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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Gibberelin A4A7 (GA4A7) - Mutagenicity Studies
Submitted under MRID Nos. 40873207, 40873206, and 40873209
EPA Registration Nos. 275-2, -32 (EPA ID 043801)

TOX Chem No.: 467
TB Project No.: 9-0440
RD Record No.: 235443

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Request

Screen the following three mutagenicity studies, all performed at Microbiological Associates, Inc. (MBA), Rockville and Bethesda, MD, required as part of tier testing, to determine additional data requirements under Biorational Guidelines Data Requirement 152-17 (Genotoxicity):

1. Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay, reported by T.E. Lawlor, MBA Project No. T8201.501014, Final Report dated September 21, 1988 (EPA MRID No. 40873207).

2. Micronucleus Cytogenetic Assay in Mice, reported by Donald L. Putman, MBA Project No. T8201.122, Final Report dated October 24, 1988 (EPA MRID No. 40873208).

3. Unscheduled DNA Synthesis Assay in Rat Primary Hepatocytes with a Confirmatory Assay, reported by Rodger D. Curren, MBA Project No. T8201.3800009, Final Report Dated October 21, 1988 (EPA MRID No. 40873209).

TE Conclusions/Recommendations

All studies submitted satisfy the data requirements for genotoxicity specified in 152-17 et seq.

Study 1 (Ames Test) was conducted according to current Agency Guidelines as well as validated (published) methodology and evaluation criteria, up to levels of toxicity (10,000 ug/ test article per plate) in two separate assays. The negative results reported (no increased his^+ revertents in any of the standard set of five histidine-negative (TA) strains of Salmonella typhimurium LT_2) are considered valid, and the study would satisfy the data requirement for gene mutation in bacteria (Tier I). Although confirmation for this genetic endpoint in a mammalian test system is desirable, no further testing in this category (i.e., Tier II gene mutation) is required.

The mouse micronucleus assay (Study 2) was also conducted according to recognized testing Guidlines, with the appropriate number of animals of both sexes injected intraperitonally with test article at doses up to 80 percent (= 1200 mg/kg) of a demonstrated acute $LD_{50/7}$ (=1465 mg/kg). No increased incidence of micronucleated-polychromatic erythrocytes (m-PCE) was found at any dose level, including the HDT at which both clinical toxicity (lethargy) and cytotoxicity (20 to 30% decrease in the ratio of PCE to total erythrocytes). Hence, this study and its negative results are adequate to satisfy the Tier II data requirement for cytogenetic (chromosomal damage) testing.

The UDS study in primary rat hepatocyte cultures (Study 3) consisted of two separate assays (initial and confirmatory) of the test substance administered up to dose levels (150, 500 ug/mL) causing moderate to severe toxicity, but no increase in mean silver grain count at any dose. Both procedures and reporting were adequate to support these negative results, and thus the study satisfies the data requirement for other mechanisms of genotoxicity.

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No further testing of gibberelin-A4A7 for genotoxicity is required at this time.