August, 1998], and the Organisation for Economic Development Guideline 416, January 22, 2001, and Revised Draft Guideline 426, October, 1999.

Donald G. Stump, Ph.D., DABT
Associate Director, Developmental
and Reproductive Toxicology
Study Director

20 June 2006
Date

Waheed H. Siddiqui, Ph.D.
Sponsor Representative

6/15/06
Date

A copy of this study is available from EPA's docket in CD format

FYI-0806-01507

DOW CORNING

CONTAIN NO CBI

August 14, 2006

Document Control Office (7407)
TSCA Data Processing Center - CBIC
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Room 6428
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Attn: TSCA Docket Clerk

Re: For Your Information Submission:

The enclosed information is submitted on behalf of Dow Corning Corporation, Midland, Michigan, 48686-0994, on a For-Your-Information (FYI) basis as a follow-up to submissions made concerning hexamethyldisiloxane (HMDS), which chemical substance was the subject of a health and safety data rule issued under Section 8(d) of the Toxic Substances Control Act (TSCA) and with an effective date of June 14, 1993 (sunset date June 30, 1998), as codified at 40 CFR 716 (Health and Safety Data Reporting). The information presented in this submission was generated as part of our Siloxane Research Program. This program was the subject of a memorandum of understanding, dated April 9, 1996, between Dow Corning and EPA.

2006 AUG 22 PM 2:02
RECEIVED
OPPT NCIC

Listed Chemical Substance:

107-46-0 Hexamethyldisiloxane (HMDS)

Final Study Report:

An Inhalation Two-Generation Reproductive Toxicity Study of Hexamethyldisiloxane (HMDS) in Rats, Including Developmental Neurotoxicity Assessment of the F2 Generation

Dow Corning Corporation
2006-I0000-56321
June 20, 2006

Dow Corning Corporation
Midland, Michigan 48686-0994
Phone: (989) 496-4000
www.dowcorning.com

297989

Manufacturer:

Dow Corning Corporation
PO Box 994
2200 West Salzburg Road
Midland, Michigan 48686-0994

For purposes of this TSCA For-Your-Information (FYI) submission, the general INTERNAL designation on the attached health and safety report is waived by Dow Corning.

If you require further information regarding this submission, please contact Michael Thelen, Manager of U.S. EPA Regulatory Affairs, at 989-496-4168 or at the address provided herein.

Sincerely,

Kathleen P. Plotzke

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

DISTRIBUTION SERVICES
(989) 496 4945
DOW CORNING CORPORATION
2200 WEST SALZBURG ROAD
AUBURN MI 48611

41 LBS

1 OF 2

SHIP TO:
DOCUMENT CONTROL OFFICER (7407
U.S. ENVIRONMENTAL PROTECTION AGENC
ROOM G-0099/:TSCA SEC,8(E) CO-ORD
DOCUMENT CONTROL OFFICE
1200 PENNSYLVANIA AVE. NW
WASHINGTON DC 20042

MD 201 9-85

UPS NEXT DAY AIR

1

TRACKING #: 1Z 464 696 01 4204 8734

BILLING: P/P

REF 1: 53878

DOW 8 0 1E UPS Thermal 2 57 08 07/2006

DISTRIBUTION SERVICES
(989) 496-4945
DOW CORNING CORPORATION
2200 WEST SALZBURG ROAD
AUBURN MI 48611

23 LBS

2 OF 2

SHIP TO:
DOCUMENT CONTROL OFFICER (7407
U.S. ENVIRONMENTAL PROTECTION AGENC
ROOM G-0099/:TSCA SEC,8(E) CO-ORD
DOCUMENT CONTROL OFFICE
1200 PENNSYLVANIA AVE. NW
WASHINGTON DC 20042

