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Attention: FYI Coordinator
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Dear Sir or Madam:

Occidental Chemical Corporation (OxyChem) hereby provides the enclosed summary of a 90-day toxicity study of **p-chlorobenzotrifluoride** (CAS Reg. No. 98-56-6) as a "For Your Information" submittal to the TSCA Section 8(e) Coordinator. This study is a follow-up to a previous study submitted to EPA on September 14, 1993 ["A Subchronic (4-week) Inhalation Toxicity Study of PCBTF in the Rat via Whole-Body Exposures"]. OxyChem has provided EPA with a copy of the full 90-day study under the TSCA Section 8(d) Health and Safety Data Reporting Rule.

The earlier submission (28-day study) had identified clinical signs of neurotoxicity at dose levels of 1000 ppm and increases in kidney and liver weights at dose levels between 250 and 1000 ppm. The current submission (90-day neurotoxicity study) *does NOT* identify any new health effects. In addition, it demonstrates no-effect levels of 250 ppm for neurotoxicity and 50 ppm for kidney and liver effects.

Information about the current study is summarized below:

Name of Study: Subchronic (90-day) Inhalation Toxicity and Neurobehavioral Study of PCBTF in the Rat

Chemical Studied: Benzene, 1-chloro-4-(trifluoromethyl)-
(p-Chloro- α,α,α -trifluorotoluene; Parachlorobenzotrifluoride; PCBTF)

CAS Registry Number: 98-56-6

Study Sponsor: Occidental Chemical Corporation
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If you have any questions or require additional information, please call me at 716-286-3108.

Very truly yours,

Kenneth F. Kubiak
Manager - Product Stewardship (Regulations)
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SUBCHRONIC (90-DAY) INHALATION TOXICITY AND NEUROBEHAVIORAL STUDY OF PCBTF IN THE RAT

Study conducted by PHARMACO LSR, East Millstone, NJ for Occidental Chemical Corporation, Niagara Falls, NY

Study Director, P.E. Newton, Ph.D., PHARMACO LSR
Study Monitor, J.B. Knaak, Ph.D., Occidental Chemical Corporation

SUMMARY

Sprague-Dawley rats (25/sex/group) were exposed in inhalation chambers, 6 hr/day, 5 days/wk for 90 days to 0, 10, 50, and 250 ppm p-chlorobenzotrifluoride (PCBTF). An additional 45 female rats were included within the 50 ppm group for toxicokinetic examinations during and after 90 days of exposure. Neurobehavior studies involving functional observation battery (FOB), and muscular activity (MA) on 10/sex/group were performed on days 0, 30, 60, and 90 of the study and 5/sex/group at the end of the 90-day recovery period. Following 90 days of exposure 10/sex/group were sacrificed, selected organs were weighed and organ/body and organ/brain weight ratios calculated. Males in the 250 ppm group had statistically significant increases in the absolute and relative kidney and liver weights. Females in this group had a similar increase in liver weights, but not in kidney weights. Complete macroscopic postmortem and microscopic examination of selected tissues were conducted. Following 90 days of recovery (10/sex/group), 5/sex/group were sacrificed and examined as indicated above. Whole-body perfusion and microscopic examination of selected nervous tissue was conducted after exposure and after recovery (5/sex/group). Body weight gain was unaffected. There were no PCBTF related macroscopic observations. Microscopically, PCBTF related centrilobular hypertrophy was present only in the livers of males and females at the high dose (250 ppm) after 90 days of exposure. No centrilobular hypertrophy was observed at any level among recovery animals. There were no PCBTF effects on the nervous system, as measured by FOB, MA, and neuropathology. The female rat tissue time-concentration data (μg of PCBTF/g of tissue) from the 50 ppm inhalation nose-only toxicokinetic study is being compared to the output from a PCBTF PBPK model. PCBTF partitions into body fat and is retained somewhat longer in this tissue than in liver or muscle.

