OVERVIEW

7/18/2000

MESOTRIONE (ZA1296)

Study Type: Non-Guideline; 90-Day Dose Response Study in Male Rats

Work Assignment No. 2-01-52F (amend 1) (MRID 44537106)

Prepared for

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OVERVIEW

STUDY TYPE: Correlation of tyrosinemia with toxicity

OPPTS Number: N/A

OPP Guideline Number: Non-Guideline

DP BARCODE: D259369
P.C. CODE: 122990

SUBMISSION CODE: S541375
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Mesotrione (96.8% purity)

SYNONYMS: ZA1296; 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione; 2-(4-mesyl-2-nitrobenzoyl-cyclohexane-1,3-dione

CITATION: Brammer, A., (1997) ZA1296: 90 Day Dose Response Study in Male Rats. Central Toxicology Laboratory, Cheshire, UK, Laboratory Report No: CTL/R/1304; Study No: XR5997, November 19, 1997. MRID 44537106. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, Delaware

Executive Summary: The stated objective of this study (MRID 44537106) was to investigate the correlation between mesotrione-induced tyrosinemia and ocular, body weight, and organ weight changes in male Alpk:Ap$_f$SD rats. Tyrosinemia occurs in animals fed mesotrione or other triketones due to an inhibition of p-hydroxyphenylpyruvate dioxygenase (HPPD). HPPD is involved in the catabolism of tyrosine by catalyzing the oxidative decarboxylation and rearrangement of 4-hydroxyphenylpyruvate (HPPA) to homogentisate. HPPA is formed from tyrosine by the action of tyrosine aminotransferase (TAT). Male Alpk:Ap$_f$SD rats (16/group with 2 control groups) were fed diets containing mesotrione (96.8% purity, batch P17) at 0, 0.5, 1, 3, 4, 5, 7.5, 10, or 100 ppm (equivalent to 0, 0.04, 0.09, 0.27, 0.35, 0.44, 0.67, 0.89, and 8.96 mg/kg/day) for 90 days. Clinical signs, body weights, food consumption, plasma tyrosine levels, urine phenolic acid levels, kidney and liver weights, and liver TAT and HPPD levels were measured and/or recorded. Liver and kidney tissue samples were examined by light and electron microscopy. Ophthalmoscopic exams were performed during the 1 to 2-week acclimatization period and during the last week of the study. Necropsies were performed at termination or upon the event of premature death.

The results of this special study are presented as attachments to this overview (Study Report Tables 4, 5, 7 through 10, 13, and 14, pages 40, 42 through 45, 50 through 54, 60, and 61).

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There were no differences of toxicological concern in body weights, body weight gains (as calculated by the reviewers), or food utilization. There were no differences in food consumption. No treatment-related observations were made at histopathological or electron microscopic examination.

Cloudy/opaque eyes were observed during clinical examinations in the 5, 7.5, 10, and 100 ppm groups (2/16, 1/16, 3/16, and 13/16 treated animals, respectively, vs 0/32 controls). At ophthalmoscopic exam, the incidence of slight to moderate hazy opacity or slight to moderate opacity was increased in the 7.5, 10, and 100 ppm animals (5/32, 6/32, and 22/32 eyes examined, respectively, vs 1/64 controls). Corneal vascularization was observed in 7.5, 10, and 100 ppm animals (1/32, 2/32, and 15/32 eyes examined, respectively, vs 0/64 controls). Ghost vascularization of the cornea was observed in one 100 ppm male only (1/32 eyes examined vs 0/64 controls). At necropsy, opaque eyes were observed in the 7.5, 10, and 100 ppm groups (1/16, 3/16, and 7/16 animals treated, respectively, vs 0/32 controls). Total urinary phenolic acids were increased in all treatment groups at week 13 (↑114-1247%), and reflect the increase in both conjugated (↑53-472%) and free (↑130-2121%) phenolic acids. The proportion of conjugated to free phenolic acids tended to decrease with increasing dose (1.13-0.17 [conjugated/free]), although not strictly dose-dependently. Plasma tyrosine concentrations were elevated ($p \leq 0.01$) with respect to controls in a dose-dependent manner at 24 hours in the 1 - 100 ppm groups (↑40-2661%) and in all treatment groups at weeks 1 (↑292-2696%) and 14 (↑102-2353%). TAT activity was increased ($p \leq 0.05$ or 0.01) at termination with respect to controls in the 3-100 ppm groups (↑35-61%), and HPPD activity was decreased ($p \leq 0.01$) at termination with respect to controls in all treatment groups (↓68-97%), although neither changes were dose-dependent. Relative liver weights were increased ($p \leq 0.05$ or 0.01) in a dose-dependent manner in the 4-100 ppm groups (↑5-15%), whereas absolute liver weights were increased ($p \leq 0.05$ or 0.01) in the 5-100 ppm groups (↑8-13%), but not dose-dependently. Relative kidney weights were increased ($p \leq 0.05$ or 0.01) in 5, 10, and 100 ppm groups (↑4-8%) and absolute kidney weights were increased ($p \leq 0.05$ or 0.01) in 5 and 10 ppm groups only (↑9-10%). There were no treatment-related observations made in the liver or kidneys at histopathological or electron microscopic examination to suggest that the changes in organ weights were other than an adaptive response.

In conclusion, treatment with increasing levels of mesotrione caused a dose-dependent tyrosinemia with associated increases in ocular lesions and urinary phenolic acids output, changes in liver enzyme activities, and adaptive changes in liver and kidney weights.

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