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

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JAN 16 1989

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: 019201-3. MCPB Data Call-In. Company Response to
Toxicology Review of Mutagenicity Studies

Tox. Chem. No. 558
Project No. 9-3314

TO: Franklin D. Rubis, PM Team No. 50
Generic Chemical Support Branch (TS-767c)
Special Review and Reregistration Division

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Record No(s). 234435

Background and Request:

Rhone-Poulenc AG Company submitted 4 mutagenicity studies in response to the MCPB data call-in. The Toxicology Branch reviewed the studies and requested additional information before the studies could be graded as acceptable by the Agency. The studies in question were an Ames Assay, a forward mutation/CHO cells assay, an in vitro cytogenetics assay and a rat hepatocyte primary culture assay (DNA damage and repair). In all four studies the Agency requested additional information on the impurities and stability of the test article. In addition, for the Ames assay, the Agency requested a rationale for changing solvents from DMSO for the cytotoxicity assay to ethanol for the definitive assay; and for the cytogenetics assay, the Agency requested data on the periodic checking of the cell line for Mycoplasma contamination and karyotype stability.

The Registrant has submitted the additional information requested and the Toxicology Branch has been requested to review and respond to the updated mutagenicity data.

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Response:

The Toxicology Branch I-IRS (TB-I) has reviewed the additional data on the mutagenicity studies submitted on MCPB and is upgrading all 4 of the studies from unacceptable to acceptable. Specific comments are as follows:

1. The Registrant stated that a detailed analysis of MCPB from the lot tested was previously submitted to the Agency in a product chemistry report. The purity of the test substance is 97.6% (U.S. analysis) and the material tested was the technical material.
2. The test material is reported to be stable for at least 15 years at ambient temperature. The Registrant stated that a report on stability is currently in preparation.
3. An acceptable rationale for changing solvents in the Ames assay was provided by the Registrant.
4. In the cytogenetics assay, the cell line was checked for mycoplasma contamination and for karyotype stability.
5. Since all of the 4 submitted studies are now upgraded to acceptable, it should be noted that MCPB tested positively in the cytogenetics study with metabolic activation at 750 ug/ml. There were statistically significant increases in aberrations/cell, and in proportion of aberrant metaphases. Dose related trends were noted at the low and mid doses (75 and 350 ug/ml). Therefore, there is concern for mutagenic activity with this chemical.