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EPA East – Room 6428
(Attn: TSCA Section 8(e) Coordinator)
U.S. Environmental Protection Agency
1201 Constitution Avenue, NW
Washington, DC 20004-3302

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Re: []; TSCA Section 8(e) Submission for Substance with TSCA Confidential Inventory Accession Number 86921

Dear Sir or Madam:

[] hereby submits to the U.S. Environmental Protection Agency (EPA) under section 8(e) of the Toxic Substances Control Act (TSCA) information regarding a draft report received on January 25, 2016 for a Reproduction/Developmental Toxicity Screening Test by the Oral Route (Gavage) in rats using the substance [], listed on the confidential TSCA Inventory with accession number 86921 (“ACCN 86921”).

[] performed a Reproduction/Developmental Toxicity Screening Test using the substance [] when administered to Sprague-Dawley rats. The study was carried out based on the guidelines described in OECD Guideline No. 421, “Reproduction/Developmental Toxicity Screening Test“, 27 July 1995.

Three groups of ten male and ten female Sprague-Dawley rats received the test item daily, by oral administration (gavage), 2 weeks before mating, during mating and, for the males, until sacrifice, for the females, throughout gestation until Day 4 *postpartum* (*p.p.*) at dose-levels of 25, 50 or 100/80 mg/kg/day (due to deaths at 100 mg/kg during the first 2 weeks of the treatment period, this high dose-level was lowered to 80 mg/kg/day). An additional group of ten

males and ten females received the vehicle control, drinking water, under the same experimental conditions. The dosing volume was 10 mL/kg/day.

Animals were checked daily for clinical signs and mortality. Body weights and food consumption were recorded weekly until mating and then at designated intervals throughout gestation and lactation.

The animals were paired for mating after 2 weeks of treatment and the dams were allowed to litter and rear their progeny until Day 5 *p.p.*. The total litter sizes and numbers of pups of each sex were recorded after birth. The pups were observed daily for clinical signs of toxicity and pup body weights were recorded on Days 1 and 5 *p.p.*.

The males were sacrificed after completion of the mating period. Dams were sacrificed on Day 5 *p.p.*. Body weights and selected organs weights were recorded and a complete macroscopic *post-mortem* examination performed, with particular attention paid to the reproductive organs.

Microscopic examination was performed on the reproductive organs from control, mid- and high-dose males and females at terminal sacrifice and from premature decedents, and on all macroscopic observations in all groups.

Pups, including those found dead before study termination, were also submitted for a macroscopic *post-mortem* examination.

Results

Mortality: Test item treatment-related deaths were recorded in 2/10 males and 8/10 females from the 100/80 mg/kg/day group. Before sacrifice for ethical reason or in the found dead rats, piloerection, round back, hypoactivity, abdominal breathing, dyspnea, ptyalism, half closed eyes and/or chromorhinorrhea, chromodacryorrhea, locomotory difficulty, and being cold to the touch were observed in most animals. Changes were observed in the lungs, spleen, stomach, ileum, cecum and/or vagina and these findings were considered to be agonal and/or to have contributed to the death or the moribund status of these animals, but the cause of death could not be ascertained.

Clinical signs: In 100/80 mg/kg/day group, piloerection, cold to the touch, hypoactivity, round back and half closed eyes were considered to be test item treatment-related and adverse. In the 50 mg/kg/day group, round back was considered to be test item treatment-related and adverse. Ptyalism was considered to be related to the treatment with the test item, but of minor toxicological significance.

Mating and fertility data: When compared with control, there was a lower fertility index at 100/80 mg/kg/day. At this dose-level, the fertility index was below the lower limit of the Historical Control Data. Therefore this finding was considered to be test item treatment-related and toxicologically significant.

Gestation and delivery data: At 100/80 mg/kg/day, the severe incidence of mortality and the limited number of dams makes hazardous any comparison with the control group and Historical Control Data. At 50 mg/kg/day and when compared with controls, there was a low mean number of pups delivered at birth (10.9 vs. 14.0, $p < 0.05$). At this dose-level the mean

number of pups delivered was also below the lower limit of the Historical Control Data. This finding was considered to be related to the test item treatment and adverse.

Pups mortality: at 100/80 mg/kg/day and when compared with controls there was a marked increase in the number of found dead, moribund and cannibalized pups as well as in the incidence of litters affected (5/6 vs. 3/10). These findings were considered to be test item treatment-related and adverse.

Pups clinical signs and external abnormalities: at 100/80 mg/kg/day and when compared with controls there was a marked increase in pups cold to the touch and with a few milk in the stomach as well as in the incidence of litters affected (3/6 vs. 2/10). These findings were considered to be the consequence of abnormal maternal behavior to be test item treatment-related and adverse. No external abnormalities were observed.

Conclusion

The test item was administered daily by oral gavage to male and female Sprague-Dawley rats, for 2 weeks before mating, during mating, and until sacrifice (for males) or throughout gestation and until Day 4 *post-partum* (for females), at dose-levels of 25, 50 or 100/80 mg/kg/day.

Based on the experimental conditions of this study:

. the No Observed Adverse Effect Level (NOAEL) for parental toxicity was considered to be 25 mg/kg/day (based on clinical signs from 50 mg/kg/day and, mortality in both sexes at 100/80 mg/kg/day),

. the NOAEL for reproductive performance (mating, fertility and delivery data) was considered to be 25 mg/kg/day (based on the lower number of pups delivered from 50 mg/kg/day),

. the NOAEL for toxic effects on progeny was considered to be 50 mg/kg/day (based on the low pup viability at 100/80 mg/kg/day).

Any material differences in the final study report from the information included in this submission will be provided in a follow-up submission.

If you have any questions regarding this submission, please do not hesitate to contact [] at [] or [].

Sincerely,

[]
[]

Enclosures: Attachment 1 - CBI Substantiation (CBI)