OVERVIEW

7/18/2000

MESOTRIONE (ZA1296)

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

Work Assignment No. 2-01-52D (amend 1) (MRID 44537103)

Prepared for

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OVERVIEW

STUDY TYPE: Reversibility of liver and kidney weight changes

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., Provan, W.M. (1997) ZA1296: 90 Day Reversibility Studies in Rats. Central Toxicology Laboratory, Cheshire, UK, Laboratory Report No: CTL/R/1302; Study Nos: PR1066 and XR6242, December 22, 1997. MRID 44537103. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, Delaware

Executive Summary: The stated objective of this study (MRID 44537103) was to investigate the reversibility of liver and kidney weight changes in rats induced by dietary administration of mesotrione for 90 consecutive days. Tyrosinemia occurs in animals fed mesotrione or other triketones due to an inhibition of the liver enzyme 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 the liver enzyme tyrosine aminotransferase (TAT). Liver TAT activity can be elevated by high serum tyrosine levels. Male Alpk:ApfSD rats (40/group with 2 control groups) were fed diets containing mesotrione (96.8% purity, batch P17) at 0, 5, 100, or 2500 ppm (equivalent to 0, 0.37, 7.52, and 192 mg/kg/day, respectively) for 90 days. Eight rats/group were terminated at 90 days, 1 week recovery (2500 ppm and 1 control group, only), 2 weeks recovery, 4 weeks recovery, 6 weeks recovery (5 and 100 ppm and 1 control group, only), and 9 weeks recovery. Clinical signs, body weights, food consumption, plasma tyrosine levels, kidney and liver weights, and liver TAT and HPPD levels were measured and/or recorded. Liver and kidney tyrosine levels were determined for the 5 and 100 ppm groups. Liver and kidney tissue samples from the 2500 ppm group and one control group were examined by light (all animals) and electron (4/group) microscopy. Ophthalmoscopic exams

were performed at the end of the 90-day treatment period and during the recovery period prior to termination. 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 3, 4, 5, and 7 through 12, pages 41, 42, 45 through 47, 49 through 51, 61 through 68, 71, 73, 76, and 78 through 82). There were no differences of toxicological concern in food consumption. No treatment-related observations of toxicological concern were made at histopathological or electron microscopic examination. No treatment-related mortalities occurred.

Adjusted (to week 1) body weights were decreased in 2500 ppm rats from weeks 3-21 of treatment (↓2-10%, $p \leq 0.05$ or 0.01). Food consumption was slightly decreased in 2500 ppm rats from weeks 5-8 and 10-13 (↓4-7%, $p \leq 0.05$ or 0.01). Decreases ($p \leq 0.05$ or 0.01) of toxicological concern in food utilization occurred in the 2500 ppm rats during the weeks 5-8 (↓9%), 9-13 (↓20%), and 1-13 (↓9%), and in the 100 ppm rats during weeks 9-13 (↓9%). During clinical examination, cloudy/opaque eyes were observed in the 5, 100, and 2500 ppm groups (1, 37, and 33/40 treated animals, respectively, vs 0 controls) during the treatment period. The opacity resolved during the recovery period, and no observations were made from week 17 onwards. It was stated that the only ophthalmoscopic finding in controls was a slight, unilateral haziness at 9 weeks of recovery; no data were provided. At ophthalmoscopic exam, the incidence of slight to marked hazy opacity or slight to marked opacity was increased in the 5, 100, and 2500 ppm animals at 90 days of treatment (10/80, 56/80, and 46/76 eyes examined, respectively, vs 0 in controls). At 1 (2500 ppm) or 2 (5 ppm) weeks of recovery, ocular opacity had completely resolved in the 5 and 2500 ppm treatment groups. One 2500 ppm animal did have slight hazy opacity after 4 weeks recovery. In the 100 ppm animals, opacity was still apparent during the recovery period at 2 weeks (4/16 eyes, slight hazy opacity), 4 weeks (8/16, minimal hazy opacity), and 6 weeks (4/16, slight hazy opacity). Corneal vascularization was observed in 5, 100, and 2500 ppm animals (2/80, 44/80, and 41/76 eyes examined, respectively, vs 0 in controls) at the end of the treatment period and had resolved by the next examination (1 or 2 weeks of recovery). Ghost vascularization of the cornea was observed during recovery in the 100 ppm group at weeks 2, 6, and 9 (10/16, 14/16, and 4/16 eyes examined, respectively) and in the 2500 ppm group at weeks 1, 2, 4, and 9 (8/14, 10/16, 8/16, and 10/14 eyes examined, respectively). Ghost vascularization was observed in one 5 ppm animal at 6 weeks recovery.