INTRODUCTION

A 90-day rat subchronic whole-body inhalation study was performed with p-chlorobenzotrifluoride to assess the toxicity, neurotoxicity, and reversibility of effects incurred during exposure for the purpose of establishing a company exposure limit. The exposure levels were selected based on the results of a 28 day inhalation study in rats conducted by PHARMACO LSR. A nose-only inhalation toxicokinetic study was performed at the end of the 90-day exposure period to obtain tissue time-concentration data during and after exposure for use in developing a physiologically-based pharmacokinetic model for PCBTF.

METHODS

Sprague-Dawley rats (25/sex/group) were used in this 90-day whole-body inhalation study. Exposures were for 6 hrs/day, 5 days/wk, for 13 weeks at target vapor concentrations of 0 (air control), 10, 50, and 250 ppm. Chamber concentrations were determined every 1.5 hrs by infra-red spectrophotometric analysis. Particulate mass and particle size distribution measurements of any airborne particles were made once per day in each chamber. Animals were examined for abnormal signs during each exposure. Detailed physical examinations were conducted twice on all animals prior to exposure and on a weekly basis during the exposure period. Eye examinations were performed on all animals prior to exposure and on the exposure day prior to sacrifice. Body weight measurements were recorded two times prior to exposure, on a weekly basis during exposure, and just prior to sacrifice. Food consumption was measured prior to exposure and on a weekly basis during exposure. Blood samples were drawn just prior to sacrifice for hematology and clinical chemistries.

At the end of the 13 week exposure period, 10 animals/sex/group were sacrificed, selected organs weighed and organ/body and organ/brain weight ratios calculated. Complete macroscopic postmortem examinations and microscopic examinations on selective tissues were conducted.

Following 3 months of recovery, 5 animals/sex/group were sacrificed and examined as indicated above.

Neurotoxicity evaluations, motor activity and functional observational battery, were measured prior to exposure, after 1, 2, and 3 months of exposure (10/sex/group), and after a 3 month recovery period (5/sex/group). Whole-body perfusion and microscopic examination of selected nervous tissue was conducted after 90-days exposure and after the 90-day recovery period.

In addition to the animals on the 90-day inhalation neurotoxicity study (15/sex/group), and on the 90-day recovery study (10/sex/group), 45 additional female animals were included within the 50 ppm group for toxicokinetic examinations. Blood was sampled pre- and post-exposure on the fifth exposure day in weeks 2, 4, 6, 8, 10 and 12. After completion of 13 weeks of exposure, these animals were then exposed via nose-only inhalation to 50 ppm PCBTF for 6 hours. During the exposure period, three animals were sacrificed and tissue samples (blood, liver, brain, kidney, fat, muscle, and lungs) collected after 0.5, 1.0, 1.5, 2.0, 3.0, 4.5, and 6 hours of exposure. Additional samples were collected 0.5, 1.0, 1.5, 2.0, 3.0, 8.0, and 24 hours post exposure. PCBTF levels were measured in each tissue taken during exposure and post exposure.

RESULTS

Exposure

The achieved mean exposure concentration for each group was very close to the respective target (0, 10, 50, and 250 ppm) and nominal concentration. Particle size and mass distributions were similar for all exposure concentrations including the control group indicating there was no measurable amount of test material present as aerosol.

No test material-related deaths occurred during the course of the study. One male rat was sacrificed on test day 74. The rat was not eating properly due to an apparent malocclusion of the incisors. There were no test material-related physical observations noted during any of the exposures at the 3 levels tested. There were no untoward observations recorded during weekly detailed observations. There was no indication of any test material-related ocular disease.

Body Weights

There were no measurable test material related effects on body weights. A possible effect on food consumption was observed during weeks 2 to 8 in females in all exposure groups. These animals consumed less food than control animals. The effect was evident earlier and persisted longer in the 250 ppm group. Decreased food consumption was also seen in males in the 250 ppm group. This effect is of minimal toxicologic significance.

