OVERVIEW

7/18/2000

MESOTRIONE (ZA1296)

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

Work Assignment No. 2-01-52K (amend 1) (MRID 44505116)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Guy Beretich, Ph.D.

Signature: Guy Beretich
Date: 4/27/00

Secondary Reviewer
Ashlee W. Duncan, M.S.

Signature: Ashlee W Duncan
Date: 4/27/00

Program Manager
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 4/28/00

Quality Assurance:
Steve Brecher, Ph.D.

Signature: Steve Brecher
Date: 4/27/00

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

FIR

EPA Reviewer: David Nixon, DVM
Registration Action Branch 1/HED (7509C)

David Nixon 7/12/2000

Work Assignment Manager: Marion Copley, DVM, DABT
Registration Action Branch 1/HED (7509C)

Marion Copley 7/18/2000

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% a.i.)

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 Dietary Dose Response Study in Mice. Central Toxicology Laboratory, Cheshire, UK, Laboratory Report No: CTL/R/1316; Study No: XR6168, December 19, 1997. MRID 44505116. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, Delaware

Executive Summary: The objective of this study (MRID 44505116) was to investigate the tyrosinemia induced by mesotrione over a range of dose levels in male and female C57BL/10J$_f$AP/Alpk mice. 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). C57BL/10J$_f$AP/Alpk mice (20/sex/group) were fed diets containing mesotrione (96.8% a.i., Batch P17) at 0, 1, 10, 50, 100, 350, 1000, 3500, or 7000 ppm (equivalent to 0, 0.16/0.19, 1.69/1.94, 8.49/10.80, 17.95/20.46, 58.46/72.70, 179.27/214.88, 599.85/714.76, or 1222.53/1436.40 [M/F] mg/kg/day) for 90 days. Ten animals/sex/group were sacrificed at 1 and 4 weeks; the remainder (10/sex/group) were sacrificed at week 14.

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 or recorded. Necropsies were performed at termination or upon the event of premature death.

2

Results of toxicological concern of this special study are presented as an attachment to this overview (Study Report Tables 6, 7, 8, 10, and 11, pages 64 through 68 and 82 through 85). There were no differences of toxicological concern in clinical signs, body weights, body weight gain (as calculated by the reviewers), and food consumption. Gross necropsy results were not reported. Differences in organ weights were minor and/or not time and dose-dependent and therefore not considered of toxicological concern.

Food utilization was decreased ($p \leq 0.05$ or 0.01) in 7000 ppm females for the overall treatment period (weeks 1-13, ↓22%), due primarily to a decrease at weeks 5-8 (↓41%). Free urinary phenolic acids were increased at week 13 in the 1-7000 ppm females (0.56-13.87 mg equivalent/mL in treated animals vs non detectable in controls) and the 10-7000 ppm males (4.20-15.52 mg equivalent/mL in treated animals vs 1.43-2.39 in controls). Conjugated phenolic acids were not detected in the male urine and detectable but not quantifiable due to very low levels in the female urine at ≥3500 ppm. Plasma tyrosine concentrations were elevated ($p \leq 0.01$) with respect to controls as follows: at week 1 in the 1-7000 ppm males (↑49-513%) and the 10-7000 ppm females (↑110-451%); at week 4 in the 10-7000 ppm males (↑139-449%) and in the 1-7000 ppm females (↑40-493%); and at week 14 in the 10 and 100-7000 ppm males (↑87-257%) and the 10-7000 ppm females (↑69-316%).

TAT activity was increased ($p \leq 0.05$ or 0.01) with respect to controls as follows: at week 1 in the 100 and 1000 ppm males (↑29-33%) and the 50, 100, 1000, and 3500 ppm females (↑37-64%); at week 4 in the 350 ppm males (↑49%) and 1-7000 ppm females (↑47-104%); at week 14 in the 3500 ppm males (↑33%) and the 50-7000 ppm females (↑41-69%). HPPD activity was decreased ($p \leq 0.05$ or 0.01) with respect to controls as follows: at week 1 in all male (↓64-94%) and female (↓69-97%) treatment groups; at week 4 in all male (↓55-97%) and female (↓58-96%) treatment groups; at week 14 in all male (↓48-92%, excluding the 50 ppm males) and 100-7000 ppm female (↓60-75%) treatment groups.

In conclusion, treatment with increasing levels of mesotrione caused tyrosinemia with associated increases in urinary phenolic acids output and changes in liver enzyme activities.

ATTACHMENT

THE FOLLOWING ATTACHMENT IS NOT AVAILABLE ELECTRONICALLY
SEE THE FILE COPY

Page _____ is not included in this copy.

Pages 5 through 13 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confi
by product registrants. If you have any questions, please
the individual who prepared the response to your request.