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Via Federal Express

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 20004

Dear 8(e) Coordinator:

8EHQ-07-16913
Fluorinated Aliphatic Alcohol

This letter is to inform you of the results of a 90-day oral study in rats with the above referenced test substance.

Ninety-five male and ninety-five female Crl:CD(SD) rats were randomly assigned to five dosage groups (Groups I through V), 10 rats per sex per group, using a computer-generated (weight-ordered) randomization procedure. An additional ten rats per sex in Groups I and V were assigned to the 1-month recovery phase of the study and an additional five rats per sex in Groups I through V were assigned to the 3-month recovery phase of the study. Rats assigned to the 10-day satellite portion of the study were assigned to five dosage groups (Groups I through V), five rats per sex per group, using a computer-generated (weight-ordered) randomization procedure; the satellite rats were designated for possible future biochemical analyses. Tissues from these rats were shipped to the Sponsor for storage. If these tissues are analyzed, the results of the analyses will be reported in a supplement to the current report. Male and female rats were administered formulations of the test substance in 0.5% (w/v) aqueous methylcellulose prepared in reverse osmosis deionized water. Control group rats were administered the vehicle. All doses were administered once daily for 10 consecutive days (satellite rats) or 90 consecutive days via oral gavage at dosages of 0 (Vehicle), 5, 25, 125, and 250 mg/kg/day and a dosage volume of 5 mL/kg.

All rats were observed for viability at least twice each day of the study and for general appearance at least weekly during the acclimation period. At the end of the first week of dosage administration and once weekly thereafter, detailed clinical observations were conducted for all male and female rats. Ophthalmological examinations were performed by a veterinary ophthalmologist for all rats assigned to the main study prior to dosage and toward the end of the dosage period. Clinical observations were recorded daily before and one to two hours after dosage administration (for each animal), and once daily during the postdosage period.

A functional observational battery (FOB) and motor activity assessment were conducted on all rats designated for the main study and recovery evaluations prior to the initiation of test substance and/or vehicle administration. During week 13 of test substance and/or vehicle administration, FOB and motor activity evaluations were conducted on the rats designated for the main study evaluation and the 1-month and 3-month recovery evaluations prior to the daily dosage administration. Additional FOB and motor activity evaluations were conducted on the rats designated for the 1-month and 3-month recovery evaluations.

Body weights were recorded at least weekly during the acclimation period (but not tabulated), weekly during the dosage period and on the day before sacrifice. Body weights were also recorded weekly during the postdosage period (recovery rats only) and on the day of sacrifice (terminal weight). Feed consumption values were recorded weekly during the dosage period and the postdosage period (recovery rats only) and on the day before sacrifice (feed left value).

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A clinical pathology evaluation was conducted on all rats designated for the main study during week 7 and 14 (prior to necropsy). Urine samples were collected during weeks 7, 9 and 14. On week 14 of study and after 1 and 3 months of recovery, whole blood was collected from main and recovery rats for plasma and urine fluoride evaluation. Bone marrow smears were collected at the time of sacrifice. Blood, liver and fat samples were also collected from all rats assigned to the main study and 1 and 3 month recovery periods for possible analyses of test substance and/or metabolite. These blood, liver and fat samples were shipped to the Sponsor for possible future analyses. If these analyses are conducted in the future, the results of the analyses will be reported in a supplement to the current report.

All rats were sacrificed by carbon dioxide asphyxiation on the day following the last administration of the test substance and/or vehicle and a gross necropsy was performed and organ weights recorded.

Rats assigned to the satellite groups were fasted after 3 PM (at least 15 hours) on the afternoon before their scheduled sacrifice. Rats were sacrificed by carbon dioxide anesthesia and exsanguination on the day following the last administration of the test substance and/or vehicle, and a gross necropsy was performed. At the time of sacrifice, liver samples were collected for possible future evaluation. Rats were discarded without further evaluation.

Summary of Results

Male Rats

At 250 mg/kg/day, there was a significant increase in the number of male rats that were either found dead or euthanized because of adverse clinical signs. Each of the deaths/early sacrifices at 250 mg/kg/day were attributed to the test substance and generally occurred after 56 to 81 dosages of the test substance had been administered. Most of these deaths were attributed to degeneration and necrosis in the kidneys. Three male rats were also observed with moderate to marked hemorrhage and acute inflammation in the nose.