MD 201 9-85

UPS NEXT DAY AIR

1

TRACKING #: 1Z 464 696 01 4150 0344

BILLING: P/P

REF 1: 53878

UOW 8 0 16 UPS Thermal 2 57 DA 07/.006

DOW CORNING CORPORATION
HEALTH AND ENVIRONMENTAL SCIENCES
TECHNICAL REPORT

WIL Research Laboratories, LLC
1407 George Road
Ashland, Ohio 44805

Report No.:	2006-I0000-56321
Title:	An Inhalation Two-Generation Reproductive Toxicity Study of Hexamethyldisiloxane (HMDS) in Rats, Including Developmental Neurotoxicity Assessment of the F_2 Generation
Study No.:	9837-101
External Testing Facility No.:	WIL-51087
Test Article:	Hexamethyldisiloxane (HMDS)
Study Director:	Donald G. Stump, Ph.D., DABT Associate Director, Developmental and Reproductive Toxicology
Sponsor:	Dow Corning Corporation 2200 W. Salzburg Road Auburn, Michigan 48611
Sponsor Representative:	Waheed H. Siddiqui, Ph.D. Associate Toxicology Scientist
Testing Facility:	WIL Research Laboratories, LLC 1407 George Road Ashland, Ohio 44805-9281
Study Completion Date:	June 20, 2006
Security Statement:	Dow Corning Internal - This report may be reproduced and shared with any Dow Corning employee. The director of the issuing department must approve distribution outside the corporation. When this INTERNAL report is no longer needed, it must be destroyed in a manner that safeguards against unauthorized disclosure.

06 AUG 17 AM 6:06

Volume 1 of 16

2006© Dow Corning Corporation. All rights reserved. No part of this work may be reproduced or transmitted in any form by any means, electronic or mechanical, including but not limited to photocopying or recording, or by any information storage or retrieval system without permission in writing from Dow Corning Corporation.

1. ABSTRACT

This study was conducted to evaluate the potential adverse effects of hexamethyldisiloxane (HMDS) on the reproductive capabilities, including gonadal function, estrous cyclicity, mating behavior, conception, gestation, parturition, lactation and weaning of the F_0 and F_1 generations and F_1 and F_2 neonatal survival, growth and development. One litter was produced in each generation. This study was also conducted to determine the potential of HMDS to cause functional and/or morphological changes to the nervous system of the developing rat (F_2 generation) following the exposure of the F_0 and F_1 generations.

Groups of male and female Crl:CD®(SD)[1] rats (30/sex/group) were exposed via whole-body vapor inhalation to the test article, hexamethyldisiloxane, for 6 hours daily for at least 70 consecutive days prior to mating. Target test article concentrations were 100, 400, 1600 and 5000 parts per million (ppm) for the F_0 and F_1 generations. Mean measured exposure concentrations were 0, 103, 401, 1609 and 5020 ppm for the F_0 generation and 0, 103, 403, 1612 and 4981 ppm for the F_1 generation. A control group of identical design was exposed to clean, filtered air on a comparable regimen. F_0 animals were approximately 7 weeks of age at the beginning of exposure. The offspring selected to become the F_1 parental generation were exposed following weaning (beginning on postnatal day [PND] 22). Exposure of the F_0 and F_1 males continued throughout mating, and through the day prior to euthanasia. The F_0 and F_1 females continued to be exposed throughout mating and gestation through gestation day 20. After parturition, exposure of the F_0 and F_1 females was re-initiated on lactation day 5 and continued through the day prior to euthanasia.

All animals were observed twice daily for appearance and behavior. Clinical observations, body weights and food consumption were recorded at appropriate intervals prior to mating and during gestation and lactation. Vaginal lavages were performed daily

[1] = Prior to January 1, 2005, this strain of rat was designated the Crl:CD®(SD)IGS BR rat.

