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DCN: 88090000081

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DOW CORNING

8EHQ-0917357

December 23, 2008

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TSCA Document Control Center (7407)
Office of Pollution Prevention and Toxics
US 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: Hexamethyldisiloxane

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 information from an inhalation 2-generation reproductive toxicity study conducted with hexamethyldisiloxane (CAS No. 107-46-0) that was recently identified during a scientific review of historical studies for which exposure gave rise to pigment accumulation in the liver. Dow Corning has not made a determination at this time that any significant risk of injury to human health or the environment is presented by these findings.

Chemical Substances

107-46-0 Hexamethyldisiloxane

88090000081

Study

An Inhalation Two-Generation Reproductive Toxicity Study of Hexamethyldisiloxane (HMDS) in Rats, Including Developmental Neurotoxicity Assessment of the F2 Generation
(Dow Corning Report: 2006-I0000-56321) as recently amended:

An Inhalation Two-Generation Reproductive Toxicity Study of Hexamethyldisiloxane (HMDS) in Rats, Including Developmental Neurotoxicity Assessment of the F2 Generation – Amendment to Report Number 2006-I0000-56321 (Dow Corning Report: 2008-I0000-59215).

CONTAINS NO CBI

Contains No CBI

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

Summary

An inhalation reproductive study of hexamethyldisiloxane in Sprague-Dawley rats was previously conducted employing exposure levels of 0, 400, 1600, and 5000 ppm and assessing reproductive and developmental endpoints in the F0, F1 and F2 generations. Microscopic examination of the liver from the F0 males at the 5000 ppm exposure level and the F1 males and females at the 1600 and 5000 ppm exposure levels identified periportal golden-brown pigment accumulation. The pigment was found to be free (extracellular), within periportal macrophages, and in bile ducts. Bile duct hyperplasia and periportal sub-acute inflammation were also noted at these exposure levels. Our recent awareness of a published review (Holsapple *et. al.*, *Toxicol Sci* **89(1)** 51-56, 2006) regarding the potential relevance of a cytotoxic mode of action for porphyrinogenic materials in liver carcinogenesis prompted our review of earlier studies for related findings. As a consequence the tissues from the subject study have been re-examined and the report amended to include designation of a no-observable-adverse-effect-level for systemic toxicity based on the liver findings. Hepatic porphoria and liver carcinogenesis was not observed in a 24-month repeated dose inhalation study of HMDS in Fischer 344 rats at exposure levels up to and including 5000 ppm.

Details

Study Design

An inhalation reproductive study of hexamethyldisiloxane in Sprague-Dawley rats was previously conducted employing exposure levels of 0, 400, 1600, and 5000 ppm. Groups of male and female Crl:CD (SD)1 rats (30/sex/group) were exposed via whole-body vapor inhalation to the test article for 6 hours per day for at least 70 consecutive days prior to mating. F0 animals were approximately 7 weeks of age at the beginning of exposure. The offspring selected to become the F1 parental generation were exposed following weaning (beginning on postnatal day 22). Exposure of the F0 and F1 males continued throughout mating, and through the day prior to euthanasia. The F0 and F1 females continued to be exposed throughout mating and through gestation day 20. After parturition, exposure of the F0 and F1 females was re-initiated on lactation day 5 and continued through the day prior to euthanasia. All F0 and F1 females were allowed to deliver and rear their pups until weaning on lactation day 21. For both generations (F1 and F2), 10 pups per litter (five per sex, when possible) were selected on PND 4 to reduce the variability among the litters. Two F1 weanlings/sex/litter were exposed to the test article from PND 22-27. From these, two F1 weanlings/sex/litter, 30/sex/group were selected on PND 28 to constitute the F1 generation. Each surviving F0 and F1 parental animal received a complete detailed gross necropsy and selected organs were weighed. Designated tissues from all F0 and F1 parental animals, and from F2 pups selected for neuropathological evaluation or exhibiting developmental abnormalities suggestive of an exposure-related effect, were examined microscopically. This study was designed to be in general accordance with the United States Environmental Protection Agency OPPTS Health Effects Test Guidelines [870.3 800, Reproduction and Fertility Effects, August, 1998, and 870.6300, Developmental Neurotoxicity Study, August, 19981] and the Organisation for Economic Development Guideline 416, January 22, 2001, and Revised Draft Guideline 426, October, 1999.