Plasma tyrosine concentrations were elevated ($p \leq 0.01$) with respect to controls at the first timepoint in the 5 (1 week), 100 (1 week) and 2500 (24 hours) ppm group (↑818%, 1460%, and 2215%, respectively) and at the end of treatment (week 14 -↑726, 1279, and 939%, respectively). Plasma tyrosine remained elevated ($p \leq 0.01$) during the recovery period in the 2500 ppm group at weeks 15 (↑240%), 16 (↑274%), and 23 (↑21%). Plasma tyrosine levels remained slightly elevated ($p \leq 0.05$ or 0.01) in the 5 and 100 ppm groups at weeks 16 (↑22-45%) and 20 (↑17-22%). Kidney tyrosine levels were increased in the 5 and 100 ppm groups at the end of treatment (week 14 - ↑246 and 402%, respectively; $p \leq 0.05$). Liver tyrosine concentration was also increased in both groups at the end of treatment (↑626 and 1102%, respectively; $p \leq 0.01$). Levels had returned to normal by week 16. TAT activity was increased ($p \leq 0.01$ in 2500 ppm group only) in all treatment groups at the end of treatment (week 14 - ↑15-66%). At week 15, TAT activity was slightly elevated in the 2500 ppm group (↑28%, p = not significant). By week

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16, TAT levels were not different from controls in any treatment group. HPPD activity was decreased ($p \leq 0.01$) at the end of treatment in all treatment groups (↓89-96%). During the recovery period, HPPD activity slowly returned to control levels, but was still depressed at week 23 (↓22-36%; $p \leq 0.01$ in 5 and 100 ppm groups, not significant in 2500 ppm group). Adjusted (to body) liver weights were increased dose-dependently at week 14 in all treatment groups (↑10-20%, $p \leq 0.01$). At subsequent timepoints (weeks 15, 16, 18, and 23), adjusted liver weights were consistently increased only in the 2500 ppm group (↑10-14%; $p \leq 0.05$ or 0.01). Absolute liver weights were increased ($p \leq 0.05$ or 0.01) in the 5 and 100 ppm groups at week 14 (↑11%), but not in the 2500 ppm group. Absolute liver weights were not increased at later dates except in the 5 ppm group at week 23 (↑12%, $p \leq 0.05$). Adjusted (to body) kidney weights were increased ($p \leq 0.05$ or 0.01) at week 14 in 5, 100, and 2500 ppm groups (↑12, 12, and 10%, respectively), whereas absolute kidney weights were increased ($p \leq 0.05$ or 0.01) in 5 and 100 ppm groups only (↑13 and 11%, respectively). Increases ($p \leq 0.05$ or 0.01) in adjusted kidney weights also occurred in the 2500 ppm group at week 15 (↑5%) and week 23 (↑15%). Increases in absolute kidney weights at later dates occurred only in the 5 ppm group at week 23 (↑12%, $p \leq 0.05$). Decreases in adjusted (to body) and absolute brain weights occurred only in the 100 ppm group at week 14 (↓4%, $p \leq 0.05$)

In conclusion, treatment with mesotrione caused tyrosinemia with associated increases in ocular lesions, changes in liver enzyme activities, and adaptive changes in liver and kidney weights. Upon removal of mesotrione from the diet, complete recovery was observed in the ocular lesions, plasma, liver, and kidney tyrosine levels, TAT activity, and kidney weights. Partial recovery was observed in HPPD activity and liver weights.

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