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Via Certified Mail



May 11, 2012

TSCA Confidential Business Information Center (7407M)
EPA East – Room 6428
Attn: Section 8(e)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001



Re: TSCA Section 8(e) Notification of Substantial Risk: 1,3-Diethenyl-1,1,3,3-Tetramethyldisiloxane (CAS No. 2627-95-4)

Dear TSCA Section 8(e) Coordinator:

In accordance with the provisions of Section 8(e) of the Toxic Substances 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, the Silicones Environmental, Health and Safety Council (SEHSC)¹ submits, on behalf of its member companies, information concerning a study with 1,3-Diethenyl-1,1,3,3-Tetramethyldisiloxane (CAS No. 2627-95-4). Neither SEHSC, nor any member company, has made a determination at this time that any significant risk of injury to human health or the environment is presented by these findings.

Chemical Substance

1,3-Diethenyl-1,1,3,3-Tetramethyldisiloxane (CAS No. 2627-95-4)

Study Title

Draft report: A Combined 28-Day Repeated Dose Oral (Gavage) Toxicity Study with the Reproduction/Developmental Toxicity Screening Test of 1,3-Diethenyl-1,1,3,3-Tetramethyldisiloxane (CAS No. 2627-95-4) in Rats Including a 14-Day Recovery

¹ SEHSC is a not-for-profit trade association whose mission is to promote the safe use of silicones through product stewardship and environmental, health, and safety research. The Council is comprised of North American silicone chemical producers and importers.

CONTAINS NO CBI

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Summary

An OECD guideline 422 study was conducted with 1,3-Diethenyl-1,1,3,3-Tetramethyldisiloxane (the test substance, CAS No. 2627-95-4) at dose concentrations of 50, 150, and 600 mg/kg body weight/day. Based on the effects on body weights and food consumption, adverse serum chemistry alterations, adverse changes in organ weights, adverse histopathology of the liver for males at 600 mg/kg body weight/day and females at 150 and 600 mg/kg body weight/day, and adverse histopathology of the kidney for males in all dose groups, a no-observed-adverse-effect level (NOAEL) for male systemic toxicity could not be determined and the NOAEL for female systemic toxicity was considered 50 mg/kg body weight/day. A dosage level of 150 mg/kg body weight/day was considered to be the NOAEL for reproductive toxicity of the test substance. A test substance-related reduction in the mean number of implantation sites was noted for reproductive phase females in the 600 mg/kg of body weight/day group. The mean numbers of pups born and live litter size in this group were lower (not statistically significant) than the control group. There were no effects on functional reproductive performance. The NOAEL for neonatal toxicity was 150 mg/kg body weight/day based on the effects on postnatal survival and pup body weights in the 600 mg/kg body weight/day group.

Details

Study Design

The test substance was administered orally by gavage in corn oil vehicle once daily to 3 groups of Crl:CD(SD) rats. Dosage levels were 50, 150, and 600 mg/kg body weight/day. A concurrent control group received the corn oil vehicle on a comparable regimen. Ten males/group selected for pairing were administered the test substance for 14 days prior to mating through 1 day prior to euthanasia for a total of 31 doses. Ten females/group in the toxicology phase were dosed beginning on study day 0 for a total of 34 doses; the dosing period was extended to accommodate behavioral testing for these females. In addition, 10 females/group selected for pairing (reproductive phase) were dosed for 14 days prior to mating, throughout mating, and continuing through lactation day 3 for a total of 39 to 47 doses. Females that failed to deliver were dosed through the day prior to euthanasia (post-cohabitation day 25 or post-mating day 25) for a total of 40 or 52 doses; females with total litter loss received 38 or 40 doses. An additional 10 males (not selected for mating) and 10 toxicology phase females in the control and high-dose groups were assigned to recovery groups, and were treated on study days 0 through 28 (males) or 31 (females), followed by 14 days without treatment with vehicle or test substance.

Results

All animals survived to their scheduled euthanasia. Clinical findings noted in the test substance treated groups included clear material around the mouth in the 150 and 600 mg/kg body weight/day groups, red material around the mouth for the 600 mg/kg body weight/day group (approximately 1 hour following dose administration), and salivation prior to dosing for females in the 600 mg/kg body weight/day group. These findings were considered test substance-related.

Test substance-related mean body weight losses or reduced mean body weight gains were generally noted for males and toxicology phase females in the 600 mg/kg body weight/day group throughout the treatment period, resulting in reductions in mean body weights. Mean body weights, body weight gains, and food consumption were unaffected by test substance administration for males and toxicology

phase females in the 50 and 150 mg/kg body weight/day groups throughout the study, for toxicology phase females in the 600 mg/kg body weight/day group during the post-treatment period, and for reproductive phase females at all dosage levels throughout the study.

Test substance-related increases in mean cumulative total and ambulatory counts were noted for males in the 600 mg/kg body weight/day group. No test substance-related effects were noted on locomotor activity for males at 50 and 150 mg/kg body weight/day or toxicology phase females at all dosage levels or on Functional Observational Battery (FOB) parameters for males and toxicology phase females at all dosage levels.

A test substance-related reduction in the mean number of implantation sites was noted for reproductive phase females in the 600 mg/kg body weight/day group. The mean numbers of pups born and live litter size in this group were lower (not statistically significant) than the control group. Two test substance-related total litter losses were noted in the 600 mg/kg body weight/day group. As a result, lower postnatal survival was noted during the postnatal period and an increased number of pups found dead and missing were noted in this group. In addition, clinical findings of cool body were noted for pups in this group. Slightly lower (not statistically significant) mean pup birth weights and body weight gains during PND 1-4 resulted in lower mean male and female pup body weights in the 600 mg/kg body weight/day group; these results were considered test substance-related and adverse.