Hematology

No test material-related differences among groups was seen in any of the hematological parameters in the males. In females, hemoglobin and hematocrit decreased about 6% in the 250 ppm group. These differences were small and within normal range and were not considered to be of any toxicologic significance. No differences were observed in the recovery groups.

Clinical Chemistry

There were no test material-related differences in any of the clinical chemistry parameters in males. In the females exposed to 250 ppm, alanine aminotransferase (ALT) was increased by about 40%, total protein was increased by about 15% and albumin was increased by about 19%. The increase in ALT may be test related because it is consistent with the increase in liver weight. The increase in albumin and protein is not believed to be of toxicological significance.

Neurobehavioral Studies

Whole body inhalation exposure to PCBTF at dose levels of 10, 50, or 250 ppm did not affect motor activity (pretest, month 1, month 2, month 3, and recovery). The number of beam breaks during the 1- hour session for the animals in the PCBTF exposure groups was comparable to control.

There were no test material effects on the nervous system, as measured by a battery of functional observation assessments. For all measurement intervals, home cage, handling, open field and sensory evaluations of animals in the treated groups were considered comparable to control or pretest data. Group mean landing foot splay and grip strength data for all treated groups were either comparable to control data or within the range of normal variation. No convulsions, tremors or abnormal movements were noted in any control or treated animal.

Terminal Organ and Body Weights, Organ/Body and Organ/Brain Weight Ratios

Males in the 250 ppm group had statistically significant increases (15%) in the absolute and relative kidney weights and about 11% in relative liver weights compared to controls. Females in the 250 ppm group had a similar 11% increase in their relative liver weights, but did not have a similar change in kidney weights. In addition, the females had a 39% decrease in their absolute and relative ovary weights.

The slight increase in liver weights correlated with the microscopic observation of centrilobular hypertrophy which is considered to be an adaptive change to PCB exposure. Morphologic changes correlating with the increased kidney weights and decreased ovary weights were evident. No dose-related differences were apparent in the ovary weights. In addition, the ovary weights in both the control and treated animals at termination of the recovery period were similar to the mean ovary weight for the high exposure group females at termination of the exposures. The kidney and ovary weight findings were considered to be of little or no toxicologic significance.

Macroscopic and Microscopic Pathology

There were no remarkable macroscopic changes present among the toxicology group or the neuropathology group of animals either at terminal sacrifice or recovery sacrifice.

There were no compound-related lesions present in the central nervous system or peripheral nerves of the neuropathology animals.

Compound-related centrilobular hypertrophy was present in the liver of 3/10 males and 3/10 females at the high-dose level (250 ppm) at the time of terminal sacrifice. This change correlated well with a statistically significant increase in the absolute and relative liver weights of males and females treated with 250 ppm at terminal sacrifice.

Centrilobular liver hypertrophy was not present among recovery sacrifice animals at any dose-level and it was not present among mid-dose level (50 ppm) animals. The NOEL was 50 ppm for this change.

Toxicokinetic Analysis

The female rat tissue time-concentration data (ug of PCBTF/g of tissue) from the 50 ppm inhalation nose-only exposure study is currently being examined using a PCBTF physiologically-based pharmacokinetic model. The model predicts PCBTF tissue concentrations in the rat. However, several changes are currently needed in the model to account for enhanced metabolism (V_{max} , K_m values) and changes in animal weight and body fat. Inhaled PCBTF is largely eliminated as PCBTF via the lung (90%). Small amounts of PCBTF are metabolized to 3-OH PCBTF (3-5%) and 2,3 diOH PCBTF (2-3%) and eliminated as glucuronic acid conjugates. PCBTF partitions into body fat and is retained somewhat longer in this tissue than in liver or muscle. Low PCBTF levels were found in nervous tissue. Livers from exposed (10, 50, and 250 ppm) and control animals are currently being analyzed for total cytochrome P-450, various forms of cytochrome P-450, and the activity of cytochrome P-450 against several substrates including PCBTF. The liver hypertrophy is believed to be associated with the induction of liver cytochrome P-450 by PCBTF.