for determination of estrous cycles beginning 21 days prior to pairing. Functional observational battery (FOB) assessments were performed on F_1 females on gestation days 6 and 12, and on lactation days 10 and 21. All F_0 and F_1 females were allowed to deliver and rear their pups until weaning on lactation day 21. For both generations (F_1 and F_2), 10 pups per litter (five per sex, when possible) were selected on PND 4 to reduce the variability among the litters. Two F_1 weanlings/sex/litter were exposed to the test article from PND 22-27. From these 2 F_1 weanlings/sex/litter, 30/sex/group were selected on PND 28 to constitute the F_1 generation. Developmental landmarks (balanopreputial separation and vaginal patency) were evaluated for the selected F_1 and F_2 rats. Forty pups/sex/group from the F_2 generation were selected for evaluation of surface-righting (PND 5 to day of positive response) and air-righting (PND 13, 17, 21 and 61) reflexes; of these, 20 F_2 pups/sex/group were selected for FOB (PND 4, 11, 21, 45 and 60), auditory startle response (PND 20 and 60), locomotor activity (PND 13, 17, 21 and 61) and/or learning and memory assessment (PND 22 or 62), and 10 F_2 pups/sex/group were selected for neurobehavioral testing, neuropathology, brain weights and/or brain dimension measurements (PND 21 or 72). Nonselected F_1 pups were necropsied on PND 21 or 28, and nonselected F_2 pups were necropsied on PND 21. Selected organs were weighed from F_1 and F_2 pups (one/sex/litter) that were necropsied on PND 21. Selected F_2 rats not allocated for neuropathology and brain dimension measurements were necropsied following completion of reflex ontogeny evaluations (PND 61) or at study termination (PND 72). Each surviving F_0 and F_1 parental animal received a complete detailed gross necropsy following the completion of weaning of the F_1 and F_2 pups, respectively; selected organs were weighed. Spermatogenic endpoints (sperm motility [including progressive motility], morphology and numbers) were recorded for all F_0 and F_1 males, and ovarian primordial follicle counts were recorded for all F_1 females in the control and high-exposure groups. Designated tissues from all F_0 and F_1 parental animals, and from F_2 pups selected for neuropathological evaluation or exhibiting developmental abnormalities suggestive of an exposure-related effect, were examined microscopically.

No test article-related mortalities were observed in this study. When evaluated across two generations, reproductive performance, offspring physical condition, offspring postnatal survival (prior to weaning) and attainment of landmarks of sexual development (balanopreputial separation and vaginal patency) were unaffected by HMDS exposure. No test article-related clinical findings or effects on gestation or lactation body weight and food consumption were noted in either parental generation. No HMDS-related clinical findings, effects on body weights, or macroscopic findings were noted for F_1 or F_2 offspring selected for evaluation of organ weights on PND 21 or euthanized prior to the end of each generation (*i.e.*, not selected for the F_1 generation or F_2 neuropathological examination, *etc.*). F_1 adult females and their offspring exhibited no exposure-related effects during the FOB assessments. No test article-related effects on anogenital distance, air-righting reflex or learning and memory were noted for F_2 offspring. Brain size and weight for F_2 animals on PND 21 and 72 were unaffected by parental test article exposure; no macroscopic, histopathological or morphometric evidence of neuropathology was observed.

Lower weekly body weight gains were noted for F_0 males and females in the 1600 and 5000 ppm groups and F_1 males in the 5000 ppm group. Mean body weights in the 1600 ppm group for both the F_0 and F_1 generations were generally similar to control group values, while those in the 5000 ppm group were reduced throughout the majority of both the F_0 and F_1 generations; food consumption was lower for the 5000 ppm group males during the premating period (F_0) and throughout the entire generation (F_1). Food consumption for F_1 females in the 5000 ppm group was reduced during the first week following weaning (week 17-18) only. Offspring body weight gains were decreased for F_1 pups in the 5000 ppm group from PND 4-21 and F_2 pups in the 1600 and 5000 ppm groups from PND 4-14. In the 5000 ppm group, these reduced body weight gains resulted in substantially lower mean body weights on PND 14 and 21 in both generations (approximately 6% to 7% lower by PND 21); lower body weights continued to be observed for the F_2 males and females through PND 56 and PND 35, respectively. In the F_2 pups in the 1600 ppm group, the lower body weight gain during PND 4-14 resulted in

significantly lower mean body weights on PND 14 (approximately 7% and 5% for male and female pups, respectively); lower body weights were also observed for the F_2 males and females in this group through PND 49 and 35, respectively.

The only test article-related effect on attainment of developmental landmarks noted for F_2 pups was a slight delay in attainment of the surface-righting response for females in the 5000 ppm group. On PND 21, decreased thymus weights were noted for F_2 male pups in the 1600 and 5000 ppm groups and F_2 female pups in the 5000 ppm group only.

