



August 10, 2009

Document Control Office (7407)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Room G-099
1200 Pennsylvania Avenue, NW
Washington, DC 20460



Attn: TSCA Docket Clerk

Re: Release of Document for External Distribution

It was brought to the attention of Dow Corning Corporation that a report submitted under TSCA Section 8(e) did not contain a release waiving the general INTERNAL designation. The submission (see attached submittal letter – Supplemental Submission of Final Report to 8EHG-02-15088 TSCA Section 8(e) Notification of Substantial Risk: Octamethylcyclotetrasiloxane) is approved by Dow Corning Corporation for release and the INTERNAL designation is waved. The report and the EPA Document Control Number have been provided for your reference.

Final Study Report:

24-MONTH COMBINED CHRONIC TOXICITY AND ONCOGENICITY
WHOLE BODY VAPOR INHALATION STUDY OF
OCTAMETHYLCYCLOTETRA-SILOXANE (D4) IN FISCHER 344 RATS

Dow Corning Corporation
2004-I0000-54091
August 16, 2004



Contains No CBI

CONTAINS NO CBI

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U.S. EPA Document Control Number - 89050000046

Sincerely,

A handwritten signature in black ink, appearing to read "Kathleen P. Plotzke". The signature is written in a cursive, flowing style.

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

cc: Robert Jones, U.S. EPA

DOW CORNING

8ehq-1104-15088 B

← 8e # (RAD) website #

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November 5, 2004

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Document Control Office (7407)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Room G-099
Attn: TSCA Section 8(e) Coordinator
1200 Pennsylvania Avenue, NW
Washington, DC 20460

mk#
280736

8EHQ-1104-15088

Re: Supplemental Submission of Final Report to 8EHQ-02-15088
TSCA Section 8(e) Notification of Substantial Risk:
Octamethylcyclotetrasiloxane

CONTAINS NO CBI

Dear Docket Clerk:

In accordance with the provisions of Section 8(e) of the Toxic Substances Control Act (TSCA), as interpreted in the Statement of Interpretation and Enforcement Policy (40 FR 11110, 16 March 1978), Dow Corning is submitting the following recently issued final study report as a supplemental submission to our initial TSCA Section 8(e) notification of February 20, 2002 (8EHQ-02-15088). This final study report has also been submitted to the Agency as a follow-up to submissions made concerning octamethylcyclotetrasiloxane under TSCA Section 8(d) (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.

Chemical Substance:

556-67-2 Octamethylcyclotetrasiloxane

Manufacturer:

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



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IMD #

8EHQ-02-15088

DCN 89050000046

← DCN #



8ehq-1104-15088 B

page 2

Final Study Report:

24-MONTH COMBINED CHRONIC TOXICITY AND ONCOGENICITY WHOLE BODY VAPOR INHALATION STUDY OF OCTAMETHYLCYCLOTETRA-SILOXANE (D4) IN FISCHER 344 RATS

Dow Corning Corporation
2004-10000-54091
August 16, 2004

Summary:

Preliminary results from an ongoing 24-month combined chronic/oncogenicity study with octamethylcyclotetrasiloxane (OMCTS, D₄) in Fischer 344 rats were submitted to the Agency as a TSCA Section 8(e) notification (February 20, 2002). The preliminary results indicated test article-related effects in the kidney (male and female) and uterus of rats exposed for 12 to 24 months. These effects included increased kidney weight and severity of chronic nephropathy, increased uterine weight, increased incidence of endometrial epithelial hyperplasia, and an increased incidence of endometrial adenomas. All of the effects were limited to the 700-ppm exposure group. Dow Corning is now submitting the final study report for the recently completed 24-month combined chronic/oncogenicity study as a supplemental submission to our previous TSCA Section 8(e) notification.

Inhalation exposure of Fischer 344 rats to OMCTS for up to 24-months resulted in notable affects in the uterus, kidney, liver, upper respiratory tract, and on survival.

A statistically significant decrease in survival was apparent for males in the 700-ppm dose group. The decrease was attributed to an increase in mononuclear cell leukemia related deaths. However the total incidence of mononuclear cell leukemia was not different from controls when assessed over the 24-month duration of the study. A statistically significant lymphocytic leukocytosis was present in the 700-ppm dose group males and females at 3, 6, and 12 months.

A statistically significant increase in uterine weight and increased incidence of endometrial epithelial cell hyperplasia was apparent in the 700-ppm dose group at 24-months. Endometrial adenomas were present in 4 out of 35 animals in the 700-ppm dose group surviving to the 24-month necropsy. No uterine adenomas were present in the 25 animals that died prior to the scheduled 24-month necropsy in this dose group, or in any of the animals in the control or intermediate dose groups. A trend analysis indicated that this incidence was statistically significant (Peto Mortality-Prevalence Test, $p < 0.05$). No treatment-related uterine affects were apparent at 12 months or in the recovery group.

