UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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JUL 27 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: In Vitro UDS Assay in Rat Hepatocytes with Ally (Metsulfuron Methyl)

TO: Walters/Taylor, PM 25
Registration Division (7505C)

FROM: Byron T. Backus, Ph.D., Toxicologist Byron T. Backus 7/22/94
Toxicology Branch 2
HED (7509C)

THROUGH: K. Clark Swentzel K. Clark Swentzel 7/22/94
Section Head, Review Section II
Toxicology Branch 2
HED (7509C)

and

Marcia van Gemert, Ph.D., Branch Chief Marcia van Gemert 7/25/94
Toxicology Branch 2
HED (7509C)

DP Barcode: D200641 Submission: S460769

Chemical: 122010

Action Requested: Review of additional information (in MRID 430356-01, a response to previous reviews by the Agency) regarding solubility of the test material in culture medium, as well as data from an additional concentration (3000 µg/mL) of the test material.

EXECUTIVE SUMMARY: The test material was assayed at its solubility limit (3000 µg/ml) in an unscheduled DNA synthesis study with primary rat hepatocytes. **There were no indications of UDS at this dose level. The test material was negative in this assay, as was observed in a previous study with doses of 0.5 to 2500 µg/ml.**

STUDY CLASSIFICATION: Acceptable. This study, when combined with the previously reviewed study with doses from 0.5 to 2500 µg/ml (MRID 417739-01), satisfies the 84-4 other genotoxic effects data requirement, and is acceptable as supporting data for purposes of registration and/or reregistration. There was no indication of any UDS activity associated with exposure to the test material under the conditions of either this or the previous assay.

Guideline Series 84: **MUTAGENICITY**

Reviewed by: Byron T. Backus, Ph.D. Byron T. Backus 7/22/94
Section II, Toxicology Branch II (7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 7/22/94
Section II, Toxicology Branch II (7509C)

DATA EVALUATION REPORT I

STUDY TYPE: in vitro UDS Assay in Rat Primary Hepatocytes

CHEMICAL: Metsulfuron-methyl

Tox. Chem. No.: 419H

PC Code: 122010

MRID NUMBER: 430356-01 SYNONYMS/CAS No.: 74223-64-6

SPONSOR: E.I. Dupont de Nemours and Company

TESTING FACILITY: Haskell Laboratory
Elkton Road, P.O. Box 50
Newark, DE 19714

TITLE OF REPORT: Assessment of IN T6376-74 in the In Vitro Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes.

Note: this is a supplemental report.

AUTHORS: Bentley, K. S.

STUDY NUMBER: Haskell Laboratory Supplemental Report No. 574-90

STUDY COMPLETION DATE: September 9, 1993

EXECUTIVE SUMMARY: The test material was assayed at its solubility limit (3000 µg/ml) in an unscheduled DNA synthesis study with primary rat hepatocytes. **There were no indications of UDS at this dose level. The test material was negative in this assay, as was observed in a previous study with doses of 0.5 to 2500 µg/ml.**

STUDY CLASSIFICATION: Acceptable. This study, when combined with the previously reviewed study with doses ranging from 0.5 to 2500 µg/ml (MRID 417739-01), satisfies the 84-4 other genotoxic effects data requirement, and is acceptable as supporting data for purposes of registration and/or reregistration. There was no indication of any UDS activity associated with exposure to the test material under the conditions of this assay.

A. MATERIALS

1. Test Material: Metsulfuron Methyl
   Description: Off-white solid
   Lot number: ? - Haskell No. reported as 20181
   Batch Code: Not reported
   Purity: 98.8%
   Receipt date: Not reported
   Stability: Not reported
   Contaminants: Not reported
   Solvent used: DMSO

2. Control Materials:
   Solvent: DMSO.
   Positive: 2-Acetylaminofluorene (2AAF) at 0.2 µg/mL.

3. Test animals: No information given.

4. Dose selection: Previously (see the study in MRID 417739-01, reviewed in Caswell document 008399, dated June 6, 1991) dose levels evaluated were 0.5 to 2500 µg/mL, with no evidence of cytotoxicity and/or unscheduled DNA synthesis at any dose level. In this study the test material was evaluated at 3000 µg/mL, along with a negative (solvent?) and positive control.

5. Criteria for a valid assay: Not given in this report, but it is stated (p. 7) that: "the procedures and materials used to assess UDS were in accordance to those described in the original report..."

   It is noted that the viability of the hepatocytes following isolation from the liver was 96.2%, and that cells were swelled in 1% sodium citrate for 8 minutes.

6. There is a signed and dated Quality Assurance Documentation sheet on p. 6 of the report. There is a signed and dated Good Laboratory Practice Statement on p. 3 of the report.

B. TEST PERFORMANCE AND RESULTS:

1. Solubility testing: From p. 7: "IN T6376-74 readily dissolved in dimethyl sulfoxide (DMSO) at concentrations ≤ 500 mg/mL. Solutions of 250, 300, 350, 400, and 500 mg IN T6376-74/mL DMSO were prepared and added to warm Williams' medium E (WME, pH 7.15) at 1% (v/v) to produce final concentrations of 2500, 3000, 3500, 4000, and 5000 µg/mL. Volumes of DMSO added to the medium did not exceed 1% since organic solvents are cytotoxic to cultured cells above this level."

The test material (when added as a solution in DMSO) formed a precipitate at doses ≥3500 μg/mL which did not clear with stirring or following incubation at 37°C for 16.5 hrs. At 3000 μg/mL the test material precipitated but redissolved with mixing. When the test material (without DMSO) was added directly to culture medium "the material would not (completely?) dissolve with vortexing and incubation at 37°."

2. Procedures and materials in the mutagenicity assay were essentially the same as previously reported (see the study in MRID 417739-01, reviewed in Caswell document 008399, dated June 6, 1991)

Results: Refer to appended page 1. There was no indication of an increase in mean nuclear grains/cell at 3000 μg/mL. The positive control (2AAF at 0.2 μg/mL) elicited the appropriate response. There was no indication of any cytotoxicity at this dose level.

C. CONCLUSIONS:

The solubility information provided in this supplementary report adequately demonstrates that 3000 μg/mL is essentially the highest concentration of test material that can be assayed in this type of UDS study. The study also demonstrates that, at 3000 μg/mL and under these experimental conditions, there were no indications of any unscheduled DNA synthesis (nor was there any indication of cytotoxicity). It has been previously noted (Caswell document 008399) that the test material was negative for UDS activity (and cytotoxicity) in rat hepatocytes at doses ranging from 0.5 to 2500 μg/mL.

This study, when combined with the previously reviewed study which utilized doses ranging from 0.5 to 2500 μg/ml (MRID 417739-01), satisfies the 84-4 other genotoxic effects data requirement, and is acceptable as supporting data for purposes of registration and/or reregistration.

PDR 011129

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Pages _____ through _____ are not included in this copy.

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