Dental effects were observed in male rats treated with 250 mg/kg/day of the test substance during the dosage period and were presumed related to the test substance. Relative to the vehicle control group values, significantly more rats in the 250 mg/kg/day dosage group had excess salivation, urine-stained abdominal fur, dehydration (based on skin turgor) and perioral substance. The dental effects noted during the dosage period persisted into the recovery period, and were noted in a significantly increased number of male rats at $\geq$ 125 mg/kg/day.

The adverse clinical signs observed during the detailed clinical observations were consistent with those observed during the standard clinical observations. At 250 mg/kg/day, significantly more male rats did not appear normal during the detailed clinical observations recorded during the dosage period and weeks 14 to 18 of the recovery period. At 250 mg/kg/day, whitened teeth also occurred in significantly more male rats during weeks 19 to 24 of the study, in addition to misaligned incisors.

All ophthalmologic examinations appeared normal for the male rats at the end of the dosage period. There were no ophthalmological effects at any dose.

The average body weight gain at 125 and 250 mg/kg/day was 14% and 11% lower, respectively, than the vehicle control group value for the entire dosage period. Interrelated with the reductions in body weight gains, mean body weights at the end of the dosage period were significantly reduced at $\geq$ 125 mg/kg/day, and remained reduced or significantly reduced during the recovery period. Feed consumption values were generally comparable among the dosage groups. There were no effects on body weight gain at 5 mg/kg/day or 25 mg/kg/day.

With the exception of the reduction in the average body weight at $\geq$ 125 mg/kg/day, as previously described, there were no effects on any parameters evaluated in the functional observational battery, and there were no changes in motor activity at any dose.

There were no biologically important changes in the urinalysis parameters at any dose.

On day 43 of study, significant reductions in hemoglobin and hematocrit levels occurred at 250 mg/kg/day. At the end of the dosage period, red blood cell counts, hemoglobin and hematocrit levels were lower or

significantly lower in male rats at ≥ 25 mg/kg/day, and mild, but statistically significant reductions in the activated partial thromboplastin time occurred in these same dosage groups. These hematological changes did not persist during the recovery period. There were no hematological effects at 5 mg/kg/day.

There were no apparent treatment-related changes in serum chemistry that occurred during the dosage period. However, at the end of the dosage period, changes in serum chemistry that were presumed to be test substance-related included an increase or significant increase in the albumin/globulin ratio at ≥ 25 mg/kg/day; and the inorganic phosphorus, protein, albumin, total bilirubin and potassium at ≥ 125 mg/kg/day. There was also a reduction or significant reduction in blood urea nitrogen levels at ≥ 125 mg/kg/day. By the end of the recovery period, these changes in serum chemistry had resolved. There were no serum chemistry effects at 5 mg/kg/day.

All necropsy observations for the male rats were considered unrelated to the test substance.

At the completion of the dosage period, a non-dosage-dependent reduction in terminal body weights occurred at ≥ 125 mg/kg/day. Terminal body weights at 250 mg/kg/day remained reduced one month after the completion of the dosage period. There were no terminal body weight effects at 5 mg/kg/day or 25 mg/kg/day.

The absolute and relative (% brain weight) weight of the liver and the paired kidneys was increased or significantly increased at ≥ 125 mg/kg/day at the end of the dosage period. Relative to body weight, these organs were significantly increased at ≥ 25 mg/kg/day at the end of the dosage period, and residual effects were noted at 250 mg/kg/day one month after the completion of the dosage period. These observations were not present three months after the completion of the dosage period. In addition, the relative weights of the paired testes and paired epidydimides was significantly increased at ≥ 25 mg/kg/day. There were no absolute or relative weight effects on paired testes and paired epidydimides at 5 mg/kg/day.

In treated male rats, plasma fluoride levels were increased above control values and were statistically significant in groups administered 25 mg/kg/day and above. Mean plasma fluoride values at the end of the dosing period were 0.1, 0.1, 0.2, 0.7 and 0.9 µg/mL for rats dosed with 0, 5, 25, 125, or 250 mg/kg/day. Following approximately one month of recovery, plasma fluoride in the 250 mg/kg/day male group (the only treated group evaluated at that time point) was still increased but had partial recovery. Plasma fluoride levels were similar to control levels following approximately 3 months recovery. There was no plasma fluoride level increase at 5 mg/kg/day.

Urine fluoride (the product of urine fluoride concentration and urine volume) was increased in a dose-related manner in all treated dosage groups (statistically significant in the ≥ 25 mg/kg/day dosage groups) during the dosing period at both the week 9 and day of study 91 time points. Samples were not collected after 1-month and 3-month recovery. There was no urine fluoride increase at 5 mg/kg/day.

