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SEHQ-0605-16065

June 17, 2005



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 20460

CONTAIN NO CBI

Re: TSCA Section 8(e) Notification of Substantial Risk: 3-(Triethoxysilyl)-propanenitrile:  
A Combined 28-Day Repeated Oral (Gavage) Toxicity Study with the Reproduction/  
Developmental Toxicity Screening Test for in Rats

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 Statement of Interpretation and Enforcement Policy (68 Federal Register 33129; June 3, 2003) and other Agency guidance, the Silicones Environmental, Health and Safety Council (SEHSC)<sup>1</sup>, on behalf of its member companies, submits the following information. 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**

919-31-3 3-(Triethoxysilyl)-propanenitrile



**Ongoing Study**

3-(Triethoxysilyl)-propanenitrile: Combined Repeated Dose Toxicity Study with the Reproduction/  
Developmental Toxicity Screening Test in the Rat. RCC Ltd., study number 851639.

<sup>1</sup> SEHSC is a not-for-profit trade association whose mission is to promote the safe use and stewardship of silicones. The Council is comprised of North American silicone chemical producers and importers. SEHSC's members include: Clariant LSM (Florida), Inc.; Degussa Corporation; Dow Corning Corporation; General Electric Silicones; Rhodia Inc.; Shin-Etsu Silicones of America; and Wacker Silicones, A Division of Wacker Chemical Corporation.

## **Summary**

Preliminary results from an ongoing study with 3-(triethoxysilyl)-propanenitrile have indicated a few differences between test animals as compared to control animals. Oral (gavage) administration of the test article in dehydrated corn oil at 1000 mg/kg/day resulted in clinical signs (in the pregnant reproductive group females only), in macroscopic renal changes (males and females), increased organ weights (kidneys, spleen, heart and liver in males; kidneys and spleen in females), and histopathological changes in kidneys (males and females) and spleen (males only).

Administration of 500 mg/kg/day resulted in increased organ weights (kidneys, heart and liver in males only) and histopathological changes in kidneys (males and females) and spleen (males only).

Administration of 100 mg/kg/day resulted in increased liver weight in males. In the absence of a histopathological correlate the increased weight was considered most probably of adaptive nature and therefore of no adverse character.

## **Details**

### **Study Design**

The objectives of this study were 1) to determine the potential of 3-(triethoxysilyl)-propanenitrile to induce toxicity when administered to rats by oral gavage for 28 days; and 2) to evaluate the potential of the test article to affect male and female reproductive performance, including gonadal function, mating behavior, conception, parturition and early postnatal development.

Four groups of male and female HanBrl:WIST (SPF) rats (10/sex/group) were administered 3-(triethoxysilyl)-propanenitrile, in the dehydrated corn oil vehicle, daily by oral gavage for 28 days. Dose levels were 0, 100, 500, and 1000 mg/kg/day for the males, unmated females (toxicity phase) and mated females (reproductive phase). A standard dose volume of two (2) mL/kg body weight, with a daily adjustment based on the actual body weight, was used. Control animals were dosed with the vehicle alone.

The males were treated daily beginning 14 days prior to mating. Treatment continued throughout mating. Additionally, the four groups of female rats which were mated with the treated males were also administered the test article by oral gavage daily for a minimum of 14 days prior to mating, throughout mating and gestation and continuing until lactation day three (3).

All animals were observed twice daily for mortalities. Clinical observations, body weights and food consumption were recorded at appropriate intervals. In addition, detailed clinical observations [locomotor activity and functional observational battery (FOB)] were conducted out of the home cage on all adult male and toxicity phase females once prior to the start of test article administration (baseline evaluations) and again during the last week of the test article administration. Males and toxicity group females were sacrificed after they had been treated for 28 days.

Clinical pathology assessments (hematology and serum chemistry) and macroscopic and microscopic examinations (including organ weights) were also performed on the appropriate groups of adult males and toxicity phase females. All reproductive phase females were allowed to deliver and rear their

offspring to lactation day 4; surviving dams and pups were euthanized and examined on lactation day 4.

## **Preliminary Results**

### ***Adult animals -***

#### General tolerability

No test item-related mortalities were noted throughout the study. Commencing around day 14 of gestation and for the duration of the remaining treatment period, all females of the high dose reproductive group treated at 1000 mg/kg/day, showed signs of discomfort after administration of the test item (pushing head through bedding material). During this period, stretched forelimbs were noted after administration on a single, or a few, day(s) in six females. For four (4) females, saltatory spasms were noted after administration of the test item on one or a few days. These clinical signs were considered to be test item related.

