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SILICONES ENVIRONMENTAL, HEALTH AND SAFETY COUNCIL NORTH AMERICA

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April 22, 2011

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

Re: TSCA Section 8(e) Notification: 2,4,6,8-Tetramethylcyclotetrasiloxane (CAS No. 2370-88-9)

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, the Silicones Environmental, Health and Safety Council (SEHSC)[1] submits, on behalf of its member companies, preliminary information concerning an ongoing study with 2,4,6,8-Tetramethylcyclotetrasiloxane (CAS No. 2370-88-9). 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
2,4,6,8-Tetramethylcyclotetrasiloxane (CAS No. 2370-88-9)

Study Title
Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test in the Wistar Han Rat.

Summary
Preliminary results from a Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test in the Wistar Han Rat are summarized as follows. Macroscopic observations in male animals show a dose related and statistically significant increased incidence of stones in the urinary bladder with an incidence of 0, 0, 40 and 60% for 0, 100, 1000, 2000/3000 ppm, respectively. Stones were also present in females at an incidence of 0, 0, 10, and 30% for 0, 100, 1000, 2000/3000 ppm, respectively; however, the incidence was not statistically significant. Microscopic findings in the kidney and urinary bladder were consistent with these

[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

observations. Pyelitis (9/10 animals) and urothelial hyperplasia (9/10) in kidney and transitional cell hyperplasia (10/10) in the urinary bladder were noted in males at the high dose level. Pyelitis (5/9 animals) and urothelial hyperplasia (4/9) in kidney and transitional cell hyperplasia (4/9) in the urinary bladder were observed in high dose females. None of these microscopic findings were noted in controls.

A reduction (17 – 20%) in group mean implantations and live litter size was observed at the high dose level, although these findings were not statistically significant when compared to control values.

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 preliminary findings.

Study Design

An inhalation OECD 422 combined repeated dose toxicity study with a reproductive/developmental toxicity screening test in Wistar Han rats was conducted with 2,4,6,8,-tetramethylcyclotetrasiloxane at exposure concentrations of 0, 100, 1000 and 2000/3000 ppm. It should be noted that the highest exposure concentration was 3000 ppm through day 11 of the study and then reduced to 2000 ppm for the remainder of the study. The decision to reduce the highest exposure concentration took place in response to early deaths involving 4 animals (3 females and 1 male). This decision was taken with the knowledge that there was the potential that 11 days of treatment at a dose level exceeding the Maximum Tolerated Dose (MTD) could have an impact on the study's final findings, particularly with respect to potential litter or pup effects. It is not possible to distinguish effects caused by exceeding the MTD from those effects that may or may not have occurred had the dose levels all been at or below the MTD. There were 10 animals/sex/group for the P generation portion of the study in which animals were exposed for 28 days and 7 weeks for males and females, respectively. The recovery group animals, 10/sex/group, were exposed for 40 days to 0 and 2000/3000 ppm followed by a 2 week recovery period.

Preliminary Results

Mortality

A total of seven animals (5 females and 2 males), all from the high dose group, were found dead during the study. In P generation animals at the high dose level, three females were found dead, one each on days 4, 11, and 14 of the pre-pairing period and one female was found dead on day 5 of gestation. In recovery groups at the high dose level, two males and one female were found dead on days 3, 8, and 29 of treatment, respectively. All remaining animals survived until scheduled necropsy. Three females at the high dose level, which died before initiation of pairing with males, were replaced with three females from the recovery group, to achieve 10 animals in the high dose P generation group.

Clinical Signs

No test item related findings were observed during the daily clinical or weekly detailed examination at any dose level except in animals of the high dose groups where clinical observations of ruffled fur, and decreased activity were observed. These were almost exclusively related to early death animals.

Functional Observational Battery and Locomotor Activity

No changes which would indicate test item effects were observed during FOB testing or measurement of the locomotor activity in P generation male and female groups.

Food Consumption and Body Weights

Males - Food Consumption

In male P generation groups, reduced food consumption was observed at the high- and mid-dose levels during most of the pre-pairing period (Days 1-14). Food consumption for the 1000 ppm group was reduced 15-17% with statistical significance. Food consumption for the 2000/3000 ppm group was reduced 22-28% with statistical significance.

Food consumption for recovery group males, high dose level, were reduced during Days 1-8, 9-15 and 15-22, by 30, 12 and 14%, respectively, with statistical significance. No statistical differences in food consumption between controls and the recovery high dose level group was observed from Study Day 22 through 40 and during the recovery period that followed from days 1-14.

No statistically significant differences were observed for males at the lower dose levels.

Males - Body Weights

Body weights were lower than control values during the pre-pairing period by ~10% in the high dose group and also reduced in the pairing period by ~ 9-10%, with statistical significance during both periods. Body weight gains at pre-pairing Day 14 were 13% and 5% for the control and high dose groups, respectively; the difference was statistically significant. During the pairing period body weight gains in the high dose group were similar to controls and not statistically different.

