OVERVIEW

7/18/2000

MESOTRIONE (ZA1296)

Study Type: Non-Guideline; Effect on Tyrosinemia in Female Rats on a High-Tyrosine Diet

Work Assignment No. 2-01-52E (amend 1) (MRID 44505111)

Prepared for

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MESOTRIONE (ZA1296) **Effect on Tyrosinemia (non-GDL)**

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OVERVIEW

STUDY TYPE: Effect on tyrosinemia in female rats given a high-tyrosine diet
OPPTS Number: N/A OPP Guideline Number: non-GDL

DP BARCODE: D259369 SUBMISSION CODE: S541375
P.C. CODE: 122990 TOX. CHEM. NO.: None

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

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

CITATION: Milburn, G. M., (1997) ZA1296: 28 Day Toxicity Study in the Rat: Central Toxicology Laboratory, Cheshire, UK, Laboratory Report No: CTL/R/1308; Study No: XR6167, November 18, 1997. MRID 44505111. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, Delaware

Executive Summary: The objective of this study (MRID 44505111) was to investigate the effect of mesotrione (96.8% purity, Batch P17) on tyrosinemia in female Alpk:Ap$_f$SD rats given a high-tyrosine diet. 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 (8/treatment group) were fed diet with 0, 0.5, 1.0, or 2.5% tyrosine or 100 ppm mesotrione diet with 0, 0.5, 1.0, or 2.5% tyrosine for 28 days. Body weights, food consumption, plasma tyrosine levels, urine ketone body levels, organ weights, and liver TAT and HPPD levels were measured. Ophthalmoscopic exams and necropsies were also performed.

The results of this special study are presented as an attachment to this overview (Study Report Tables 2 through 9, pages 26 through 33). Cloudy eyes were observed at clinical examinations in 8/8 animals in the 3 mesotrione/tyrosine-treated groups, only. Body weights (↓9-11%) and body weight gains (↓23-31%) were reduced ($p \leq 0.01$) with respect to controls in animals receiving 100 ppm mesotrione/2.5% tyrosine (100 ppm/2.5% Tyr), only. Decreased food consumption was observed in the 100 ppm/2.5% Tyr animals (↓8-17%) throughout the study. Food utilization (bodyweight gain [g]/100 g food consumed) was not significantly different between treated and control groups. At the ophthalmoscopic exam, minimal to marked corneal opacity was observed

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in all mesotrione-treated groups, the effect becoming more pronounced with increasing tyrosine levels (1/16 - 16/16 eyes treated vs 0/16 controls). Corneal vascularization was observed in the 100 ppm/1.0% Tyr (10/16 eyes) and 100 ppm/2.5% Tyr (16/16 eyes) treatment groups (vs 0/16 control eyes). Plasma tyrosine concentrations were elevated with respect to controls at all timepoints in the 2.5% Tyr groups (↑73-139%) and in a dose-dependent manner in all mesotrione-treated groups (24 hours post-dose -↑1236-3026%; 1 week post-dose -↑778-2535%; termination - ↑1012-2522%). Urine ketone level were not reported. It was stated that no acetoacetate was detected in any of the urines analyzed, but that HPPA was probably present in high concentrations. TAT activity was increased ($p \leq 0.01$ or 0.001) with respect to controls in the 2.5% Tyr group (↑123%) and in all mesotrione-treated groups (↑189-365%), although not dose-dependently. HPPD activity was decreased ($p \leq 0.05$ or 0.01) with respect to controls in the 2.5% Tyr group (↓54%) and in all mesotrione-treated groups (↓78-93%); the decrease was inversely proportional to the dietary tyrosine concentration. Relative liver weights were increased ($p \leq 0.05$ or 0.01) in all mesotrione-treated groups (↑10 -11%) and in the 0.5% Tyr group (↑6%), whereas absolute liver weights were increased ($p \leq 0.05$) only in the 100 ppm/0% Tyr (↑11%) and the 100 ppm/0.5% Tyr (↑8%). Relative kidney weights were increased in the 100 ppm/0.5% Tyr (↑8%) and 100 ppm/2.5% Tyr (↑15%) groups. At necropsy, cloudy eyes were observed in all mesotrione/tyrosine-treated animals (24/24 treated).

In conclusion, 100 ppm mesotrione in combination with tyrosine in the diet caused marked tyrosinemia and associated ocular lesions and changes in liver enzyme activities. In general, treatment with a combination of mesotrione and tyrosine caused more marked effects than treatment with either compound alone.

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