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

JUL 30 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID No. 8340-17: Triphenyltin Hydroxide - Review of Mutagenicity Studies: Gene Conversion in S. cerevisiae D4 and Unscheduled DNA Synthesis in Rat Primary Hepatocytes

TOX CHEM NO. 896E
TOX PROJECT No. 1266
Record No. 166079

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Background

The American Hoescht Corporation has submitted two mutagenicity studies with triphenyltin hydroxide (TPTH) in response to the data requirements as indicated in the Registration Standard for this chemical. These studies were reviewed as below.

Studies Reviewed

Study	Results	Comments
Gene Conversion in S. cerevisiae D4	Negative up to and including 5 ug/mL nonactivation system and 15 ug/mL with the S-9 activation system.	ACCEPTABLE

84-2A, 84-4 MRID 155521, 155522

Study	Results	Comments
Unscheduled DNA synthesis in rat primary hepatocytes.	Negative at up to and including dose levels that are cytotoxic (i.e., 0.5 ug/ml).	ACCEPTABLE

HOE 029664 - Substance Technical Grade:
Gene Conversion Test in S. cerevisiae D4

Instituo di Ricerche Biomediche "Antoine Marxer" (Italy) Study No. M890, October 24, 1985, EPA Accession No. 260962.

In this study type, mutagenic activity is evaluated as the capacity of the test substance to cause an increase in gene convertant frequency as revealed by growth in selective media or media deficient in adenine or tryptophan, because the susceptible genes are involved in the biosynthesis of these chemicals.

The test materials used for this study were triphenyltin hydroxide (TPTH, 97.2% pure) and the positive control substances methylmethane-sulfonate (MMS) and cyclophosphamide (CP). The TPTH was dissolved in DMSO for testing. The test dose levels used were selected based on preliminary rangefinding studies and were 0, 0.1, 1, 3, and 5 ug/mL for the nonactivation system and 1, 5, 10, and 15 ug/mL for the activation system. Four plates per condition were prepared. The test protocol was modeled after the EEC Guidelines (Annex V, 6th Amendment). The test organism, Saccharomyces cerevisiae D4 was originally supplied by the "Laboratorie di Mutagenesi e Differenziamonte" in Pisa, Italy. The S-9 mix was prepared from rats pretreated with 500 mg/kg of Aroclor 1254. Statistical evaluations were made with the Chi-square method.

Results

The positive controls responded as expected, giving convertant frequencies of 13 to 14 for the trp 5 gene and 19 to 20 for the Ade 2 gene in the presence of metabolic activation and 15 and 14 to 15 for these gene locuses when metabolic activation was absent.

TPTH did not show evidence of a positive mutagenic response in any condition. At the higher dose levels TPTH was clearly cytotoxic to the yeast cells.

Conclusion

This study is ACCEPTABLE. TPTH was not demonstrated to induce mutations in this study at dose levels up to and including cytotoxic levels.

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Evaluation of Fentinhydroxide, Substance Technical Grade (Code: HOE 029664 2D97 0004) In the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay

Litton Bionetics, Inc., Study or Project No. 20991, October 1985, EPA Accession No. 260962.

The principle of this study type is that rat liver hepatocytes will not take up 3H-thymidine into their DNA at significant levels unless an agent induces DNA damage and the cells respond by making more DNA to repair the damaged nuclear material.

The test materials used were triphenyltin hydroxide (TPTH, 97.2% pure) and 2-acetyl aminofluorene (2-AAF) used as a positive control. TPTH was tested at 0.01, 0.025, 0.05, 0.1, 0.25, 0.5, 1.0, and 2.0 ug/mL and the test material was incorporated into the media with DMSO. The net nuclear grain count of radioactivity was determined for 50 randomly selected cells on each coverslip for each assay replication (3). Unscheduled DNA synthesis was evaluated after 18 to 19 hours of incubation. The study report included an extensive discussion of assay acceptance criteria.

Results

The positive control gave the expected positive response and was 22- to 23-fold higher than the control for the UDS grains/nucleus. The test chemical TPTH at dose levels up to 0.5 ug/mL (higher doses were lethal to the cells) did not result in increases in UDS grains/nuclei or show other signs of a positive mutagenic response.

Conclusion

This study is ACCEPTABLE and demonstrates that TPTH at dose levels up to and including dose levels that are cytotoxic did not induce unscheduled DNA damage.

[Note: The raw data were not presented but are reported as being on file at Litton Bionetics.]