

September 4, 2001

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



8EHQ-01-14868

Re: Supplemental Submission to 8EHQ-01-14868  
TSCA Section 8(e) Notification of Substantial Risk: A 90-Day Oral  
(Gavage) Toxicity and One Generation Reproductive Toxicity Study of  
Trifluoropropylmethylcyclotrisiloxane (TFPMCT) in Rats

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 as a supplemental submission to our initial and amended TSCA Section 8(e) notifications of February 27, 2001 and April 6, 2001, respectively (8EHQ-01-14868)

**Chemical Substance:**

2374-14-3 Cyclotrisiloxane, 2,4,6-trimethyl-2,4,6-tris(3,3,3-trifluoropropyl)  
Trifluoropropylmethylcyclotrisiloxane (TFPMCT)

**Manufacturer:**

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

**Ongoing Study:**

A 90-DAY ORAL (GAVAGE) TOXICITY AND ONE GENERATION  
REPRODUCTIVE TOXICITY STUDY OF TRIFLUOROPROPYLMETHYL-  
CYCLOTRISILOXANE (TFPMCT) IN RATS

Dow Corning Study No. 9506



89010000307

RECEIVED  
DPPT/NCIC  
2001 SEP 13 AM 10:50

Contain NO CBI

## **Summary:**

Preliminary results from an ongoing 13-week subchronic and one generation reproductive study with TFPMCT show test article-related changes in liver, heart, and skeletal muscle.

In the liver, periportal hepatocyte enlargement with micro to macrovacuolation of the cytoplasm was observed at a Lowest Observed Effect level (LOEL) of 0.8 mg/kg/day. In the heart, test article-related or test article-exacerbated cardiomyopathy was observed at a LOEL of 4.0 mg/kg/day (and possibly at 0.8 mg/kg/day in males). Degeneration in the skeletal muscle was seen at a LOEL of 20 mg/kg/day and was characterized by changes in the shape and size of myocytes, loss of cross striations, and increased cellularity (mononuclear inflammatory cells and/or regenerative myocyte nuclei).

## **Details:**

### *90-Day Phase*

In the 90-day phase, trifluoropropylmethylcyclotrisiloxane (TFPMCT) was administered at dose levels of 0.8, 4, 20 or 50 mg/kg/day to four groups of 10 animals/sex/group (20 animals/sex/day for 50 mg/kg/day group) once daily (5 days per week) for a minimum of 90 days. A concurrent control group of 20 animals/sex received the vehicle, sesame oil, on a comparable regimen. The route of administration was oral (gavage). Because of excessive toxicity following two days of administration of TFPMCT at 50 mg/kg/day, the dose level for the high dose group was lowered to 35 mg/kg/day. Following the 90-day dosing period, the surviving animals were necropsied and gross and microscopic examinations were conducted on required tissues and organs.

Preliminary histopathologic evaluation identified test article-related changes in liver, heart, and skeletal muscle. In the liver, there was periportal hepatocyte enlargement with micro to macrovacuolation of cytoplasm. These vacuoles were small, clear and round, giving a pale and foamy appearance. Large vacuoles were less common but were prominent in moderately severe cases. Minimal vacuolation was seen in 2 of 10 males and 3 of 10 of the females that were dosed at 0.8 mg/kg/day. The incidence and severity of this change increased with dose. At doses of 50/35 mg/kg/day, minimal to moderate vacuolization was seen in 9 of 10 males and females that survived to study completion. The finding was less apparent in rats that were found dead or that were euthanized in *extremis* and was not found in any controls.

In the heart, test article-related or test article-exacerbated cardiomyopathy was observed. Both types were morphologically similar to the common, age-related

cardiomyopathy of the rat, though more extensive in cases graded more than minimally severe. In the lower two dose groups the change was always characterized as subacute, in the higher two dose groups it was characterized as chronic. Chronic cardiomyopathy was characterized by expansion of the myocardial interstitial tissue (mononuclear inflammatory cells and/or fibroplasia) with scattered degeneration and necrosis of individual myocytes. Minimal to moderate chronic cardiomyopathy was seen in all of the males and in 7 of 8 females that were dosed at 20 mg/kg/day and survived to study completion. The incidence and severity in the 50/35 mg/kg/day group was comparable. Minimal to mild chronic cardiomyopathy was seen in about half of the treated rats that died or were euthanized *in extremis*. Minimal chronic cardiomyopathy, similar to that seen in the treated rats, was seen in a control male that survived to study completion.

Subacute cardiomyopathy was the term used to describe focal degeneration of cardiac myocytes with local accumulation of mononuclear cells, primarily macrophages. Unrelated to the test article, minimal subacute cardiomyopathy was seen in controls (4 of 10 males and 2 of 10 females), representing the early stages of spontaneous age-related cardiomyopathy. In both sexes there was an exacerbation of subacute cardiomyopathy at 4 mg/kg/day, and, in males, there was an apparent increase in subacute cardiomyopathy (statistical analysis not yet available) suggesting a possible test article-related effect at the 0.8 mg/kg/day dose; however the severity was minimal and similar to that seen in controls,

Degeneration in the skeletal muscle was characterized by changes in the shape and size of myocytes, loss of cross striations, and increased cellularity (mononuclear inflammatory cells and/or regenerative myocyte nuclei). This finding was present at 20 and 50/35 mg/kg/day.

**Actions:**

These findings from the aforementioned study will be communicated to appropriate internal and external audiences including employees and customers. Dow Corning will notify EPA of any further relevant information that may be developed concerning this material and will provide the Agency with a copy of the final report from this study when it is available.

If you have technical questions concerning these studies, please contact Dr. Robert Meeks at 989-496-8629 or at the address provided herein. If you require further general information regarding this submission, please contact Dr. Rhys G. Daniels, Senior Regulatory Compliance Specialist, Regulatory Compliance Group, HERA Americas, at 989-496-4222 or at the address provided herein

Sincerely,

A handwritten signature in black ink, appearing to read "Laura L. Perkins". The signature is fluid and cursive, with the first name "Laura" being the most prominent part.

Laura L. Perkins  
Director of Environmental, Health and Safety  
(989) 496-8568

RGD01225