Body weights of males in the high dose recovery group were decreased by ~6% on Study Days 8, 15 and 22, with statistical significance. From Study Days 29-40 (treatment) and 14 days of recovery, body weights were reduced; however the reduction, ~2%, was not statistically significant.

No statistically significant differences were observed for males at the lower dose levels.

Females - Food Consumption

In females of the P generation group, food consumption was reduced with statistical significance at the high dose level during the pre-pairing period; Days 1-5, 5-8, and 8-12 with reductions of 34%, 21% and 17%, respectively. During the gestation and lactation periods, food consumption was not reduced at a statistically significant level; however, food consumption was always lower than for controls.

Food consumption for recovery group females in the high dose was reduced during Days 1-8, 8-15, by 24% and 14%, respectively, with statistical significance. There were no statistical differences in food consumption between controls and the recovery high dose level from Study Day 15 through 40 and during the recovery period that followed from days 1-14.

No statistically significant differences were observed for females at the lower dose levels.

Females – Body Weights

At the high dose level in the P generation, statistically significantly lower body weights were noted on day 5 of the pre-pairing period, 7%. After Study Day 5, body weights were not statistically significantly different from the respective control values. Body weight gain at the high dose level was not statistically significantly reduced during the pre-pairing, gestation and lactation periods.

Body weights of females in the high dose recovery group were decreased by ~4% on Study Day 40, with statistical significance and again on Day 8 of the recovery period by the same percentage. On the

fourteenth day of recovery body weights were lower than control group values without statistical significance.

No statistically significant differences were observed for females at the lower dose levels.

Terminal Findings

Organ Weights - Males

At the high dose level in P generation males, terminal body weight was decreased by 9.5% which was statistically significant when compared to controls. A statistically significant 14% increase in relative kidney weights was noted in males. In males of the recovery group, at the high dose level, relative kidneys weights were increased by 11% with statistical significance.

Macroscopic Observations - Males

Macroscopic observations in high-dose male animals, P generation, (scheduled necropsy) show that the presence of stones is statistically significant in the urinary bladder with an incidence of 0, 0, 40 and 60% for the animals in the 0, 100, 1000, 2000/3000 ppm dose groups, respectively.

Stones were also present in the urinary bladder of recovery group males at an incidence of 60% with statistical significance. Urinary bladder stones were not present in the control recovery group.

Macroscopic Observations - Females

Stones were also present in high dose and mid-dose females, P generation, (scheduled necropsy) at an incidence of 30 and 10%; respectively; however, the incidence was not statistically significant.

Stones were also present in the urinary bladder of recovery group females at the high dose at an incidence of 43% without statistical significance (3/7 animals). No stones were observed in the urinary bladder of respective controls.

In Progress

Preliminary histopathological and clinical chemistry evaluations are in progress. Consistent with the observations of stones in urinary bladders, microscopic findings in the kidney and urinary bladder were noted in high dose group male and female animals.

In males at the high dose level, the following key findings were noted in the kidney: pyelitis (9/10 animals), urothelial hyperplasia (9/10), urothelial ulcer/erosion (8/10), pelvic dilation (8/10), granular deposits (10/10) and hyaline droplets (7/10). The following key findings were noted in the urinary bladder: transitional cell hyperplasia (10/10), inflammation/mucosal, submucoscal (6/10), and granular deposits (4/10). None of these findings were noted in control males, except in the case of the hyaline droplets where this observation was noted in 4/10 control animals.

In females at the high dose level, the following key findings were noted in the kidney: pyelitis (5/9 animals), urothelial hyperplasia (4/9), urothelial ulcer/erosion (2/9), pelvic dilation (1/9), and granular deposits (4/9). The following key findings were noted in the urinary bladder: transitional cell hyperplasia (4/9), and inflammation/mucosal, submucoscal (1/9). None of these findings were noted in control females.

Reproduction and Breeding

With the exception of three females (one each at the low, mid- and high dose level), all females mated within seven days of the pairing period and no effects on mating performance were apparent. As noted

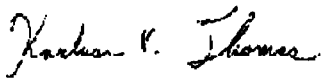
previously, one female in the high dose group died on gestational day 5, therefore there were only 8 litters in the high dose level group.

A reduction in group mean implantations per dam was observed at the high dose level. The number of implantations per dam decreased by 17% in the high dose group compared to controls. The mean number of implantations per litter was 12.7, 13.2, 12.9 and 10.5 in the 0, 100, 1000, 2000/3000 ppm dose groups, respectively. Correlating with the decrease in implantations was a lower mean number of pups/litter at first litter check (mean live litter size). The mean live litter size was 11.8, 12.2, 11.4 and 9.5, for the following exposure groups: 0, 100, 1000, 2000/3000 ppm, respectively. These findings were not statistically significant when compared to control values. No pup mortality was noted during the four days of lactation. At the high dose level, body weights of pups at birth and during the lactation period were statistically significantly higher when compared to the control groups. In males on day 1, mean pup body weight was increased 15% and in females mean pup body weights were 12% greater than controls.

Actions

SEHSC will provide EPA with a copy of the final report 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

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