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I have attached the only information I have for this submission. A trip to the pocket was not fruitful.

I am not sure if this is a file that was damaged in the flood or not but it falls into the correct timeframe.

If you have a copy of your cover letter and ~~the~~ a CD of the study I will make sure it is restored,

Andrew M. Basalla
202-564-7672

November 5, 2004

Document Control Office (7407)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Room G-099
Attn: TSCA Section 8(e) Coordinator
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Supplemental Submission of Final Report to 8EHQ-02-15088
TSCA Section 8(e) Notification of Substantial Risk:
Octamethylcyclotetrasiloxane

Dear Docket Clerk:

In accordance with the provisions of Section 8(e) of the Toxic Substances Control Act (TSCA), as interpreted in the Statement of Interpretation and Enforcement Policy (40 FR 11110, 16 March 1978), Dow Corning is submitting the following recently issued final study report as a supplemental submission to our initial TSCA Section 8(e) notification of February 20, 2002 (8EHQ-02-15088). This final study report has also been submitted to the Agency as a follow-up to submissions made concerning octamethylcyclotetrasiloxane under TSCA Section 8(d) (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.

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Dow Corning Corporation
2004-I0000-54091
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Preliminary results from an ongoing 24-month combined chronic/oncogenicity study with octamethylcyclotetrasiloxane (OMCTS, D₄) in Fischer 344 rats were submitted to the Agency as a TSCA Section 8(e) notification (February 20, 2002). The preliminary results indicated test article-related effects in the kidney (male and female) and uterus of rats exposed for 12 to 24 months. These effects included increased kidney weight and severity of chronic nephropathy, increased uterine weight, increased incidence of endometrial epithelial hyperplasia, and an increased incidence of endometrial adenomas. All of the effects were limited to the 700-ppm exposure group. Dow Corning is now submitting the final study report for the recently completed 24-month combined chronic/oncogenicity study as a supplemental submission to our previous TSCA Section 8(e) notification.

Inhalation exposure of Fischer 344 rats to OMCTS for up to 24-months resulted in notable effects in the uterus, kidney, liver, upper respiratory tract, and on survival.

A statistically significant decrease in survival was apparent for males in the 700-ppm dose group. The decrease was attributed to an increase in mononuclear cell leukemia related deaths. However the total incidence of mononuclear cell leukemia was not different from controls when assessed over the 24-month duration of the study. A statistically significant lymphocytic leukocytosis was present in the 700-ppm dose group males and females at 3, 6, and 12 months.

A statistically significant increase in uterine weight and increased incidence of endometrial epithelial cell hyperplasia was apparent in the 700-ppm dose group at 24-months. Endometrial adenomas were present in 4 out of 35 animals in the 700-ppm dose group surviving to the 24-month necropsy. No uterine adenomas were present in the 25 animals that died prior to the scheduled 24-month necropsy in this dose group, or in any of the animals in the control or intermediate dose groups. A trend analysis indicated that this incidence was statistically significant (Peto Mortality-Prevalence Test, $p < 0.05$). No treatment-related uterine effects were apparent at 12 months or in the recovery group.

A modest statistically significant elevation ($\leq 15\%$) in kidney weight was present for 700-ppm dose group males and females at 12 and 24 months of exposure and for 150-ppm dose group females at 24 months. A statistically significant increase in kidney weight was apparent for 700-ppm females in the recovery group. Chronic nephropathy was common in animals surviving to 24 months and a statistically significant increase in incidence and severity grade was present for the 150-ppm and 700-ppm dose group females. Likewise a statistically significant increase in severity grade was identified for males in the 24-month exposure group (700-ppm) and in the recovery group at exposure concentrations of 30 ppm and higher.

Statistically significant liver weight increases were apparent at 6 months in males exposed to 30 ppm and greater and in the 700-ppm group females. At 12 months of exposure, a significant liver weight increase was observed in males and females exposed to 150-ppm and 700-ppm of OMCTS. Males exposed for 24 months to 700-ppm and females exposed at 150-ppm and 700-ppm also showed a significant increase in liver weight. Hepatocyte centrilobular hypertrophy was unique to the 700-ppm dose group males and the incidence varied with exposure duration (60% of the 700-ppm dose group males at 12 months and 8% of the 700-ppm dose group males at 24 months). No treatment-related liver affects were apparent for recovery group animals.

Treatment-related effects within the nasal cavity after 12-months included increased incidence and/or severity of goblet cell hyperplasia, squamous epithelial cell hyperplasia, suppurative inflammation, and eosinophilic globules at exposure concentrations of 150-ppm and 700-ppm. Continued exposure for 24 months resulted in increased incidence and/or severity of goblet cell hyperplasia, squamous epithelial cell hyperplasia, and eosinophilic globules at exposure concentrations of 150-ppm and 700-ppm for males and at exposure concentrations of 30-ppm and higher in females. Recovery group animals showed an increase in severity of eosinophilic globules (700-ppm males and females) and an increase in incidence of goblet cell hyperplasia (700-ppm males) and nasolacrimal duct suppurative inflammation (150-ppm and 700-ppm males).

