8ehq_1208_17356A
DCN: 88090000080

MR# 315987

DOW CORNING

8EHQ-09-17356

December 23, 2008

RECEIVED
08 DEC 24 AM 9:11

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: Dimethylsilanediol

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 is submitting information from an acute oral gavage toxicology study conducted with dimethylsilanediol (CAS No. 1066-42-8) in mice. 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

1066-42-8 Dimethylsilanediol

88090000080

Ongoing Study

An Acute Oral Gavage Study in Mice to Determine the Maximum Tolerated Dose and Systemic Availability of Dimethylsilanediol

Summary

This study was conducted to determine the desired dose level for a single oral gavage dose and systemic absorption potential of the test article for proposed studies with mice. Groups of male and female mice were dosed once with test material (2000 mg/kg body weight; water as vehicle). The study was split into two phases, Phase 1 and Phase 2. The objective of Phase 1 was to determine the maximum tolerated

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

Contains No CBI
CONTAINS NO CBI

dose not to exceed 2000 mg/kg body weight. Six female mice each received a dose level of 2000 mg/kg body weight of the test article and were observed for signs of toxicity for 14 days post dose administration. There were no deaths attributable to the test article during this experimental phase. Based on this result, 21 male and 21 female mice were dosed at the 2000 mg/kg dose level during Phase 2. During Phase 2, three male and three female mice were sacrificed at defined time points post dose administration to determine total silicon content in plasma. There were no deaths directly attributable to the test article during this experimental phase. However, during both Phase 1 and 2 there were test article-related clinical observations of toxicity observed 30 minutes or more after dose administration which included incoordinated gait, absent and decreased activity, abnormal muscle contractions, respiratory effects, fully and partially closed eye lids, and cold to the touch. These effects did not persist beyond 24-72 hours.

Details

Study Design

The purpose of this study was to determine the Maximum Tolerated Dose (MTD) (Phase 1) for dimethylsilanediol (DMSD) following a single oral dose administration to mice and to determine systemic availability (Phase 2) of DMSD following its administration as determined by assessing total plasma silicon content.

This study was split into two phases, Phase 1 and Phase 2. During the Phase 1, a preliminary toxicity study was conducted using the stepwise approach described in the OECD 423 guideline to determine the highest dose level that could be tolerated, but not induce test article related mortality within three days of administration. A total of six female mice were used during Phase 1. Once the desired dose level was determined, 21 male and 21 female mice were dosed at the 2000 mg/kg dose level. Blood was collected post-administration from three male and three female mice each at 1, 2, 4, 6, 12, 24, and 48 hours.

Preliminary Results

One animal each from Phase 1 and 2 were found dead during the experimental phase. The death in phase 1 was related to a gavage injury. It could not be determined if the death in phase 2 was test article related. Test article related clinical observations were noted at or after 30 minutes of dosing (Phase 1 and Phase 2 data pooled) which included incoordinated gait, absent and/or decreased activity, abnormal muscle contractions, respiratory effects, fully and partially closed eye lids, and cold to the touch. These effects did not persist beyond 24 – 72 hours.

These clinical signs resolved with time. Incoordinated gait, which was observed in all males and in 22/27 females, was absent by 48 hours. Absent and/or decreased activity, which was observed in 16/21 males and 23/27 females, was absent by 72 hours. Abnormal muscle contractions, which was observed in 7/21 males and 14/27 females, was resolved by 72 hours. Respiratory effects, which were observed in 7/21 males and in 18/27 females, was absent by 48 hours. Fully and partially closed eye lids, present in 8/21 males and 17/27 females, was absent by 72 hours. The observation of cold to the touch was observed in 1/21 males and in 6/27 females and absent by 48 hours.

Body weight loss was typically observed (< 15% reduction) in the 72 hour period after dose administration. In phase 1 individual animal body weights had returned to pre-dosing levels with exception of one female. Phase 2 animals were sacrificed on or before 48 hours post dose administration; so while body weight loss observed was similar to that seen during Phase 1, the experimental duration of Phase 2, 48 hours, wasn't long enough to observe a similar recovery to the pre-dose body weight.

As indicated by the total silicon analysis of plasma from treated male and female mice DMSD and/or a derivative was systemically absorbed. The individual animal variation was such that the kinetics of absorption could not be definitively determined using this method of analysis.

There were no visible lesions noted at necropsy in any of the animals surviving to its scheduled necropsy. One female was observed to be thin with no food in the stomach.

Under the conditions of this study, the highest dose to induce signs of toxicity, but not test article related mortality within three days after administration, was 2000 mg/kg body weight. The test article or derivative was considered to be absorbed and systemically available following a single oral administration.

Discussion

DMSD is not a commercially available product. However, it has been shown that hexamethyldisiloxane (HMDS), octamethylcyclotetrasiloxane (D_4), and decamethylcyclopentasiloxane (D_5) can be metabolized by animals to DMSD, and studies in humans with D_4 and D_5 have confirmed a similar metabolic pathway as seen in the animal studies. These parent materials have been extensively studied and any effects associated with the parent materials and/or the metabolites including DMSD would have been assessed in these studies; however the findings reported in this letter on DMSD were not seen in the above referenced studies of the parent materials.

Actions

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

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, Ph.D.
Director, Health and Environmental Sciences
(989) 496-8046