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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
1201 Constitution Ave., NW
Washington, DC 20460

8EHQ-07-17005

Dear 8(e) Coordinator:

Hexafluoropropylene Oxide
CAS # 428-59-1

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 (OECD 422) in rats with the test substance referenced above.

Crl:CD®(SD) rats (12/sex/concentration) were exposed whole body to 0, 50, 250, or 1000/500 ppm of the test substance. Due to excessive toxicity, the 1000 ppm concentration was reduced to 500 ppm beginning with exposure 7 (on test day 9). Concentrations of the test substance were generated by dilution in conditioned, filtered air. Exposures for males and females were conducted for 6 hours per day, 5 days per week from the initiation of the study through the 14 day premating period. Subsequently, males and non-pregnant females were exposed 7 days a week through the terminal sacrifice. Exposures for females with evidence of mating were conducted for 6 hours per day, 7 days per week during the cohabitation period (up to 2 weeks in duration) and during gestation days 0–19. Gestating P_1 females were not exposed after gestation day 19. Offspring were not exposed in the inhalation chambers.

Careful clinical observations were recorded once daily post exposure. Detailed clinical observations were recorded once during pretest and weekly thereafter. Body weights and food consumption were recorded weekly for P_1 males and females (premating), on days 0, 7, 14, and 21 of gestation; and on days 0 and 4 of lactation. Food consumption was not measured during cohabitation or thereafter for males, or for females with any evidence of copulation. An abbreviated neurobehavioral evaluation consisting of a functional observational battery and motor activity was conducted in P_1 rats (12/sex/group) once during pretest and prior to cohabitation. Clinical pathology parameters were measured in P_1 rats (5/sex/group) at the end of the premating period (hematology, clinical chemistry) and at terminal sacrifice (coagulation). F_1 litter examinations (pup viability, individual pup weights, pup sex, and clinical observations) were performed at birth and on lactation day 4.

All P_1 rats were given a gross pathological examination and selected tissues were weighed and collected from all adult rats. Uterine implantation sites and ovarian corpora lutea were counted in P_1 females. A histological examination was conducted on selected tissues.

The mean concentrations (± standard error of the mean) of the test substance were 50 ± 0.098 and 250 ± 0.16 in chambers targeted at 50 and 250 ppm, respectively. For the first 6 exposures while the concentration in the

high level chamber was targeted to 1000 ppm, the mean concentration was 1000 ± 1.3 ppm. After the concentration was reduced to 500 ppm, the mean concentration was 500 ± 0.58 ppm.

Test substance-related mortality (4/24 with 3 rats showing cerebrocortical necrosis at 1000 ppm), clinical signs of toxicity, reductions in body weight, weight gain, food consumption and/or food efficiency occurred in P_1 males and females exposed to 1000/500 ppm of the test substance, and in 250 ppm P_1 males.

Clinical signs during exposure to 1000/500 ppm included increased activity and hypersensitivity to sound. Post exposure clinical signs in rats exposed to 1000/500 ppm included aggressive behavior, rapid breathing, hyperactivity, hypersensitivity, hyper-reactivity, dehydration, hunched posture, abnormal gait and lethargy. In addition, decreased offspring body weight occurred in the 250 ppm and above groups on postnatal day 4.

Effects on clinical pathology parameters occurred in rats exposed to 250 ppm and above. Red cell mass parameters were decreased in males and females exposed to 1000/500 ppm. In addition, white blood cell count parameters were decreased in 250 ppm and above females. Glucose was increased in males at 250 ppm and above. Test substance-related decreases in motor activity were observed in 1000/500 ppm females. There were no test substance-related effects on reproductive function, or on offspring clinical observations, or offspring survival.

Test substance-related changes in organ weights occurred in P_1 males at 250 ppm and above, and in 1000/500 ppm P_1 females. Increased brain weights occurred in 1000/500 ppm males and females and correlated with the observation of neuronal necrosis and/or vacuolar degeneration of neuronal fibers in the brain. Males and females exposed to 250 ppm and above had similar brain lesions without changes in brain weight parameters. Lung weights were increased in 1000/500 ppm females and in 250 ppm and above males. The changes in lung weight correlated with the observation of increased alveolar histiocytosis in 250 ppm and above males, and 1000/500 ppm females. Absolute and relative spleen weights were increased in males exposed to 250 ppm and above, and correlated with the observation of increased extramedullary hematopoiesis. Absolute and relative thymus weights were decreased in 1000/500 ppm males, however there was no morphological correlate for this change. In addition, 1000/500 ppm females had erythrocytic hyperplasia of the bone marrow. There were no test substance-related morphological changes in males or females exposed to 50 ppm.

Under these experimental conditions, the findings described above appear to be reportable, based upon EPA's TSCA Section 8(e) reporting criteria.

Sincerely,

A. Michael Kaplan

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

AMK/LAM: clp
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