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



Dear 8(e) Coordinator:

8EHQ-06-16436/8EHQ-06-16478
Perfluorinated Aliphatic Carboxylic Acid, Ammonium Salt

This letter is to inform you of the results of a repeated dose 28-day oral toxicity study in rats and mice with the R&D test substance referenced above.

Rats:

The test substance was administered to male and female Crl:CD®(SD)IGS BR rats by oral gavage for 28 consecutive days. The following table presents the study group arrangement:

	Dosage (mg/kg/day)	Number of Animals
Males		
1	0	20 ^a
2	0.3	10
3	3	10
4	30	20 ^b
Females		
1	0	20 ^a
2	3	10
3	30	10
4	300	20 ^a

a 10 animals/sex/group was submitted for necropsy on test day 28. The remaining 10 animals/sex/group in groups 1 and 4 were necropsied on test day 56 after a 28-day recovery.

Body weights, food consumption, and clinical observations were evaluated. Clinical pathology and gross and microscopic pathology endpoints were evaluated. Liver samples were collected for evaluation of total cytochrome P-450 content and beta-oxidation activity.

Minimal decreases in red cell mass parameters (RBC count, hemoglobin, and hematocrit) were present in male rats administered 3 or 30 mg/kg/day. There were no treatment-related hematological effects in female rats. In male rats, decreases in serum cholesterol were present in all dosed groups. Triglycerides were also decreased in male rats but decreases were statistically significant only in the 3 mg/kg/day group. Albumin was increased and globulin was decreased in the 30 mg/kg/day male group. Globulin was also decreased in the 3 mg/kg/day male group. Albumin/globulin ratio was increased in 3 and 30 mg/kg/day males. BUN and glucose, were increased in male rats administered 30 mg/kg/day. These changes were very slight, were not associated with correlative histology (BUN) or were within laboratory historical values (glucose). These changes were of uncertain relationship to treatment and considered non-adverse. Treatment-related changes in females were



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limited to a decrease in globulin (with an associated increase in albumin/globulin ratio) at 300 mg/kg/day. Changes in clinical pathology parameters were reversible following the 4-week recovery period.

In male rats, statistically significant increases in kidney and liver weights were present in the 3 and 30 mg/kg/day groups. In females, organ weight changes were limited to increases in liver weight relative to body weight in the 300 mg/kg/day group. All organ weight changes were reversible, as no statistically significant increases in organ weights were observed in the 4-week recovery groups.

Multifocal centrilobular hypertrophy of the liver was observed in the male 30 mg/kg/day group and in the female 300 mg/kg/day group. Reversibility of this change was observed in male and female rats necropsied after a 4-week recovery.

The test substance was an inducer of hepatic peroxisomal β -oxidation activity, a measure of peroxisome proliferation, in male rats after administration of 0.3, 3 and 30 mg/kg/day and in female rats after administration of 30 and 300 mg/kg/day. Total hepatic microsomal cytochrome P-450 enzyme content was increased at a dosage of 30 mg/kg/day in male rats but not in females. β -oxidation activity (male and female) and total cytochrome P-450 content (male) had returned to control levels after approximately 28 days of recovery.

Mice:

The test substance was administered to male and female Crl:CD-1(ICR) mice by oral gavage for 28 consecutive days. The following table presents the study group arrangement:

Group Number	Dosage (mg/kg/day)	Number of Animals
Males		
1	0	20 ^a
2	0.1	10
3	3	10
4	30	20 ^a
Females		
1	0	20 ^a
2	0.1	10
3	3	10
4	30	20 ^a

a 10 animals/sex/group were submitted for necropsy on test day 28. The remaining 10 animals/sex/group in groups 1 and 4 were necropsied on test day 56 after a 28-day recovery.

Body weights, food consumption, and clinical observations were evaluated. Clinical pathology and gross and microscopic pathology endpoints were evaluated. Liver samples were collected for evaluation of total cytochrome P-450 content and beta-oxidation activity.

