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October 14, 1999

Via Federal Express

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Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street SW
Washington, D.C. 20460-0001

MR 27576

Company Sanitized

Dear 8(e) Coordinator:

Hydrazinecarboxylic acid, [(2S)-5-chloro-2,3-dihydro-2-hydroxy-2-(methoxycarbonyl)-1H-inden-1-ylidene]-, phenylmethyl ester

CAS #173903-19-0

This letter is to inform you of the preliminary results of a 28-day feeding study in rats with the above referenced test substance.

Four groups (10 or 20 per group) of male and female Crl:CD[®](SD)BR rats were fed diets containing 0 (n=20), 500 (n=10), 1500 (n=10) or 4000 ppm (n=20) of the test substance. Body weight, food consumption and food efficiency parameters were determined weekly. Prior to test substance administration and then during the fourth week of treatment, functional observations and motor activity tests were also conducted. Following the 4-week neurobehavioral assessment, 10 rats from the control and high dose groups and all surviving rats from the low and middle dose groups were necropsied, and a gross examination was performed on all animals. Selected tissues were examined histologically. The remaining males and females rats in the control and 4000 ppm groups were allowed a 2-week recovery period during which neurobehavioral observations and motor activity continued. At the end of the recovery period, the remaining animals were necropsied and examined histologically.

There was a 10% reduction in survival in male rats fed 4000 ppm compared to controls. There were no treatment-related decreases in survival in female rats. Treatment-related reductions in mean body weight, food consumption and food efficiency were observed in males fed 1500 and 4000 ppm and in females at 4000 ppm. Males were affected more severely than females in each category. During recovery, body weight gain, food consumption and food efficiency in male and female rats given 4000 ppm in the diet were similar to or exceeded respective values observed in control rats.

Males and females fed diets containing 4000 ppm exhibited a constellation of behavioral changes (high arousal, exaggerated response to tail pinch, increased vocalization, changes in muscle tone, difficulty in removal from the cage and in handling) that were suggestive of hyper-responsiveness to external stimuli. In addition, 4000 ppm males had lower motor activity during the week 4 evaluation and the first week of recovery. No morphological changes were observed in nervous system tissues. It can not be determined from these data whether the tendency

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toward hyper-responsive behavior and lower motor activity are primary effects of the test substance on the nervous system or secondary to systemic toxicity.

Clinical pathology examinations at the end of the exposure period indicated that females fed 4000 ppm had significant decreases (12-16% of control group mean) in mean hemoglobin, red cells, and hematocrit, and increased reticulocytes. Male and female rats fed 4000 ppm had increased mean counts for white blood cells (mostly lymphocytes, neutrophils, and monocytes) and platelets. In addition, some individual male and female rats fed 1500 ppm had similarly increased white blood cells and platelets. The individual animals fed 1500 or 4000 ppm with increased white blood cells generally also had decreased globulin and increased albumin, consistent with the white cell effects indicating inflammation.

Hepatocellular changes (increased ALT, AST, and SDH) and cholestasis (increased cholesterol, alkaline phosphatase and bilirubin) were significantly increased in male and female rats fed 4000 ppm, and in individual males and females fed 1500 ppm. Effects of the test substance on indicators of kidney function (urea nitrogen, phosphorus, and creatinine) were discordant. In male and female rats, urea nitrogen and phosphorus were significantly increased at 4000 ppm, while the measured creatinine concentration was significantly increased at all dose levels in both sexes.

Histopathologically, biliary hyperplasia was observed in male rats fed 1500 and 4000 ppm and in females at all dose levels. In addition, treatment-related increases in focal hepatic necrosis occurred in the 4000 ppm male and female rats and the 1500 ppm male rats. The severity of biliary hyperplasia increased after 2 weeks of recovery with the males being more severely affected than the females. In addition, focal areas of hepatocellular hyperplasia and renal tubular or papillary degeneration/necrosis were observed in males and/or females after 2 weeks of recovery.

Under these experimental conditions, the findings described above would appear to be reportable, based on EPA guidance regarding the reportability of such data under TSCA Section 8(e) criteria.

Sincerely,