# OVERVIEW

7/18/2000

MESOTRIONE

Study Type: Non-Guideline; Extent of Tyrosinemia and Ocular Lesions Induced by 50 Triketone Herbicides in Rats

Work Assignment No. 2-01-52L (MRID 44505110)

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

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|---|---|
| Primary Reviewer<br>Kelley Van Vreede, M.S. | Signature: Kelley Van Vreede<br>Date: 7/28/00 |
| Secondary Reviewer<br>Guy Beretich, Ph.D. | Signature: Guy Beretich<br>Date: 4/28/00 |
| Program Manager<br>Mary L. Menetrez, Ph.D. | Signature: Mary L Menetrez<br>Date: 9/28/00 |
| Quality Assurance<br>Steve Brecher, Ph.D. | Signature: Steve Brecher<br>Date: 4/28/00 |

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**MESOTRIONE (ZA1296)** **Correlation of Tyrosinemia and Ocular Lesions with 50 Triketones (non-GDL)**

EPA Reviewer: David Nixon, D.V.M.
Registration Action Branch 1/HED (7509C)

David Nixon 7/12/2000

Work Assignment Manager: Marion Copley, D.V.M., D.A.B.T.
Registration Action Branch 1/HED (7509C)

Marion Copley 7/18/2000

## OVERVIEW

STUDY TYPE: Subchronic Oral Toxicity feeding - rats
OPPTS Number: NA
OPP Guideline Number: non-GDL

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

TEST MATERIAL (PURITY): Over 50 triketone compounds (purities not provided)

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

CITATION: Provan, W.M. Whitfield, A.C., Naylor, J.L. (1994). The Extent of Tyrosinemia and Ocular Lesions Induced by 50 Triketone Herbicides in Rats. Zeneca Central Toxicology Laboratory, Cheshire, UK. Laboratory Report No. CTL/R/1204, October 30, 1994. MRID 44505110. Unpublished.

SPONSOR: Zeneca, Inc. Agricultural Products, Wilmington, DE

EXECUTIVE SUMMARY: The objective of this study (MRID 44505110) was to compile the results of 15 studies in which over 50 triketone compounds were evaluated to assess the relationship between plasma and ocular tyrosine levels and between plasma tyrosine and the incidence of corneal lesions in the Alpk:Ap$_f$SD rat. Each study consisted of 1 negative control group (typically 8 males), one positive control group (typically 12 males treated with SC0735 or ICIA0051), and up to 6 groups (typically 16 males/group) treated with one of the triketone analogues. Exposure periods ranged from 4 to 13 weeks.

The studies compiled in this report were designed to evaluate the ocular toxicity of a group of structurally divergent triketones in the rat and to identify those structural features of a triketone which affect its ocular toxicity potential. The identities of the tested compounds and the details of the study designs are presented in an attachment (Study report Tables 1 and 2, pages 50-54). In the initial studies, rats were dosed orally by gavage with triketones (10 mg/kg, nominally) daily for up to 6 weeks. In the later studies, dietary dosing was conducted and test substances were administered at 1 to 80 ppm daily for 4-13 weeks. The NOAEL for ocular toxicity induced by ICIA0051, the positive control used for the dietary studies, has been defined in a 2 year rat bioassay as 1 ppm; therefore, comparison of the ocular toxicity of novel triketones with ICA0051 over a 6 week period was expected to give an indication of the relative ocular toxicity potential of these compounds in a 2 year bioassay. Ophthalmoscopic examinations were conducted before



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and during the study, and at study termination. In addition, plasma and ocular tyrosine measurements were made during the study and/or at study termination.

The following conclusions were drawn from these gavage and dietary studies of triketones in the rat:

- Many triketones caused increased plasma and ocular tyrosine concentrations and induced ocular lesions.
- Structurally similar triketones can have markedly different potencies.
- The least potent test substances included enamine pro-herbicide derivatives of triketones.
- Plasma and ocular tyrosine concentrations are closely related; ocular tyrosine levels are generally twice as high as plasma tyrosine levels (See attachment, Study report Figure 16, page 48).
- Higher plasma tyrosine concentrations increased the risk of corneal lesions (See attachment, Study report Figure 17, page 49).
- Evidence suggests that there may be a tyrosine threshold (1000 nmol/mL in plasma) for ocular lesion development.
- The ocular lesion produced by triketones is due to prolonged tyrosinemia rather than a direct effect of the triketone on the cornea.

ATTACHMENT

THE FOLLOWING ATTACHMENT IS NOT AVAILABLE ELECTRONICALLY
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Page _____ is not included in this copy.

Pages 5 through 11 are not included in this copy.

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_____ 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.

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