Because the findings related to the liver, kidney, nasal cavity, and survival are of doubtful toxicological relevance to humans and that lesions in the uterus emerged upon chronic exposure to 700-ppm OMCTS, an exposure level greatly exceeding typical workplace or consumer exposures, we do not believe the results of this study represent a substantial risk to health or the environment. Nevertheless, we are reporting them to EPA to ensure our compliance with the letter and spirit of TSCA Section 8(e).

Details:

Study Design:

Male and female Fischer 344 rats were exposed to vapor concentrations of 0-, 10-, 30-, 150-, or 700-ppm OMCTS for 6 hr/day, 5 days/week, for up to 24-months. The study animals were divided into four groups. Group A animals (6/sex/dose level) were exposed for six months and then sacrificed for the determination of the OMCTS concentration in liver, fat, and plasma. Group B animals (10/sex/dose level) were exposed to OMCTS for 12 months and then sacrificed. Group C animals (20/sex/dose level) were exposed to OMCTS for 12 months only and then observed for an additional 12 months to determine the possible reversibility of any effects. Group D animals (60/sex/dose level), were exposed to OMCTS for 24 months. Group C and D animals were sacrificed at 24 months. A complete histopathology examination was performed on all animals in groups B, C, and D that either were sacrificed or died *in extremis*.

Results:

Survival was unaffected by treatment for all groups except the 700-ppm group D males. Survival for group D males was 58, 60, 58, 58, and 38% for exposure concentrations of 0-, 10-, 30-, 150-, and 700-ppm OMCTS, respectively. The increase in early deaths was attributed to an increase in Fischer rat mononuclear cell leukemia induced morbidity/mortality. However the total incidence of mononuclear cell leukemia in the 700-ppm group D males was not different from the control group when evaluated for the entire study period (24 months). Treatment related effects on body weight were minimal (< 10%), expressed only in the last few months of the study, and were generally limited to the 700-ppm group D males. Fischer rat mononuclear cell leukemia is a common age-related neoplasia in rats expressed at very high incidence rates especially in males. This type of leukemia is generally considered non-relevant to humans. Chronic exposure to OMCTS did not result in an increased incidence of mononuclear cell leukemia.

Clinical pathology assessments at 3, 6, and 12 months demonstrated a consistent lymphocytic leukocytosis in 700-ppm group males with a 25-29% increase in the number of lymphocytes. Lymphocyte leukocytosis was also present in the 150-ppm and 700-ppm females with a 32-48% and 56-64% increase in lymphocytes, respectively. There was also a consistent decrease in serum alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase activities in the 700-ppm group males and females.

Statistically significant increases in kidney weight were observed in males and females in each of the three exposure paradigms; 12-months (Group B), 24-months (Group D), and 12-months exposure/12-months recovery (Group C). The effect in Group B was greater in males (~12% increase) than females (~5% increase) and limited to the 700-ppm groups. Increased kidney weight in Group D was ~ 15% for males and females at 700-ppm and ~ 6% for females at 150-ppm. Kidney weight increases of ~8% in Group C were limited to 700-ppm males and females. Chronic nephropathy was diagnosed in 80-100% of males and 40-80% of females in Group B and in 95-100% of males and 85-98% of females in Group D. All of the males and 75-90% of the females in Group C were diagnosed with chronic nephropathy. The incidence of chronic nephropathy in OMCTS-exposed groups was not statistically different from control in Groups B, C, or D except for the 150-ppm and 700-ppm Group D females. The increase in incidence for Group D females was ~12% and was accompanied by statistically significant increases in severity grade (~0.5 grade). Statistically significant severity grade increases were demonstrated for 700-ppm Group D males (~1 grade) and Group C males (~0.5 grade) at exposure concentrations of 30 ppm and higher. These data demonstrate that chronic exposure to OMCTS can increase kidney weight in male and female rats and elevate the incidence/severity of chronic nephropathy, a common age-related renal lesion. The effects on the kidney were minimal in character and incidence and as such, are not considered to be of toxicological significance with regard to human health.

