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for Health and Environmental Sciences
1090 Elkton Road, P.O. Box 50
Newark, DE 19714-0050

January 18, 2011

Via Federal Express

8EHQ-06-16436

Document Processing Center (Mail Code 7407M)
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Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Ave., NW
Washington, DC 20004

8911000000070

11 JAN 19 AM 10:58

Dear 8(e) Coordinator:

8EHQ-06-16436/8EHQ-06-16478
2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propionic acid, ammonium salt
CAS # 62037-80-3

This letter is a supplement to our letter of July 15, 2010 and summarizes the final results of a reproduction/developmental toxicity screening study in mice with the above referenced test substance. This test substance is subject to a Consent Order, P-08-509.

The test substance was administered once daily via oral gavage to groups of F_0 mice (CD-1; 25 per sex per dose group) at doses of 0 (deionized water), 0.1, 0.5, or 5 mg/kg/day at a dose volume of 10 ml/kg/day. Male mice (F_0) were dosed for a minimum of 70 days prior to mating and continued until the day of scheduled euthanasia. Female mice (F_0) were dosed for a minimum of 14 days prior to mating and continued throughout mating, gestation, and lactation until the day of scheduled euthanasia following weaning of offspring. For females that did not have positive signs of mating or delivery, dosing continued until the day of euthanasia. F_1 males and females were dosed beginning in postnatal day (PND) 21 until the day of euthanasia. Clinical signs, body weights, and food consumption were recorded throughout the study. At scheduled euthanasia, all animals underwent a gross external and internal examination; selected organs/tissues were weighed and/or retained for histopathologic examination. Reproductive performance was assessed by gonadal function, mating behavior, conception, parturition and lactation of the F_0 generation and the development of offspring from conception through day 40 of postnatal life. Developmental landmark data (vaginal patency and balanopreputial separation) were collected for F_1 offspring. Plasma samples for toxicokinetic analyses were collected from culled pups and pooled by litter on PND 4. Plasma samples for toxicokinetic analyses were also prepared from a terminal bleed for F_0 females, weanlings that were not selected for developmental landmarks (PND 21), and weanlings designated for developmental landmarks (PND 40).

F_0 and F_1 survival were unaffected by test substance administration at all dosage levels. Test substance-related, but non-adverse increases in body weights/gains and food consumption were observed in F_0 males and females at 5 and 0.5 mg/kg/day. Test substance-related lower mean body weights and body weight gains were noted for F_1 males and females in the 5 mg/kg/day group throughout the pre-weaning period. Mean body weights in the 5 mg/kg/day females were similar to the control group by PND 35 and the differences in body weights observed in the males were progressively less from PND 21-40. There were no test substance-related body weight or body weight gain differences from the control group in F_1 males and females in the 0.1 and 0.5 mg/kg/day groups.

Delays in the attainment of balanopreputial separation and vaginal patency were noted in the F_1 males and females in the 5 mg/kg/day group when compared to the control group. However, these delays were attributed to the effects on mean body weight noted in this group during the pre-weaning period and not considered to be a direct effect of

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test substance administration. No test substance-related effects were observed on F_0 reproductive performance (mating, fertility, or copulation indices, and mean days between pairing and coitus), mean gestation length, the process of parturition, mean numbers of implantation sites, or unaccounted-for sites. Mean numbers of F_1 pups born, live litter size, percentage of males at birth, postnatal survival, and the general physical condition of the F_1 pups were unaffected by test substance administration at all dosage levels.

A slight increase in the incidence of gross white areas in liver in the 5 mg/kg/day F_0 females correlated with microscopic focal necrosis. There were no test substance-related gross findings in the F_0 males and females in the 0.1 and 0.5 mg/kg/day groups or in the F_0 males in the 5 mg/kg/day group. F_1 necropsy findings did not indicate any correlation to test substance administration.

Microscopic examination of the reproductive organs of both males and females revealed no test substance-related effects at any dose level tested. Microscopically, minimal to moderate hepatocellular hypertrophy was present in both sexes of F_0 adults at dose levels of 0.5 and 5 mg/kg/day. A corresponding increase in liver weight parameters was observed at both dose levels. Hepatocellular hypertrophy was characterized by cytoplasmic eosinophilic stippling that is consistent with peroxisome proliferation. In the 5 mg/kg/day F_0 males and females, other liver lesions included increases in single cell necrosis, mitotic figures, lipofuscin pigment, and focal necrosis (females only). A low incidence of single cell necrosis was also present in the 0.5 mg/kg/day male group. Microscopic examination of the kidneys of all F_0 adults revealed a minimal increase in non-adverse tubular cell hypertrophy in males given 0.5 and 5 mg/kg/day. This finding correlated with an increase in mean absolute kidney weight in both sexes given 5 mg/kg/day.

The mean maternal plasma concentrations of test substance measured two hours after dosing on day 21 of lactation were 903, 4966, and 36420 ng/ml in the 0.1, 0.5, and 5 mg/kg/day dose groups, respectively. In postnatal day 4 F_1 pups, mean plasma levels were lower (approximately 2- to 4-fold) than the lactation day 21 maternal values. In postnatal day 21 F_1 pups, mean plasma levels of test substance in all dose groups were markedly less (approximately 40- to 60-fold lower) than the respective lactation day 21 maternal values. In the F_1 offspring samples on postnatal day 40 that had been directly dosed since weaning on postnatal day 21, mean plasma levels of test substance were similar to those of the respective maternal dose groups sampled at postnatal day 21.

This information is submitted in accordance with current guidance issued by EPA indicating EPA's interpretation of Section 8(e) of the Toxic Substances Control Act or, where it is not clear that reporting criteria have been met, it is submitted as a precautionary measure and because it is information in which EPA may have an interest.

Sincerely,

S. Satheesh Anand, Ph.D., DABT
Senior Research Toxicologist

SSA/SMM: clp
(302) 366-5314

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