



DuPont Haskell Global Centers
for Health and Environmental Sciences
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Document Processing Center (Mail Code 7407M)
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

Dear 8(e) Coordinator:

8EHQ-92-13171/8EHQ-08-17263
2-Amino-2-Methylpropanenitrile



This letter is to inform you of the results of a recently conducted combined repeated dose toxicity study with a reproduction/developmental toxicity screening test with the test substance referenced above. DuPont's manufacture of this test substance is only for use within the Company as an intermediate.

Four groups of Crl:CD(SD) rats (12/sex/dose level) were administered 0, 2.5, 10, and 25 mg/kg/day once daily by gavage. On the first day of dosing (test day 0), four males and 5 females were found dead within 30 minutes of dosing and 2 males were sacrificed *in extremis* in the 25 mg/kg/day group. Clinical signs observed in the rats that died include labored breathing, convulsions (clonic and tonic), splayed limb, abnormal gait, high posture, eyelid ptosis, immobility, and prostrate. Rats that survived the 25 mg/kg/day dose did not show any clinical signs. The rats that died were replaced with spare animals of the same age and the mid and high doses were reduced to 7.5 and 15 mg/kg/day, respectively. From test day 1, the doses were 0, 2.5, 7.5, and 15 mg/kg/day. This information was submitted to the Agency on September 17, 2008.

Following an approximately 2-week pre-mating period, P₁ males and females were cohoused for up to 2 weeks within their respective treatment groups to produce F₁ litters. Dams were allowed to deliver and rear their offspring until postpartum day 4. Detailed clinical observations were recorded weekly. Body weights were collected weekly for P₁ males until sacrifice and for females, weekly during pre-mating, on days 0, 7, 14, and 21 of gestation and on days 0 and 4 of lactation. Food consumption was measured weekly during pre-mating for males and females and on days 0, 7, 14, and 21 of gestation and on days 0 and 4 of lactation for females. An abbreviated neurobehavioral was conducted in P₁ rats during pretest and prior to cohabitation. Clinical pathology parameters were measured in P₁ rats (5/sex/group) at the end of the pre-mating period (hematology, clinical chemistry and urinalysis) and at terminal sacrifice (coagulation). Selected tissues were weighed from all adult rats. Uterine implantation sites and ovarian *corpora lutea* were counted in P₁ females. A histological examination of reproductive organs was conducted for all animals in the control and high-dose groups. Histologic examination of all other tissues was conducted for 5/sex/group in the high-dose and control groups. Reproductive indices (mating index, fertility index, and pre- and post-implantation loss) were calculated. F₁ litter examinations (pup viability, individual pup weights, and clinical observations) were performed at birth and on lactation day 4.

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Mating (83% vs. 92%) and fertility (80% vs. 100%) indices were lower in the 15 mg/kg/day group compared to control. Minimal, but non-statistically significant decreases in body weights and body weight gains were noted in high dose males. Sporadic and non-dose-dependent incidents of abnormal gait, hyperactivity, hyperreactivity, wet fur (chin), high posture, lethargy, salivation and splayed limb were observed throughout the study. No test substance-related effects were noted in other parameters. Under the conditions of the study, the no-observed-adverse-effect levels (NOAEL) for systemic and reproductive toxicities were 15 and 7.5 mg/kg/day, respectively.

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 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/SSA: clp
(302) 366-5260