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

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SEP 28 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Memorandum

Subject: Azinphos-methyl (Guthion) Registration Standard, EPA Identification No. 3125-108: Submission of Mutagenicity Study. Caswell No. 374

From: John H.S. Chen, D.V.M. John H.S. Chen 9/18/87
Review Section I
Toxicology Branch
Hazard Evaluation Division (TS-769C)

To: Dennis Edward, Product Manager (12)
Insecticide and Rodenticide Branch
Registration Division (TS-767C)

Thru: Robert B. Jaeger, Section Head RBJ 9/18/87
Review Section I
Toxicology Branch
Hazard Evaluation Division (TS-769C) 9/22/87

Action Requested:

Review and Assessment of the Salmonella/Mammalian-Microsome Mutagenicity Assay with Guthion. Microbiological Associates, Inc. Study No. T5573.501, August 5, 1987.

Petitioner:

Mobay Corporation, Stilwell, KS 66085

Toxicology Branch Recommendation:

The Ames test with Guthion was conducted in a manner to generate valid results. This study is acceptable to support the data requirements for Azinphos-methyl registration standard. Negative response at 33 through 4000 ug/plate with and without metabolic activation.

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84-2 - Salmonella Mutagenicity Test

Reviewed by: John H.S. Chen 9/18/87
Section I, Toxicology Branch (TS-769C)
Secondary reviewer: R.B. Jaeger 9/18/87
Section I, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: Gene Mutation in Bacteria

TOX. CHEM. No.: 374

Accession No.:

MRID No.: 403013-01

Test Material: Guthion (Lot No. 79-R-225-42)
88.8% Purity

Study Number(s): T5573.501

Sponsor: Mobay Corporation, Stilwell, KS 66085

Test Facility: Microbiological Associates, Inc. Bethesda, MD 20816

Title of Report: Samonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with Guthion

Author(s): Timonthy E. Lawlor

Report Issued: August 5, 1987

Conclusions:

Guthion (lot No. 79-R-225-42) was found to be nonmutagenic to TA1535, TA1537, TA1538, TA100 and TA98 strains of Salmonella typhimurium with and without metabolic activation at the concentrations tested (33 through 4000 ug/plate).

Concentrations tested: 1st Experiment: 33, 100, 333, 1000 and 2000 ug/plate
2nd Experiment: 100, 333, 1000, 2000, 3333, and 4000 ug/plate

Classification of Data: Acceptable

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Title of Study: Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with Guthion
Microbiological Associates, Inc. Study No. T5573.501
August 5, 1987

Procedure:

1. The mutagenicity of Guthion dissolved in DMSO at seven concentrations (33, 100, 333, 1000, 2000, 3333 and 4000 ug/plate) was evaluated by the Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay in the presence or absence of metabolic activation (Ames et al., Mutation Res. 31: 347-364, 1975; Maron and Ames, Mutation Res. 113: 173-215, 1983). Five histidine-requiring strains of Salmonella typhimurium (TA1535, TA1537, TA1538, TA100 and TA98) were used in this study. Mutations were quantified on triplicate plates for each strain by counting the His^+ revertant colonies after 48 hours of incubation at 37°C. on a selective agar plate. If the compound is mutagenic, it would demonstrate at least two-fold increase of the number of revertant colonies over the control value and also exhibit a dose-related increase in the number of histidine-independent colonies. The toxic effects of the test compound to TA100 culture were also recorded. Positive controls and solvent control were run concurrently with the test compound in this study.

2. The in-vitro mammalian metabolic activation system consisted of liver homgenate (S-9) from Aroclor 1254 treated male Sprague-Dawley rats and the cofactor solution described by Ames et al. (1975). One ml of the microsomal enzyme reaction mixture (S-9 mix) contained the following components: S-9, 0.1 ml; 0.2M $MgCl_2$/0.825M KCl, 0.04 ml; 0.04M NADP, 0.1 ml; 0.05M Glucose-6-Phosphate, 0.1 ml; 1M NaH_2PO_4/K_2HPO_4, pH7.4, 0.1 ml; H_2O, 0.56 ml.

Results:

1. Following the exposure to an overnight TA100 culture with ten concentrations of Guthion (10, 33, 67, 100, 333, 667, 1000, 3333, 6667 and 10000 ug/plate) on a selective minimal agar plate for 48 hours at 37°C. in the presence and absence of rat liver microsomes, cytotoxicity was detectable in the highest concentrations tested (3333, 6667 and 10000 ug/plate - Table 1). The appropriate maximum dose to be plated in the mutagenicity study would be 2000 ug/plate. However, this dose subsequently proved to be inappropriate as adequate toxicity was not observed in the initial mutagenicity assay (See attached Tables 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11). For this reason, a second mutagenicity assay was performed with a maximum dose of 4000 ug/plate and appropriate test compound toxicity was observed (See attached Tables 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21).

2. The specific procedures for confirming the genotypes of TA1535, TA1537, TA1538, TA98 and TA100 strains of Salmonella typhimurium are considered adequate.

3. The spontaneous revertant colonies for each of the five strains Salmonella typhimurium were found within the normal range of His+ revertant colonies recommended by the Ames Test (i.e., W/O S9: TA1535, 10-50; TA1537, 5-19; TA1538, 10-30; TA100, 100-200; TA98, 15-45. W/S9: TA1535, 4-26; TA1537, 5-19; TA1538, 13-39; TA100, 100-200; TA98, 15-50) (See attached Tables 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21).

4. The strain specific control compounds (2-nitrofluorene, sodium azide and 9-aminoacridine) and the positive control (2-aminoanthracene) to ensure the efficacy of the activation system have given strongly the positive responses as expected (See attached Tables 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21).

5. No statistically significant increases (less than 2-fold) in the number of revertant colonies for any tester strains were observed following exposure to the test compound (33 through 4000 ug/plate) in either the presence or absence of metabolic activation (See attached Tables 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21).

Conclusion:

Under the test conditions reported, the assay was conducted in a manner to generate valid results. Therefore, the test compound, Guthion, was not mutagenic in the Ames Salmonella/Mammalian-Microsome Mutagencity Test either with or without metabolic activation at the concentrations tested (33 through 4000 ug/plate). The study is acceptable.

Azinphos-methyl RIN: 7365-92

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