Histopathological effects in the liver were observed at terminal sacrifice in the male rats at 125 (single cell hepatocellular vacuolation) and 250 mg/kg/day (hepatocellular hypertrophy, single cell necrosis, biliary hyperplasia, periportal inflammation and hepatocellular vacuolation). At 250 mg/kg/day, effects on the teeth (ameloblastic dysplasia and degeneration or attenuation of the ameloblastic epithelium) were also observed at terminal sacrifice. Acinar cell apoptosis was also observed in the 250 mg/kg/day treated male rats. There were no histopathological effects at 5 mg/kg/day.

The liver findings were no longer apparent in the male rats at 250 mg/kg/day by the 1-month recovery sacrifice. Although decreased, effects on the teeth (ameloblastic dysplasia and enamel dysplasia) and acinar cell apoptosis were apparent at the 1-month recovery sacrifice. There were no effects observed in the male rats at the 3-month recovery sacrifice.

Female Rats

At 125 mg/kg/day, one female rat was sacrificed due to adverse clinical signs. There was also a significant increase in the total number of female rats at 250 mg/kg/day that were either found dead or sacrificed due to adverse clinical signs during the study. These deaths/early sacrifices generally occurred after 19 to 73 dosages and were considered test substance-related. Most of these early deaths were attributed to degeneration and necrosis in the kidneys. No mortality was observed at 5 mg/kg/day or 25 mg/kg/day.

Dental effects were observed in female rats dosed with 125 and 250 mg/kg/day of the test substance during the dosage period and were presumed to be test substance-related. Significantly more female rats at 125 and 250 mg/kg/day had urine-stained abdominal fur, piloerection and scant feces, while excess salivation, dehydration (based on skin turgor), hunched posture, coldness to the touch, ungroomed coat, decreased motor activity and pale extremities were noted in significantly more female rats at 250 mg/kg/day. The dental effects noted during the dosage period persisted into the recovery period, and were noted in a significantly increased number of female rats at 125 and 250 mg/kg/day. There were no adverse clinical signs (including dental effects) observed at 5 mg/kg/day or 25 mg/kg/day.

The adverse clinical signs observed during the detailed clinical observations were consistent with those observed during the standard clinical observations. At 125 mg/kg/day, there was a significant increase in the number of female rats that did not appear normal during the detailed clinical observations recorded during the dosage period. These adverse observations included a significant increase in the number of female rats observed with whitened teeth and urine-stained abdominal fur in comparison with the vehicle control group. At 250 mg/kg/day, there was an increase or significant increase in the number of female rats that did not appear normal during the evaluation, which included dental effects; mild dehydration; urine-stained abdominal fur; coldness to the touch; ungroomed coat; decreased motor activity; ataxia; periorbital swelling; brown fur on the lower midline; hunched posture; and slight excess salivation. There were no adverse clinical signs observed during detailed clinical observations at 5 mg/kg/day or 25 mg/kg/day.

All eyes appeared normal for both sexes at the ophthalmologic examination prior to dosage administration. There were no ophthalmological effects at any dose.

There were no test substance-related effects at any dose on body weight or body weight gain observed in the female rats during the dosage or recovery periods.

At 250 mg/kg/day, absolute and relative feed consumption values were lower or significantly lower during the entire dosage period. In general, female rats at 250 mg/kg/day consumed less or significantly less feed on a g/day and/or a g/kg/day basis at each tabulated interval within the dosage period. There were no effects on absolute and relative feed consumption values at 5, 25 or 125 mg/kg/day.

With the exception of a single occurrence of unusual posture noted in the open field at 250 mg/kg/day, there were no additional effects on any of the parameters evaluated in the functional observational battery, and there were no changes in motor activity at any dose.

Significantly more female rats at $\geq$ 125 mg/kg/day had trace amounts of blood present in the urine at day 63 of study. In addition, a small amount of hemolyzed trace blood was present in the urine of five rats in the 25 mg/kg/day dosage group compared to one in the vehicle control group. A moderate amount of hemolyzed trace blood was present in the urine of three rats in the 5 mg/kg/day dosage group; a large amount of hemolyzed trace blood was present in the urine of one rat in the vehicle control group at this same time point. These changes resulted in a statistically significant reduction in the number of female rats at $\geq$ 25 mg/kg/day with blood absent in the urine. There were no statistically significant changes observed in trace amounts of blood present in urine at any dose at any other time point. At the end of the dosage period, the specific gravity of the urine at 25 and 125 mg/kg/day were significantly lower, and there were trace amounts of protein present in the urine at $\geq$ 125 mg/kg/day. There were no biologically important changes in the urinalysis parameters at the end of the recovery period at any dose.