Results

Minimal to mild golden-brown pigment in the periportal areas of the liver (6 of 30), as well as periportal sub-acute inflammation (5 of 30) and bile duct hyperplasia (4 of 30) in a small number of 5000 ppm group F0 males were considered test article-related; the pigment was observed in a statistically significant ($p<0.05$) manner when compared to the control group. Pigment was typically free, but also occurred in periportal macrophages and within bile ducts. Examination of this pigment with polarized light demonstrated bright red birefringence and a central dark Maltese cross typical of porphyrin (Churukian, 2002). Sub-acute inflammation in the liver was mononuclear inflammatory cells around periportal pigment deposits. Bile duct hyperplasia was seen as clusters of bile ducts where typically there are only 1 or 2. The above findings were not present in F1 females at any exposure level.

Test article-related periportal golden-brown pigment was identified in the liver of F1 males (24 of 30) and females (7 of 30) at 1600 ppm and in 29 of 29 males and 26 of 28 females at 5000 ppm. The severity of this finding was minimal to moderate in the 1600 ppm group and minimal to severe in the 5000 ppm group. Pigment was typically free but also occurred in periportal macrophages and within bile ducts, and responded to polarized light (bright red birefringence and a central dark Maltese cross typical of porphyrin [Churukian, 2002]). Bile duct hyperplasia was only observed at the 5000 ppm exposure level for F1 males (24 of 29) and females (12 of 28). The incidence was statistically significant. Periportal sub-acute inflammation was present in F1 males at 1600 ppm (9 of 20) and at 5000 ppm (29 of 29). Statistical significance was achieved for both. Periportal sub-acute inflammation was present in F1 females at 1600 ppm (2 of 28) and at 5000 ppm (16 of 28) with statistical significance demonstrated only at 5000 ppm. Tissues from the adult F2 generation were not collected as microscopic examination of tissues from the adult F2 generation was not specified in the study protocol.

These findings were reviewed in light of our recent discovery of the publication (Holsapple *et. al.*, *Toxicol Sci* **89(1)** 51-56, 2006) denoting the significance of hepatic protoporphyrinosis and subsequent tumor formation in animal models with regard to human relevance and risk assessment. This paper summarizes a workshop focused on applying the human relevance framework concept, developed by the International Programme on Chemical Safety and the International Life Sciences Institute's Risk Science Institute, to defining the human relevance of five different modes of action for rodent hepatocarcinogenesis. The working group concluded that porphyrinogenic compounds have a defined mode of action for inducing hepatocarcinogenesis in rodents involving a threshold and a chronic dose-dependent sustained hepatocellular injury and compensatory hyperplasia. They further concluded that this "cytotoxicity" mode of action should be considered relevant in human cancer risk assessment unless it is known that the underlying mechanism(s) of action giving rise to porphyrinosis in rodents is not relevant to humans.

The study report has been amended to specify a no-observable-adverse-effect-level of 400 ppm based on the liver microscopic findings related to pigment accumulation.

Actions

Testing of this material was conducted as a part of the Siloxane Research Program, a voluntary testing effort focused on understanding the basic toxicology profile of siloxanes. The initial study report was previously shared with the USEPA on an For-Your-Information (FYI) basis. The document control number for this submission is 84060000005. A copy of the report amendment is included with this submission. 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
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.:	2008-I0000-59215
Title:	An Inhalation Two-Generation Reproductive Toxicity Study of Hexamethyldisiloxane (HMDS) in Rats, Including Developmental Neurotoxicity Assessment of the F_2 Generation - Amendment to Report Number 2006-I0000-56321
Study No.:	9837-101
External Testing Facility No.:	WIL-51087
Test Article:	Hexamethyldisiloxane (HMDS)
Study Director:	Donald G. Stump, PhD, DABT Associate Director, Developmental and Reproductive Toxicology
Sponsor:	Dow Corning Corporation 2200 W. Salzburg Road Auburn, Michigan 48611
Sponsor Representative:	Waheed H Siddiqui, PhD Associate Toxicology Scientist
Testing Facility:	WIL Research Laboratories, LLC 1407 George Road Ashland, Ohio 44805-8946
Date Final Report Issued:	20 June 2006
Date Amendment Issued:	2 September 2008
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

