

DATA EVALUATION REPORT

STUDY: Rat Two Year Dietary Exposure¹

LABORATORY: International Research and Development Corporation, Mattawn, MI.

STUDY NUMBER & DATE: DTX-80-0016

ACCESSION NUMBER: 071527

MRID:

MATERIAL TESTED: DS 3701 (100%)

ANIMALS: Charles River CD Rats

METHODS:

ENVIRONMENTAL PARAMETERS: Standard GLP

HUSBANDRY: Standard GLP

"Groups of Sprague-Dawley CD rats (75 males and 75 females/group) were administered 4-hydroxy-2,5,6-trichloroisophthalonitrile in the diet at dosage levels of 0, 0.5 and 3 mg/kg/day for 104 weeks. Original dosage levels of 15 and 30 mg/kg/day were reduced at week 30 to 10 and 20 mg/kg/day, respectively, because of poor survival and anemia. Animals were observed daily for mortality and gross signs of toxicity/general appearance. Individual body weights and food consumption were measured regularly during the study. Clinical laboratory studies were performed periodically throughout the study on 10 rats/sex/group at six month intervals. Ophthalmological examinations and urinalyses were performed routinely, and feces were collected and examined to evaluate the observed anemia. Interim sacrifices were performed after 1 year on 10 rats/sex in all groups except for the high dose animals which were all necropsied. Terminal necropsies were performed on all surviving animals after 2 years, selected organs weighed, and complete histopathological examinations conducted.

RESULTS:

Pale skin and eyes were evident for the first 30 weeks in high dose males and females with similar but less marked findings in the 15 mg/kg group. Mortality was significantly increased in the 30 mg/kg group males and females, and in the 15 mg/kg group females. The high dose group was sacrificed at 12 months after the dose level had been reduced to 20 mg/kg at week 30. Decreasing the 15 mg/kg/day dose level at week 30 to 10 mg/kg similarly improved the survivability, which was comparable to controls for the remainder of the study. Body weight was

¹ From: Jaeger, R.B., et al. WHO/FAO Report, 1983, Geneva.

reduced in the 10/15 and 20/30 mg/kg males and females throughout the study, even after reduction of doses. Food consumption was unremarkable except for decreases in 10/15 and 20/30 mg/kg females and 20/30 mg/kg males, consistent with decreased body weights and increased mortality during the first 30 weeks. There were similar decreases in total serum protein, albumin, globulin, and cholesterol in 20/30 mg/kg males and females and 10/15 mg/kg females after 6 months. These returned to control levels for the remainder of the study, after doses were reduced to 20 and 10 mg/kg, respectively.

There were significant hemopoietic effects in the 10/15 and 20/30 mg/kg animals, particularly females, during the first 6 months. Evidence of microcytic anemia was provided by reduced RBC counts, hematocrit, hemoglobin, MCV, and MCH with accompanying increases in MCHC, reticulocytes and metarubricytes. Segmented neutrophils were increased with corresponding decrease in percentage of lymphocytes. Specially stained bone marrow presented evidence of hypocellularity. Mallory's stain of liver tissue revealed an increased iron content (hemosiderin). After 18 and 24 months exposure the 10/15 mg/kg group females continued to present evidence of anemia (decreased Hct, Hgb, MCV, MCH and increased MCHC) with a positive bone marrow response (increased cellularity with a shift to increasing number of immature erythroid cell types and increase number animals with a 1:1 M/E ratio). Prussian Blue staining demonstrated the presence of hemosiderin in the 10 mg/kg males and females, not considered significant at 3 mg/kg. After 24 months exposure there were decreased serum potassium levels in all dosed females. Urinalyses and examination for fecal occult blood were unremarkable, except for increased urine volume at 6 months in the high dose group animals.

Ophthalmological examination at 6 months revealed increased pale ocular structures and spontaneous hemorrhage in high dose male and female animals. At 24 months there were increased numbers of dilated pupils (not responding to light) and increased bilateral cataract disease in high dose males.

Comparison of selected organ weights demonstrated decreased absolute organ weights for kidney, heart and brain in high dose males with no significant relative organ-to-body weight changes. High dose females had decreased absolute kidney and heart weights with no relative weight changes except for spleen and brain. Microscopic examination failed to confirm any compound related effects on these organs. There were no significant compound related non-neoplastic organ changes except for hemosiderin in the liver of high dose females and hemorrhage in CNS tissues, hypocellular bone marrow and post-mortem congestion of lymph in high dose male and female rats.

Examination of tissues/organs for neoplastic changes did not indicate any compound related effects at any level tested.

Data presented in this study demonstrate that the metabolite, 4-hydroxy-2,5,6-trichloroisophthalonitrile, is without adverse effects on male and female rats at levels up to and including 3 mg/kg/day for 2 years (McGee et al., 1983)."

CORE Rating: Guideline.

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