In female rats, red blood cell counts, hemoglobin levels and hematocrit levels were significantly lower at $\geq$ 125 mg/kg/day relative to vehicle control group values on day 43 of study. In addition, the percent red cell distribution width, percent reticulocytes and absolute reticulocytes were increased in these same dosage groups. These findings, with the exception of the changes in reticulocytes, were consistent with observations noted at the end of the dosage period; however, values at 250 mg/kg/day reflected the only surviving female in this dosage group. Similar to male rats, exposure of female rats to the test substance at dosages of 125 or 250 mg/kg/day resulted in mild, but statistically significant reductions in the activated partial thromboplastin time at the end of the dosage period. There were no effects observed on red blood cell counts, hemoglobin levels, hematocrit levels, percent reticulocytes and absolute reticulocytes at 5 mg/kg/day or 25 mg/kg/day.

In female rats, changes in serum chemistry that were presumed related to treatment with the test substance included a significant increase in cholesterol at ≥ 25 mg/kg/day; albumin, total bilirubin and triglyceride levels at ≥ 125 mg/kg/day; and creatinine levels, blood urea nitrogen levels, calcium levels and inorganic phosphorus levels at 250 mg/kg/day. By the end of the dosage period, most of the changes in clinical chemistry had resolved with the exception of the changes in total bilirubin levels. Additional findings that occurred at the end of the dosage period included an increase or significant increase in cholesterol levels at ≥ 125 mg/kg/day, and elevations in aspartate aminotransferase and alkaline phosphatase at ≥ 25 mg/kg/day. The elevations in aspartate aminotransferase and alkaline phosphatase were consistent with changes in liver weights that occurred in these same dosage groups. There were no residual effects of the test substance noted on serum chemistry parameters evaluated at the end of the recovery period. There were no serum chemistry effects at 5 mg/kg/day.

All necropsy observations in the female rats were considered unrelated to the test substance.

Terminal body weights were unaffected by dosages of the test substance as high as 250 mg/kg/day at the end of the dosage period and during the recovery period.

The absolute and relative (% body weight and % brain weight) weight of the liver and the paired kidneys was increased or significantly increased at ≥ 25 mg/kg/day at the end of the dosage period. One month after the completion of dosage administration, the weights of the liver and paired kidneys remained significantly increased at 250 mg/kg/day. In general, residual effects were noted in these organs three months after the completion of the dosage period at ≥ 25 mg/kg/day; however, these increases did not reach statistical significance when compared to the vehicle control group values. There were no absolute or relative organ weight effects at 5 mg/kg/day.

In treated female rats, plasma fluoride levels were increased above control values and were statistically significant in groups administered ≥ 125 mg/kg/day. Mean plasma fluoride values at the end of the dosing period were 0.1, 0.1, 0.1, 0.6 and 1.1 µg/mL for rats dosed with 0, 5, 25, 125, or 250 mg/kg/day. Following approximately one month of recovery, plasma fluoride in the 250 mg/kg/day female group was still increased but had partial recovery. Plasma fluoride levels were similar to controls following approximately 3 months of recovery. There were no plasma fluoride increases at 5 mg/kg/day or 25 mg/kg/day.

Urine fluoride (the product of urine fluoride concentration and urine volume) was increased in a dose-related manner in all treated female dosage groups (statistically significant in the female rats dosed with ≥ 25 mg/kg/day) during the dosing period at both the week 9 and day of study 91 time points. Samples were not collected after 1-month and 3-month recovery. There was no urine fluoride increase at 5 mg/kg/day.

Histopathological effects in the liver were observed at terminal sacrifice in the female rats at 25 (oval cell hyperplasia) and 125 mg/kg/day (single cell necrosis and oval cell hyperplasia). There was only one female rat remaining at terminal sacrifice in the 250 mg/kg/day dosage group and there were no histopathological effects observed in this female. There were no histopathological effects in the liver at 5 mg/kg/day.

At 250 mg/kg/day, the liver findings (oval cell hyperplasia and periportal pigmentation), effects on the teeth (loss of ameloblastic epithelium and enamel dysplasia) and acinar cell apoptosis were all apparent at the 1-month recovery sacrifice. The only finding present at the 3-month recovery sacrifice was a few female rats in the 125 and 250 mg/kg/day dosage groups with residual biliary hyperplasia.

Sincerely,