DOW CORNING

[redacted]

February 4, 2003

OPPT Public Docket #42071-A
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

Attn.: Docket Clerk

Re: Memorandum of Understanding - Siloxane Product Stewardship Program

Dow Corning Corporation is pleased to submit the attached document as per reporting outlined in the Memorandum of Understanding (MOU) that was signed with EPA on April 9, 1996. The attached document is a copy of the TSCA Section 8(e) Notification of Substantial Risk concerning decamethylcyclopentasiloxane, one of six materials covered in the MOU. As per the communication element of the product stewardship program, this document provides EPA preliminary findings from an ongoing 24-month combined chronic/oncogenicity study with decamethycyclopentasiloxane (D_5) in Fischer 344 rats.

The attached filing with the Section 8(e) Coordinator indicates that these effects occurred only at 160 ppm, a level that greatly exceeds typical workplace or consumer exposures. Based on the current understanding of the use and exposure of decamethylcyclopentasiloxane, we do not believe that the results of this study represent a risk to health or the environment.

If you have any questions concerning this information, please contact Michael Thelen at (989) 496-4168 or Dr. Robert G. Meeks, Scientific Director, Toxicology and Risk Assessment at (989) 496-8629.

Sincerely,

Michael E. Thelen
Manager, Regulatory Affairs
Environmental, Health and Safety

cc: David R. Williams

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

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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: TSCA Section 8(e) Notification of Substantial Risk:
Decamethylcyclopentasiloxane

Dear Sir:

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 information concerning an ongoing study. 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:

541-02-6 Decamethylcyclopentasiloxane

Manufacturer:

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

Ongoing Study:

DECAMETHYLCYCLOPENTASILOXANE (D5): A 24-MONTH COMBINED CHRONIC TOXICITY AND ONCOGENICITY WHOLE BODY VAPOR INHALATION STUDY IN FISCHER-344 RATS

Dow Corning Study No. 9346

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

Summary:

Preliminary results from an ongoing 24-month combined chronic/oncogenicity study with decamethylcyclopentasiloxane (DMCPS, D_5) in Fischer 344 rats indicate an increase in uterine endometrial tumors for rats exposed for 12 to 24 months.

Details:

Study Design:

In a 24-month combined chronic/oncogenicity inhalation study, male and female Fischer 344 rats were exposed to vapor concentrations of 0, 10, 40, or 160 ppm DMCPS for 6 hr/day, 5 days/week, for up to 24-months. The study animals were divided into four groups. Group A animals consisting of six animals per sex were exposed for six months and then sacrificed for the determination of the DMCPS concentration in liver, fat, and plasma. Group B, consisting of 10 animals per sex, were exposed to DMCPS for 12 months and then sacrificed. Group C animals, consisting of 20 animals per sex, were exposed to DMCPS for 12 months only and then observed for an additional 12 months to determine the possible reversibility of any effects. Group D animals, consisting of 60 animals per sex, were exposed to DMCPS for 24 months. Both group C and D animals were sacrificed at 24 months. The lungs, liver, kidney, nasal cavity, gross lesions and tissue masses from all group B, C, and D animals were submitted for histological examination. A complete histopathology examination was performed on all tissues from the control and high dose group animals from groups B, C, and D as well as suspected target organ tissue from intermediate exposure level groups.

Findings:

The findings of interest concern the diagnoses of uterine endometrial adenoma, adenomatous polyp, and adenocarcinoma. None of the female rats in group B (1 year exposure and sacrifice) were diagnosed with these lesions.

The incidence of endometrial adenocarcinoma was 1, 1, 0, and 2 for female rats in the 0, 10, 40, and 160-ppm exposure groups in group C, respectively. Endometrial adenomatous polyp was diagnosed in one female rat in the 160-ppm exposure group of group C. Combining this with the adenocarcinoma data, the incidence becomes 1, 1, 0, and 3 for female rats in the 0, 10, 40, and 160 ppm exposure groups of group C, respectively. Uterine endometrial adenoma was not present in group C female rats.

