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

November 5, 2001

Via Federal Express



8EHQ-01-14915

Document Processing Center (7407)
Room G99 East Tower
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street SW
Washington, D.C. 20460-0001

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Dear 8(e) Coordinator:

8EHQ-01-14915

This letter is a follow-up to our August 10, 2001 letter, in which we described preliminary results of an ongoing 90-day oral gavage study with a one-generation reproduction study, conducted in rats with the above referenced test substance. The current letter contains additional results from the completed study.

Groups of 40 or 50 male and female Crl:CD®(IGS)BR rats, ~ 6-8 weeks of age at study initiation, were administered oral gavage doses of 0, 25, 100, or 500 mg/kg/day of the test substance for approximately 90 days. The rats were evaluated for body weight changes, food consumption, clinical signs of toxicity, functional observational battery (FOB) and motor activity assessments, hepatic beta-oxidation activity, clinical pathology, and gross and microscopic anatomic pathology. A subgroup of animals was evaluated in a one-generation reproduction study.

Body weight and/or nutritional parameters were statistically significantly reduced in males and females dosed with 500 mg/kg/day and in males dosed with 100 mg/kg/day. Both sexes dosed with 500 mg/kg/day demonstrated clear oral discharge (especially at the time of dosing), wet fur (chin/ perineum), stained fur or skin (multiple sites including perineum), and hair loss over multiple sites.

Male rats dosed with 500 mg/kg/day had reduced forelimb and hindlimb grip strength during the 13-week evaluation and reduced hindlimb grip strength during the 1-month recovery evaluation. These differences were associated with reduced body weight and body weight gain in this group. There were no compound-related effects on other FOB or motor activity endpoints.

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Adverse changes occurred in the red cell mass of female rats dosed with 500 mg/kg/day. Female rats dosed with 500 mg/kg/day had decreased red cell mass parameters (decreased red cell count, hemoglobin, and hematocrit). Female rats also had alterations in hematologic parameters indicating regeneration of red cells, and altered red cell shape, size, and hemoglobin content. Hematologic changes that were present at the end of dosing were generally of greater magnitude or incidence than those present at mid-study. After one month of recovery, females previously dosed with 500 mg/kg/day still had minimally decreased red cell mass, but showed some recovery. After 3 months of recovery, red cell mass was similar to controls.

Similar types of changes occurred in females dosed with 100 mg/kg/day, and in males dosed with 100 or 500 mg/kg/day, but these were not considered adverse because the magnitude of change was not expected to have an adverse impact on function of red cells.

Several other statistically significant, compound-related, but non-adverse changes occurred in hematology, clinical chemistry, coagulation, and urinalysis parameters during treatment and after 1 and 3 months of recovery.

Increased chronic progressive nephropathy, sometimes accompanied by increased kidney weight in females, was present in 500 mg/kg/day males and 100 and 500 mg/kg/day females at the 90 day sacrifice, in 500 mg/kg/day males and females at the 1-month recovery sacrifice, and in 100 and 500 mg/kg/day females at the 3-month recovery sacrifice. Hypertrophy of thyroid follicular epithelium was present in 100 and 500 mg/kg/day males and females at the 90-day sacrifice, in 500 mg/kg/day males and females at the 1-month sacrifice, and in 500 mg/kg/day males at the 3-month sacrifice. Compound-related increases in splenic extramedullary hematopoiesis were observed in 100 and 500 mg/kg/day males and females at the 90-day sacrifice and in 500 mg/kg/day males and females at the 1-month recovery sacrifice. Increased pigment was also observed in the spleen in 100 and 500 mg/kg/day males and females at the 90-day sacrifice, in 500 mg/kg/day males at the 1-month recovery sacrifice, and in 100 and 500 mg/kg/day males and females at the 3-month recovery sacrifice. In females, the splenic changes were usually associated with increases in relative spleen weight in the 100 and 500 mg/kg/day dose groups.

Liver weights were elevated in all dosed male and female groups evaluated at the 90-day sacrifice and at the 1-month recovery sacrifice. They were still elevated after 3-month recovery in 500 mg/kg/day male and female rats and in 100 mg/kg/day female rats. Minimal to mild diffuse hepatocellular hypertrophy was observed in all dosed male groups and in 100 and 500 mg/kg/day female groups at 90 days, and in 500 mg/kg/day male and female groups at the 1-month sacrifice. Increases in liver β -oxidation were observed in 100 and 500 mg/kg/day male rats after 10 days of exposure and in 500 mg/kg/day male rats after approximately 90 days of dosing and 1-month recovery.

In addition to the findings reported in our previous letter for the one-generation reproduction study, female rats exposed to all doses had a reduced fertility index (55%, 58%, and 65% of control in 25, 100, and 500 mg/kg/day groups, respectively) and increased estrus cycle length (112%, 114%, and 112% of control in 25, 100, and 500 mg/kg/day groups, respectively). Groups of male rats exposed to all doses had reduced epididymal sperm counts (88%, 91%, and 88% of control in 25, 100, and 500 mg/kg/day groups, respectively), however, the counts were within historical control ranges. Females dosed with 500 mg/kg/day also had a reduction in the number of uterine implantation sites (70% of control).

Under these experimental conditions, the findings described above appear to be reportable based upon guidance given in the EPA TSCA Section 8(e) Reporting Guide (June 1991).

Sincerely,

A handwritten signature in black ink that reads "A. Michael Kaplan". The signature is written in a cursive style with a long horizontal line extending from the end of the name.

A. Michael Kaplan, Ph.D.

Director – Regulatory Affairs

AMK/SAM:clp

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