#### Functional Observational Battery (FOB)

None of the parameters under investigation during the functional observational battery gave any indication of test item-related effects.

#### Body Weight

Body weight development was unaffected by treatment with test item at any dosage.

#### Food Consumption

Food consumption was unaffected by treatment with test item at any dosage.

#### Reproduction data

The fertility rate was high resulting in at least 9 litters per group for evaluation of reproduction data. There were no treatment-related effects on precoital time, fertility indices, mean duration of gestation, number of implantations, post-implantation loss, pup survival or litter size from birth to scheduled sacrifice on day 4 post partum at any dosage.

#### Clinical Laboratory Investigations

The assessment of clinical laboratory data was generally unremarkable.

#### Terminal Examinations

At 1000 mg/kg/day, macroscopic renal changes were noted for three males and a thickened liver was noted for one male. At 1000 mg/kg/day, macroscopic renal changes were noted for three toxicity group females. These renal findings were considered to be test item related since they correlated with histopathological findings.

### Organ Weights - Males

Increased absolute and/or relative organs weight were noted for the following organs: heart (500 and 1000 mg/kg/day), liver (100, 500 and 1000 mg/kg/day), kidneys (500 and 1000 mg/kg/day) and spleen (1000 mg/kg/day). The changes, in the kidneys and spleen weights correlated with histopathological findings, below. The changes in the heart weights were without a histopathological corollary. Changes in the liver weights are most probably reflective of adaptive change due to treatment and are of no adverse character.

### Organ Weights - Females

At 1000 mg/kg/day, increased absolute and/or relative organs weight were noted for the following organs: kidneys and spleen. These findings, for the kidney correlated with the findings at histopathological examination, where severe renal changes were noted.

### Histopathological Examination - Males and Females

The main target organ was the kidney. Chronic tubular lesion of minimal to moderate severity was observed in animals of both sexes. This diagnosis was made for both the 500 and 1000 mg/kg/day dose groups, as 6/10 male and 3/10 female animals and 8/10 male and 8/10 female animals, respectively, were observed to have this finding. This correlated with macroscopic renal discoloration and foci and increased kidney weights recorded at necropsy. As evident from the data, males were more severely affected than females. Hyperplasia of transitional cell epithelium of the renal pelvis was seen at 500 and 1000 mg/kg/day in both sexes, mostly in conjunction with chronic tubular lesions. This effect was recorded in 8/10 male and 5/10 female animals and 5/10 male and 6/10 female animals in the 500 and 1000 mg/kg/day groups respectively. Further, minimal to slight acute renal pyelonephritis, always in conjunction with the chronic tubular lesions, was observed in 3/10 male animals from the 500 mg/kg/day group, while 2/10 male and 3/10 female animals from the 1000 mg/kg/day group were observed to have this finding. Extramedullary hematopoiesis in the spleen was observed in slightly increased incidence and severity in males of the 1000 mg/kg/day group corresponding to an increase organ weight. Seven of 10 (mean grade 1.6) males were affected versus 3/10 (mean grade 1.3) males in the control group (4/10 males in the 100 mg/kg/day and 3/10 males in the 500 mg/kg/day groups). This finding is considered to be a secondary effect, where chronic kidney injury with inflammation may have enhanced the hematopoietic activity in the affected rats.

No test item-related histopathological findings were noted in the reproductive organs of either sex. In particular, the assessment of the integrity of the spermatogenic cycle did not reveal any evidence of impaired spermatogenesis.

### ***Litter data -***

No abnormal findings were noted for pups at first litter check or during the first 4 days post partum. Sex ratios at first litter check and on day 4 post partum were unaffected by treatment with the test item. Mean pup weights on day 0 and day 1 post partum were unaffected by treatment with the test item. Mean pup weight development during the first 4 days post partum lactation was unaffected by treatment with the test item.

F1 Pups, Necropsy Findings

No macroscopic findings were noted during necropsy of F1 pups.

Actions

SEHSC will notify EPA of any further relevant information that may be developed concerning this material. SEHSC also will provide EPA with the copy of the final report containing these study results when it is available. If you have any questions concerning this study, please contact me at (703) 904-4322, [rmanning@sehsc.com](mailto:rmanning@sehsc.com), or at the address provided herein.

Sincerely,

  
Reo Menning  
Executive Director