

8EHQ-0601-14847

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DuPont Haskell Laboratory
for Toxicology and Industrial Medicine
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DuPont Haskell Laboratory

June 6, 2001

Via Federal Express

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



8EHQ-01-14847



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Dear 8(e) Coordinator:

8EHQ-01-14847
Cis-2-Pentenenitrile
[CAS # 25899-50-7]

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

Groups of young, adult male and female CrI:CD® (IGS)BR rats were administered oral gavage doses of 0, 10, 30, or 100, mg/kg/day of the test substance for 28 (male) or 29 (female) days. The high dose was reduced to 75 mg/kg/day after approximately one week of dosing, due to mortality (3 males) and excessive toxicity. The rats were evaluated for body weight changes, food consumption, and clinical signs of toxicity, and 10 rats/sex/dose received a functional observational battery (FOB) and motor activity assessment. Ten rats/sex/dose were evaluated for clinical pathology at the end of the dosing phase, then were sacrificed and evaluated for gross and microscopic pathology. An additional 10 rats/sex/dose in the control and high-dose groups were held with no treatment for a 2-month recovery period. These rats were evaluated for body weight changes, food consumption, and clinical signs of toxicity. FOB and motor activity assessment endpoints were re-evaluated after the 2-month recovery phase of the study. Rats were evaluated for clinical pathology, then sacrificed at the end of the recovery phase and evaluated for gross and microscopic pathology.

During the course of the study, deaths occurred in 4 male rats in the high-dose group. Compound-related clinical signs observed in high-dose males and/or females during the dosing phase included corneal opacity, head tilt, abnormal gait, head shaking or bobbing, circling, hyperreactivity, and hyperactivity. These signs diminished in incidence and/or severity when the dose was reduced to 75 mg/kg/day and only corneal opacity was still observed during the recovery phase.

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The following effects were observed at the 4-week neurobehavioral evaluation. Forelimb grip strength was decreased in the high dose males and females and in the 30 mg/kg/day female group. Hindlimb grip strength was decreased in high dose and 30 mg/kg/day males and females, and in 10 mg/kg/day females. Statistical significance was variable. During the motor activity evaluation, the duration of movements was slightly lower in the high dose males and females, and number of movements was also slightly lower in the high dose females, although none of these effects was statistically significant. High dose males and females had an increased incidence of curled up posture in the home cage, sleeping in the home cage, and blue haze on the cornea, compared to the control group. Statistical significant was variable.

Hindlimb grip strength was significantly decreased in high-dose females during recovery. All other effects on FOB/MA parameters demonstrated complete recovery at this time.

High-dose female rats had mildly decreased red cell mass parameters (HGB, RBC, HCT) associated with decreased red cell size (decreased MCV, MCH) after 28 days of dosing. These changes were accompanied by increased reticulocytes and splenic extramedullary hematopoiesis, indicating active regeneration of red cell mass. After a 2-month recovery period, RBC mass parameters in high-dose females were similar to control group values.

High-dose males and females had mildly increased serum bilirubin. After a 2-month recovery period, bilirubin in high-dose rats was similar to control group values. Urine volume was increased in high-dose rats (males and females) and in female rats dosed with 30 mg/kg/day. Increased urine volume was associated with decreased urine specific gravity and osmolality. After a 2-month recovery period, urine volumes were still greater than in controls.

Histopathology lesions considered biologically significant were microscopically detected in noses of male and female rats administered all doses of the test substance. These lesions were characterized by necrosis of the olfactory mucosa, often accompanied by submucosal fibrosis and olfactory fiber degeneration. The lesion severity was greatest in the dorsal arch of the nose. Incidence and severity varied in dosed groups. These nasal lesions were still present in high-dose rats evaluated at the end of the recovery phase. Corneal degeneration was observed in high-dose males and females at the end of the dosing phase, but was not observed at the end of the recovery phase. Additionally, spermatid retention was observed in high-dose and 30 mg/kg/day male rats at the end of the dosing phase. This lesion was not observed in males at the end of the recovery phase.

Other statistically significant changes were observed in clinical pathology and histopathology but were not considered to be biologically significant.

Body weight and nutritional parameters were all reduced (relative to control) during the dosing phase in the high-dose males and females, but demonstrated recovery. These parameters were also generally lower than control in the other dose groups (variable statistical significance), due mainly to effects early in the dosing phase.

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 flourish at the end.

A Michael Kaplan, Ph.D.

Director – Regulatory Affairs

AMK/SAM:clp

(302) 366-5260