Test substance-related alterations in hematology parameters in the 600 mg/kg body weight/day group were considered non-adverse. Hematology parameters were unaffected for males and toxicology phase females in the 50 and 150 mg/kg body weight/day groups.

Serum chemistry changes were noted only in the 600 mg/kg body weight/day group at the primary necropsy and included higher mean cholesterol and GGT for males and toxicology phase females, higher mean bilirubin, ALT, and AST for males, and higher globulin and total protein for toxicology phase females. Alterations in bilirubin, ALT, AST, and GGT were associated with absolute and relative liver weight changes and microscopic changes in the liver and were considered adverse. At the recovery necropsy, no test substance-related serum chemistry changes were noted.

Test substance-related organ weight alteration at the primary necropsy included higher absolute and relative (to final body weight and brain weight) liver weights for males (all treatment groups) and females in the 150 and 600 mg/kg body weight/day groups and lower absolute and relative to brain weight adrenal gland weights for males in the 600 mg/kg body weight/day group. At the recovery necropsy, test substance-related increases in mean absolute and relative (to body weight and brain weight) liver weights persisted in the males and females in the 600 mg/kg body weight/day group. Test substance-related macroscopic findings were limited to pale kidneys for 1 male in the 600 mg/kg body weight/day group; this finding corresponded to microscopic findings of hyaline droplet nephropathy for this male.

Bile duct hyperplasia, peribiliary fibrosis, and brown pigment in the bile duct were noted microscopically for males and toxicology phase females in the 600 mg/kg body weight/day group at the primary necropsy; bile duct hyperplasia was also noted for females in the 150 mg/kg body weight/day group at the primary necropsy. These findings corresponded to higher mean absolute and relative liver weights and higher mean bilirubin, ALT, AST, and/or GGT levels noted for males and toxicology phase females in the 600 mg/kg body weight/day group at the primary necropsy and were considered adverse in the 600 mg/kg body weight/day group males and the 150 and 600 mg/kg body weight/day group females.

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Examination of the brown pigment by polarized light revealed red birefringence with "Maltese cross" formation, consistent with porphyrin pigment. These microscopic and organ weight changes persisted at the recovery necropsy with similar incidence and severity in the 600 mg/kg body weight/day group males. In addition, hepatocellular hypertrophy was noted in the liver of males and toxicology phase females in all treatment groups at the primary necropsy; this finding was considered non-adverse. At the recovery necropsy, the incidence and severity of the hypertrophy was decreased when compared to the primary necropsy, indicating a trend toward recovery.

Microscopic findings of hyaline droplets (non-adverse) were noted in the kidney for males at all dosage levels at the primary necropsy. This finding progressed to hyaline droplet nephropathy (adverse) at all dosage levels. Immunohistochemistry for alpha-2u globulins was negative. The hyaline droplet nephropathy persisted at the recovery necropsy. Adrenal cortical atrophy and cytoplasmic vacuolation of the pituitary were noted for males at all dosage levels at the primary necropsy; these findings were considered non-adverse. The adrenal cortical atrophy corresponded to lower absolute and relative adrenal gland weights for males in the 600 mg/kg body weight/day group at the primary necropsy. The cytoplasmic vacuolation observed in the pituitary at the primary necropsy was observed at the recovery necropsy with decreased incidence and severity, indicating a trend toward recovery. Adrenal cortical changes were not observed at the recovery necropsy.

Based on the effects on body weights and food consumption, adverse serum chemistry alterations, adverse changes in organ weights, adverse histopathology of the liver for males at 600 mg/kg body weight/day and females at 150 and 600 mg/kg body weight/day, and adverse histopathology of the kidney for males at all dose levels, a NOAEL for male systemic toxicity could not be determined and the NOAEL for female systemic toxicity was considered 50 mg/kg body weight/day. The NOAEL for reproductive toxicity of the test substance when administered orally by gavage to CrI:CD(SD) rats was 150 mg/kg body weight/day. A test substance-related reduction in the mean number of implantation sites was noted for reproductive phase females in the 600 mg/kg of body weight/day group. The mean numbers of pups born and live litter size in this group were lower (not statistically significant) than the control group. There were no effects on functional reproductive performance. The NOAEL for neonatal toxicity was 150 mg/kg body weight/day based on the effects on postnatal survival and pup body weights in the 600 mg/kg body weight/day group.

Action

A copy of the final report "A Combined 28-Day Repeated Dose Oral (Gavage) Toxicity Study with the Reproduction/Developmental Toxicity Screening Test of 1,3-Diethenyl-1,1,3,3-Tetramethyldisiloxane (CAS No. 2627-95-4) in Rats Including a 14-Day Recovery" will be provided when it is available.

If you have any questions concerning this submission, please contact me at (703) 788-6570, kthomas@sehsc.com, or at the address provided herein.

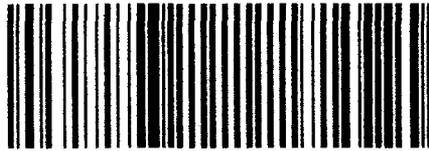
Sincerely,

Karluss Thomas
Executive Director

SEHSC

2201 Cooperative Way
Suite 600
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CERTIFIED MAIL™



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