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Amendment to the Final Report

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AMENDMENT TO THE FINAL REPORT

Section 1. Abstract
Original Report Page: 37
Amendment to Final Report Page: 6

and

Section 13. Conclusions
Original Report Page: 140
Amendment to Final Report Page: 7

Change: The following sentence was added to the concluding paragraph regarding the no-observed-adverse-effect (NOAEL) for parental systemic toxicity: Based on the microscopic liver findings observed in the F_0 males in the 5000 ppm group and the F_1 males and females in the 1600 and 5000 ppm groups, the NOAEL for parental systemic toxicity was considered to be 400 ppm.

Reason for Change: Due to the absence of a statement regarding the NOAEL for parental systemic toxicity in the original final report, a sentence was added clarifying the appropriate dosage level based on the microscopic findings in this study

The changes to this report had no impact on the scientific validity of the results of this study.

The amendment did not entail generation of new data, revision of calculations or modification of previously submitted data. The revisions to the final report included in the amendment may have resulted in changes in pagination in the final report; any potential changes in pagination are not addressed in this amendment.

DC Study No - 9837-101
External No. - WIL-51087

D.C Report No. - 2008-I0000-59215
Security - INTERNAL

The signatures below certify that the revised pages have been reviewed and approved by the study director.

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

2 Sept 2008
Date

Waheed H. Siddiqui, PhD
Sponsor Representative

11 August 2008
Date

Paul Jean, PhD
Dow Corning Corporation
HES Management

08Aug08
Date

DC Study No. - 9837-101
External No. - WIL-51087

D.C. Report No. - 2008-I0000-59215
Security - INTERNAL

QUALITY ASSURANCE UNIT STATEMENT

Date(s) of Inspection(s)	Phase Inspected	Date(s) Findings Reported to Study Director	Date(s) Findings Reported to Management	Auditor(s)
25-Aug-2008	Final Report Amendment	25-Aug-2008	2-Sep-2008	H.Johnson

This amendment was inspected in accordance with current Good Laboratory Practice Regulations for Nonclinical Laboratory Studies of the United States Food and Drug Administration (21 CFR Part 58) and Environmental Protection Agency (40 CFR Parts 160 and 792), the Principles of Good Laboratory Practice of the Organisation for Economic Cooperation and Development, the standard operating procedures of WIL Research Laboratories, LLC and the sponsor's protocol and protocol amendments. Quality Assurance findings, derived from the inspections during the conduct of the study and from the inspections of the raw data and draft report, were documented and reported to the Study Director. A status report was submitted to management monthly.

This amendment accurately reflects the data generated during the study. The methods and procedures used in the study were those specified in the protocol, its amendments and the standard operating procedures of WIL Research Laboratories, LLC.

This amendment to the final report will be stored in the Archives at WIL Research Laboratories, LLC, or another location specified by the sponsor.

Amendment Audited and Reviewed By:

Heather L. Johnson, BS, RQAP-GLP
Manager, Quality Assurance

2 Sep 2008
Date

REVISED PAGES

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. Based on the microscopic liver findings observed in the F_0 males in the 5000 ppm group and the F_1 males and females in the 1600 and 5000 ppm groups, the NOAEL for parental systemic toxicity was considered to be 400 ppm. 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.

13. CONCLUSIONS

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. Based on the microscopic liver findings observed in the F_0 males in the 5000 ppm group and the F_1 males and females in the 1600 and 5000 ppm groups, the NOAEL for parental systemic toxicity was considered to be 400 ppm. 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.