Effects on developmental neurobehavioral endpoints consisted of increased motor activity for F_2 females in the 5000 ppm group on PND 13 and 21. The higher total activity counts on PND 21 were the result of an attenuated habituation. By PND 61, a normal pattern of habituation was observed for these females. No effects on motor activity were observed for F_2 males at any exposure level. Decreases in the average and peak responses to the acoustic startle response stimulus (V_{AVE} and V_{MAX}, respectively) were observed on PND 20 for F_2 males and females at 5000 ppm. However, no effects on the time from latency to peak response to the acoustic startle response stimulus (T_{MAX}) were observed.

Test article-related higher kidney weights were noted for F_0 and F_1 males in the 1600 and 5000 ppm groups. Corresponding histopathological effects of HMDS in this study were similar to those previously reported (Cassidy *et al.*, 2001) in rats following long-term inhalation exposure at 593 and 5012 ppm. These findings included hyaline droplets (F_0 and F_1 males at 5000 ppm) and increased incidence and severity of basophilic tubules in the kidneys (F_0 males, F_1 males and F_1 females at 5000 ppm). Male rat-specific hyaline droplet (consistent with α-2 urinary globulin) nephropathy was associated with the increase in basophilic tubules. Other test article-related microscopic findings, including golden-brown pigment in the periportal areas of the liver for F_0 males in the 5000 ppm group and F_1 males and females in the 1600 and 5000 ppm groups. This pigment was accompanied by infiltration of primarily mononuclear inflammatory cells and/or bile duct hyperplasia in the liver in the F_0 and F_1 5000 ppm groups, and

corresponded to higher mean relative liver weights for the F_1 males in the 1600 and 5000 ppm groups. The golden-brown pigment demonstrated bright red birefringence with a central dark Maltese cross under polarized light, characteristic of porphyrin (Churukian, 2002). In the 5000 ppm group F_1 males and females, golden-brown pigment was also noted in the medullary macrophages of the mesenteric lymph nodes and alveolar macrophage aggregates were noted for F_0 and F_1 males and females in the 5000 ppm group.

Based on the results of this study, an exposure level of 5000 ppm was considered to be the NOAEL (no-observed-adverse-effect level) for parental reproductive toxicity of hexamethyldisiloxane (HMDS) when administered via whole-body inhalation exposure to rats. The NOAEL for neonatal toxicity was considered to be 1600 ppm due to decreased offspring weights at 5000 ppm, and the NOAEL for developmental neurobehavioral endpoints was considered to be 1600 ppm due to the lack of habituation exhibited in the locomotor activity assessments and delayed attainment of the surface righting response in the 5000 ppm group F_2 females, and decreases in average and peak acoustic startle response on PND 20 in the 5000 ppm group F_2 males and females. The NOAEL for neuropathologic endpoints was considered to be 5000 ppm.

2. GLP COMPLIANCE STATEMENT

This study, designated WIL-51087, was conducted in compliance with the Good Laboratory Practice Regulations for Nonclinical Laboratory Studies of the United States Food and Drug Administration (21 CFR Part 58), October 5, 1987, and Environmental Protection Agency (40 CFR Parts 160 and 792), October 16 and September 18, 1989, respectively; the Principles of Good Laboratory Practice [C (97) 186/Final] of the Organisation for Economic Cooperation and Development, November 26, 1997; the standard operating procedures of WIL Research Laboratories, LLC and the protocol as approved by the sponsor, with the exception of the following GLP deviation. The initial test article purity analysis was conducted on December 3, 2003, which was six days prior to the GLP-defined study initiation date (date of protocol signature by the study director). This GLP deviation did not negatively impact the study or the data interpretation.

The protocol was designed to be in general accordance with the United States Environmental Protection Agency OPPTS Health Effects Test Guidelines [870.3800, Reproduction and Fertility Effects, August, 1998, and 870.6300, Developmental Neurotoxicity Study, August, 1998], and the Organisation for Economic Development Guideline 416, January 22, 2001, and Revised Draft Guideline 426, October, 1999.

Donald G. Stump, Ph.D., DABT
Associate Director, Developmental
and Reproductive Toxicology
Study Director

20 June 2006
Date

Waheed H. Siddiqui, Ph.D.
Sponsor Representative

6/15/06
Date

A copy of this study is available from EPA's docket in CD format