A statistically significant increase in mean uterine weight was observed in female rats exposed to 700-ppm for 24 months. Statistically significant increases in uterine weight were also present in recovery group females. However, the increases were not considered to be treatment-related for lack of dose-responsiveness. Uterine weight for females exposed to OMCTS for 12 months was not different from controls. Associated with the increased organ weight at 24-months was a marked increase in incidence (19% in control; 50% at 700-ppm) and severity (1.7 for control; 2.5 for 700-ppm) of uterine endometrial epithelial cell hyperplasia. Uterine endometrial epithelial cell hyperplasia was not observed at 12 months of exposure. In contrast, this lesion was present in each of the recovery groups, but the incidence among dose groups was not dose-related. Accompanying the increase in uterine weight and endometrial epithelial cell hyperplasia at 700-ppm was an increased incidence of uterine endometrial adenoma. Four of the 35 females that survived to the 24-month necropsy were diagnosed with this lesion. Uterine adenomas were not present in any of the females that died prior to the scheduled necropsy from this dose group. Uterine adenomas were also not detected in females at the 12-month necropsy or in any of the other dose groups within the 24-month exposure group. However, there were two findings within the recovery group animals, a uterine adenoma was detected in a 30-ppm dose group animal and a uterine adenocarcinoma was detected in a 150-ppm dose group animal. The incidence of uterine adenoma in the 700-ppm dose group was not statistically different from control; however, the incidence trend across the dose groups was significant (Peto Mortality-Prevalence Test, $p < 0.05$). The combination of increased uterine weight, increased incidence of endometrial epithelial hyperplasia and significant trend of a rare tumor supports the conclusion that chronic exposure to 700-ppm OMCTS induces a hyperplastic/neoplastic response in the rat

uterus. Research focused on understanding the possible mechanisms responsible for the uterine response to OMCTS exposure and relevance to humans is ongoing.

Statistically significant and dose-responsive liver weight increases ranging between 14 and 30 percent were apparent at 6 months for males exposed to 30-ppm OMCTS and higher and for females exposed to 700-ppm. Following 12 months of exposure, liver weight increases were seen in male and females exposed at 150 and 700 ppm. A liver weight increase was seen at 24 months in males exposed to 700 ppm and in females exposed to 150 and 700 ppm. Hepatocyte centrilobular hypertrophy was present in the 700-ppm dose group males and the incidence varied greatly with exposure duration (60% of the 700-ppm Group B males; 8% of the 700-ppm Group D males). Reports demonstrating the effect of OMCTS exposure on liver weight and hepatocyte hypertrophy in the rat exist in the open literature and the results obtained in this bioassay are generally consistent with those reports. The information born out of this bioassay extends that knowledge base and has demonstrated that chronic inhalation exposure to OMCTS induces a prolonged adaptive hepatic response without induction of hepatic neoplasia.

There were a number of histopathological changes identified in the nasal cavity tissue of OMCTS exposed groups. In exposure group B both males and females in the 700-ppm dose groups had statistically significant increases in incidence and severity grade of eosinophilic globules, respiratory epithelium goblet cell hyperplasia, squamous epithelium hyperplasia, and suppurative inflammation (males only). The only finding not limited to the high dose group was eosinophilic globules in the 150-ppm dose group females for which the severity grade was statistically greater than that of the control. In exposure group D the incidence and severity grade for eosinophilic globules was elevated significantly in the 700-ppm dose group males and in females exposed at 30 ppm and higher. The incidence and severity of this lesion was also greater than control in the 10-ppm dose group females however only the severity grade proved to be statistically significant. Other statistically significant differences included an increase in the incidence of respiratory epithelium goblet cell hyperplasia for males (150- and 700-ppm dose groups) and females (700-ppm dose group) and an increase in the incidence of squamous epithelium hyperplasia for males in the 700-ppm dose group. A statistically significant increase in incidence of eosinophilic globules (~0.5 grade) was present for males and females in Group C at 700-ppm. There was also a modest 15% increase in the incidence of nasolacrimal duct suppurative inflammation at 150 ppm and 700 ppm and respiratory epithelium goblet cell hyperplasia (700-ppm) in treated males. These findings are consistent with that expected for chronic inhalation exposure to materials with slight irritant properties, such as OMCTS.

Actions:

Dow Corning is conducting further studies to determine the potential relevance of these findings. Additionally, Dow Corning is revising its current exposure assessment to provide support for a quantitative risk assessment. These findings will be communicated to appropriate internal and external audiences.

Dow Corning will notify EPA of any further relevant information that may be developed concerning this material. Dow Corning also will provide EPA the final copy of the report for this study when it is available.

If you have any questions concerning any of the aforementioned studies, please contact Dr. Robert G. Meeks, Scientific Director of Toxicology and Risk Assessment at 989-496-8629 or at the address provided herein. If you require further general information regarding this submission, please contact Michael E. Thelen, Manager of U.S. EPA Regulatory Affairs, at 989-496-4168 or at the address provided herein.

Sincerely,

A handwritten signature in cursive script that reads "Laura L. Perkins". The signature is written in black ink and includes a horizontal flourish at the end.

Laura L. Perkins, Ph.D.
Director, Environment, Health and Safety
(989) 496-8568