Minimal decreases in one or more red cell mass parameters (RBC count, hemoglobin, and hematocrit) were present in male mice administered 3 or 30 mg/kg/day. These changes were reversible following the 4-week recovery period. Statistically significant increases in monocytes and large unstained cells were also present in 30 mg/kg/day males but these changes were not associated with changes in other red cell mass parameters. There were no treatment-related hematological effects in female mice.

Albumin was increased in the 30 mg/kg/day male group, while globulin (and albumin/globulin ratio) was decreased in both males at females at 3 and 30 mg/kg/day. All serum protein changes were reversible following the 4-week recovery period. In male mice administered 30 mg/kg/day, liver enzymes (ALT, AST, SDH, ALKP) were statistically increased at the end of the exposure period. In females only ALKP and SDH were increased. All of these changes in liver enzymes were reversible except for a slight increase in SDH in the 30 mg/kg/day males. Other statistically significant changes observed at the end of the exposure period were a slight decrease in

chloride and increase in BUN in males administered 30 mg/kg/day. Changes in these parameters were minimal and not associated with correlative microscopic changes.

All other statistically significant changes in clinical pathology parameters were either not dose related or only occurred in recovery groups.

In male mice, statistically significant increases in liver and adrenal weights (absolute and relative to body or brain weight) were present in the 3 and 30 mg/kg/day groups. Liver weights were mostly, but not completely, reversible, as slight but statistically increases in liver weight were present in the 30 mg/kg/day male group after 4 weeks of recovery. In female mice, statistically significant increases in liver weights (absolute and relative to body or brain weight) were present in the 3 and 30 mg/kg/day groups. As in males, liver weight increases were mostly but not completely reversible (statistically increased for relative to body weight) in the 30 mg/kg/day female group after 4 weeks of recovery. Uterine weights (absolute and relative to body or brain weight) were statistically decreased in the 30 mg/kg/day female group. This change reversed after 4 weeks of recovery.

Adrenal cortical hypertrophy, suggestive of systemic stress, was observed in the 30 mg/kg/day males at the primary necropsy. Adrenal cortical hypertrophy was not observed in the 30 mg/kg/day males at the recovery necropsy. Hepatocellular hypertrophy was observed in the 3 and 30 mg/kg/day group males and females at the primary necropsy. The hepatocellular hypertrophy was characterized by expansion of the hepatocellular cytoplasm by numerous fine eosinophilic granules lending a generalized eosinophilic tinctorial change to the affected livers. The distribution of the hepatocellular hypertrophy was centrilobular when of minimal or mild severity and diffuse when of moderate severity. These changes are consistent with peroxisomal proliferation. Other findings in the liver at the primary necropsy were multifocal single cell hepatocellular necrosis in the 3 and 30 mg/kg/day group males and 30 mg/kg/day group females and increased mitotic figures in the 30 mg/kg/day group males and females. All liver changes were reversible, as hepatocellular hypertrophy, single cell hepatocellular necrosis and increased mitoses in the liver were not observed in the 30 mg/kg/day group males and females at the recovery necropsy.

There were an increased number of animals in the diestrus stage of the estrous cycle in the 30 mg/kg/day group females compared to control group females at the primary necropsy. These changes are likely secondary to systemic stress (as indicated by adrenal hypertrophy). Decreased estrous cycling is common in stressed mice. The number of animals in the diestrus stage of the estrous cycle was equal in the control and 30 mg/kg/day group females at the recovery necropsy.

All other findings were consistent with gavage injuries or were considered to be incidental findings or related to some aspect of experimental manipulation other than administration of the test substance.

The test substance was an inducer of hepatic peroxisomal β -oxidation activity, a measure of peroxisome proliferation, in male mice after administration of 0.1, 3 and 30 mg/kg/day and in female mice after administration of 3 and 30 mg/kg/day for 28 days. Total hepatic microsomal cytochrome P-450 enzyme content was decreased at a dosage of 3 and 30 mg/kg/day in male mice but not in females. β -oxidation activity in both male and female mice had returned to control levels after approximately 28 days of recovery while total cytochrome P-450 content remained below control levels in the males.

Sincerely,