The incidence of endometrial adenocarcinoma in group D was 0, 1, 0, and 5 for female rats in the 0, 10, 40, and 160 ppm exposure groups, respectively. One female rat in the 10 ppm exposure group was diagnosed with endometrial adenoma and one female rat in the 0 ppm and one female rat in the 40 ppm exposure groups were diagnosed with endometrial adenomatous polyps. The combined tumor incidence for female rats in group D is, therefore, 1, 2, 1, and 5 in the 0, 10, 40, and 160 ppm exposure groups, respectively.

It is important to highlight that there was a complete lack of an increase in incidence or severity of uterine endometrial hyperplasia in Group B, C and D females. Endometrial hyperplasia is considered an essential precursor lesion commonly associated with uterine adenoma/carcinoma.

Classical statistical procedures applied to these data include the Peto analysis and a pairwise comparison (i.e. Fisher's Exact test). The Bailer-Poitier poly-3 trend test, which is more sensitive than the Cochran-Armitage trend test, was also applied to these data. These analyses were applied to the incidence of uterine adenocarcinomas and to the combined incidence of uterine adenocarcinomas, adenomas, and adenomatous polyps (i.e., the total uterine tumor incidence).

For Group C females, Peto's test showed there was no significant trend among the groups ($p=0.4159$) when all tumors were combined. Likewise, when the adenocarcinomas were analyzed separately, there was no significant trend ($p=0.8227$). Fisher's Exact test showed there was no significant difference in the proportion of tumor occurrences among the groups ($p=0.3867$) when all tumors were combined or when the tumors were analyzed separately ($p=0.8988$). The poly-3 test showed there was no significant trend among the groups when all tumors were combined ($p=0.0580$). When the adenocarcinoma tumors were analyzed separately using the poly-3, there was no significant trend ($p=0.1754$).

For animals exposed for 2 years (Group D), Peto's test showed there was no significant trend among the groups when all tumors were combined ($p=0.1314$). When the adenocarcinomas were analyzed separately, a significant trend was found ($p=0.0130$). Fisher's Exact test showed there was no significant difference in the proportion of tumor occurrences among the groups when all tumors were combined ($p=0.3233$). There was a significant difference when the adenocarcinoma tumors were analyzed separately ($p=0.0166$). Analysis of the tumor incidence in females exposed for two years using the poly-3 test showed a significant trend among the groups when all tumors were combined ($p=0.0219$) and when the adenocarcinomas tumors were analyzed separately ($p=0.0008$).

While several of the statistical methods applied showed a statistically significant trend for uterine endometrial adenocarcinomas, statistical significance was reduced or eliminated when the adenomas and adenomatous polyps were combined with the adenocarcinomas. Further, these data are difficult to interpret.

It is generally expected that cellular hyperplasia precedes the formation of an adenoma, which precedes the formation of an adenocarcinoma. There are no observations in this bioassay that support the normal progression of these tumors. There is neither an increase in the incidence or severity of hyperplasia and there is no dose-related or statistically significant increase in adenomas. There is also no indication of hormonal alteration or cycle disruption in this study or any previous studies that would provide a potential mode of action for this lesion. In other words, there does not appear to be a biologically plausible explanation for these tumors.

These data suggest an apparent increase in uterine endometrial adenocarcinomas at a DMCPS exposure concentration of 160 ppm. However, whether or not this increase in incidence is truly related to exposure to DMCPS is questionable and yet to be determined. The 160-ppm exposure concentration greatly exceeds workplace or consumer exposure. We do not believe the results of this study represent a 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).

Actions:

Dow Corning is considering 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 of 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,

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

Table 1. Significance Level (p-values) Summary

		Trend Tests				Fisher Exact Test			
Treatment Group	Neoplasia	Poly-3 Test	Cochran-Armitage	Jonckheere-Terpstra	Peto Mortality-Prevalence Test	Fisher's Exact Test (global)	Fisher's Exact Test (control verses treatment group comparisons) (ppm D5)		
							10	40	160
Group D	Adenocarcinoma	0.0008	0.0096	0.0098	0.013	0.0166	1	1	0.0573
	Combined	0.0219	0.0946	0.0953	0.1314	0.3233			
Group C	Adenocarcinoma	0.1754		0.6484	0.8227	0.8988			
	Combined	0.058		0.3047	0.4159	0.3867			