OVERVIEW

7/18/2000

MESOTRIONE (ZA1296)

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

Work Assignment No. 2-01-52G (amend 1) (MRID 44537107)

Prepared for

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OVERVIEW

STUDY TYPE: Correlation of tyrosinemia with toxicity

OPPTS Number: N/A

OPP Guideline Number: non-GDL

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 Female Rats. Central Toxicology Laboratory, Cheshire, UK, Laboratory Report No: CTL/R/1315; Study No: XR6195, November 19, 1997. MRID 44537107. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, Delaware

Executive Summary: The objective of this study (MRID 44537107) was to investigate the correlation between mesotrione-induced tyrosinemia and ocular, body weight, and organ weight changes in female 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). Female Alpk:Ap$_f$SD rats (20/group) were fed diets containing mesotrione (96.8% purity, Batch P17) at 0, 1, 5, 10, 50, 100, 1000, or 2500 ppm (equivalent to 0, 0.09, 0.48, 0.95, 4.82, 9.54, 94.83, and 236.75 mg/kg/day) for 90 days. Four animals/group were sacrificed at 7 and 29 days; the remainder (12/group) were sacrificed at 90 days.

Clinical signs, body weights, food consumption, plasma tyrosine levels, urine ketone levels, kidney and liver weights, and liver TAT and HPPD levels were measured or recorded. Ophthalmoscopic exams were performed during the last week of the study. Necropsies were performed at termination or upon the event of premature death.

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Results of toxicological concern of this special study are presented as an attachment to this overview (Study Report Tables 3, 4, 5, and 8 through 12, pages 34, 38, 42, 43, 49, 50, 52, 55, 56, 57, and 58). There were no differences of toxicological concern in food consumption, food utilization, or kidney weights. Gross necropsy results were not reported.

Body weights were decreased in the 2500 ppm group from week 4 to 14, although not continuously (↓4-6%, $p \leq 0.05$ or 0.01). Body weight gain (as calculated by the reviewers) was decreased in the 2500 ppm group (↓9%). Cloudy eyes were observed during clinical examinations in the 1000 and 2500 ppm groups (7 animals in each treated group vs 0 controls). At ophthalmoscopic exam, the incidence of slight to moderate hazy opacity or slight to moderate opacity was increased in the 100, 1000, and 2500 ppm animals (2/24, 16/24, and 15/24 eyes examined, respectively, vs 1/24 controls). Corneal vascularization was observed in 1000 and 2500 ppm animals (3/24 and 2/24 eyes examined, respectively, vs 0/24 controls). Ghost vascularization of the cornea was observed in one 1000 and one 2500 ppm female (1/24 eyes examined each vs 0/24 controls). Total urinary phenolic acids were increased at week 5 in 100, 1000, and 2500 ppm treatment groups (1.82, 6.95, and 23.0 mg equivalents, respectively, vs not detected in controls). The proportion of conjugated to free phenolic acids tended to decrease with increasing dose (100% conjugated in the 100 ppm group, 18% conjugated in 1000 ppm group, and 12% conjugated in 2500 ppm group). Plasma tyrosine concentrations were elevated ($p \leq 0.01$) with respect to controls in a dose-dependent manner in the 5 - 2500 ppm groups at weeks 2 (↑94-1389%), 5 (↑77-1123%), and 14 (↑72-1154%; Note - 1000 ppm change [1154%] slightly exceeded 2500 ppm change [1108%]). TAT activity was increased ($p \leq 0.05$ or 0.01) with respect to controls at week 2 in the 5-2500 ppm groups (↑65-153%), and at week 5 (↑87-113%) and 14 (↑27-43%) in the 1000 and 2500 ppm groups. HPPD activity was decreased ($p \leq 0.01$) with respect to controls in all treatment groups at week 2 (↓56-99%), week 5 (↓71-98%), and week 14 (↓60-99%). The effect plateaued at ≥5 ppm. Adjusted (to body) liver weights were increased ($p \leq 0.05$ or 0.01) at week 5 in the 5, 50, 100, and 2500 ppm groups (↑6-14%) and at week 14 in the 1000 and 2500 ppm groups (↑6-7%), whereas absolute liver weights were increased ($p \leq 0.01$) in the 50, 100, and 2500 ppm groups at week 5 only (↑19-22%). The increases were not dose-dependent.

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 weights.

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