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July 20, 2010

8EHQ-0710-16436O

Via Federal Express

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Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency, ICC Building
1201 Constitution Ave., NW
Washington, DC 20004

DCN: 89100000281

Dear 8(e) Coordinator:

8EHQ-06-16436/8EHQ-06-16478

This letter is a supplement to our letter of February 5, 2010 and summarizes the final results of a developmental toxicity study in rats with the above referenced test substance. This test substance is subject to a Consent Order, PMN P-08-509.

Groups of 22 time-mated Crl:CD(SD) rats were administered solutions of the test substance in deionized water at dose levels of 0, 10, 100, or 1000 mg/kg/day. Dosing was initiated on gestation day (GD) 6 and continued through GD 20. During the in-life portion of the study, maternal body weights and food consumption as well as clinical observations data were collected. On GD 21, dams were euthanized and underwent a gross external and internal examination. Weights for maternal livers and kidneys were recorded and these tissues were examined microscopically. The gravid uteri were removed, weighed, and dissected. Uterine contents were described and fetuses were counted, weighed, sexed, and examined for external, visceral, head, and skeletal alterations.

There was a dose-related increase in the number of dams found with early deliveries on GD 21. There were 0, 0, 4, and 9 dams found delivered at 0, 10, 100, and 1000 mg/kg/day, respectively. In addition, mean fetal weight was 8 and 28% lower (statistically significant) than controls at 100 and 1000 mg/kg/day, respectively. Maternal kidney weights were significantly higher at 1000 mg/kg/day and maternal liver weights were significantly higher at 100 and 1000 mg/kg/day. These changes were reported in the previous letter. The following is a complete summary of the study.

One female in the 1000 mg/kg/day was found dead on gestation day 20. This female had lower mean body weight gains and/or food consumption compared to the control group during gestation days 12-18. The test substance-related liver and kidney changes (moderate coagulative necrosis in the liver and fibrin thrombi in the glomerular capillaries) noted microscopically were considered the cause of death in this animal. Four and 9 females in the 100 and 1000 mg/kg/day groups, respectively, delivered early on gestation day 21. The mortality in the 1000 mg/kg/day group and early deliveries in the 100 and 1000 mg/kg/day groups were considered test substance-related. All other females survived to the scheduled necropsy.

Test substance-related clinical findings were noted in the 1000 mg/kg/day group and consisted of yellow material on various body surfaces and salivation or evidence thereof (clear material around the mouth). Mean body weight, mean body weight gain, mean food consumption, and mean gravid uterine weight in the 1000 mg/kg/day group were lower than control. At 100 mg/kg/day, mean gravid uterine weight was lower compared to control. An edematous pancreas was noted in 2 females that delivered early in the 1000 mg/kg/day group at necropsy; the relationship of this finding to the test substance is uncertain. Other macroscopic findings occurred in single females and/or are not uncommon in females that deliver. Higher mean liver weights were noted in the 100 and 1000 mg/kg/day group females, and higher mean kidney weight was observed in the 1000 mg/kg/day group. There were no microscopic correlates to the higher mean kidney weight. Focal necrosis of the liver was noted in some females in the 100 and

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1000 mg/kg/day groups in a dose-related manner. In addition, test substance-related hepatocellular hypertrophy was noted at 1000 mg/kg/day; hypertrophy was morphologically consistent with a PPARα agonist.

Mean fetal weights were 8.8% and 28.1% lower in the 100 and 1000 mg/kg/day groups, respectively. Intrauterine survival was not affected by test substance administration at any dosage level. There were no test substance-related fetal malformations. A higher mean litter proportion of 14th rudimentary ribs was observed in the 1000 mg/kg/day group, resulting in a higher mean litter proportion of total skeletal variations and total developmental variations. Although considered test substance-related, the increase in the number of fetuses with this finding was not considered adverse because it has been suggested that 14th rudimentary ribs are resorbed during postnatal development.

The no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity was considered to be 10 mg/kg/day based on mortality and lower mean body weight gains and food consumption at 1000 mg/kg/day and early deliveries, microscopic findings in the liver (focal necrosis), and lower mean fetal weights at 100 and 1000 mg/kg/day. At 1000 mg/kg/day, there were additional test substance-related effects that were not considered adverse and consisted of higher kidney and liver weights and hepatocellular hypertrophy.

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,

A. Michael Kaplan

A. Michael Kaplan, Ph.D.
Director - Regulatory Affairs

AMK/SMM: clp
(302) 366-5260

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