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

JUN 12 1990

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: Azinphos-Methyl (Guthion)
ID Number 3125-108
Tox Chem No. 374
HED Project No. 9-2284

From: John H.S. Chen, D.V.M. John H.S. Chen 6/12/90
Review Section I
Toxicology Branch II
Health Effects Division (H7509C)

To: Dennis Edwards, PM 12
Insecticide-Rodenticide Branch
Registration Division (H7505C)

Thru: Yiannakis M. Ioannou, Ph.D., Section Head Y.M. Ioannou 6/8/90
Review Section I
Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief Marcia Van Gemert 6/11/90
Toxicology Branch II
Health Effects Division (H7509C)

Registrant: Mobay Corporation
Kansas City, MO 64120-0013

Action Requested: Review of the Registrant's Response to the Previous Review Comments Concerning the In-Vitro Cytogenetic Assay with Azinphos-Methyl in the Human Lymphocyte Culture (TB MEMO 3/14/88 J. Chen)

Registrant's Response: "The dose levels selected for the definitive study were based on a pilot test. In the pilot test, mitotic activity of cultures treated at 5, 10, 50, 100 and 500 ug/ml was assessed. In the absence of S9 mix, Azinphos-Methyl caused significantly reduced mitotic activity at dose levels of 50 ug/ml and above. Based on these data, 100 ug/ml was selected as the

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highest dose level for the definitive study because this dose level would "show evidence of ... reduced mitotic activity" as specified in the guidelines. The results of the definitive study confirmed that this dose level was appropriate because a 72% reduction in mitotic activity was observed at this dose level. The lower dose levels were also appropriate as demonstrated by an 8.2% reduction in mitotic activity at the mid-dose (10 ug/ml) and no decreased mitotic activity at the low dose (1 ug/ml). These data demonstrate that the dose levels were appropriate and since the without metabolic activation portion of the study was negative, there is no need for further testing. On the basis of the above discussion, we request that the Agency reconsiders the acceptability of the without metabolic activation portion of this study."

Reviewer's Comments: The provided rationale for choosing the highest dose level (100 ug/ml; 72% reduction in mitotic activity) is considered acceptable. We do not believe that the middle dose level (10 ug/ml) was properly selected for this study in accordance with the test protocol recommended by Preston et al. for performing the in-vitro cytogenetic assay (A Report of Gene-Tox Program for Mammalian In-Vivo and In-Vitro Cytogenetic Assay, Mutation Research 87: 143-188, 1981). Preston et al. recommended specifically the following concerning the dose selection for the in-vitro cytogenetic studies:

"There should be 3 doses, covering a 10-fold range, the highest within a factor of 2 of that which gives a significant toxic effect."

However, because the test material does not indicate any mutagenic concerns at the dose range from 1 ug/ml to 100 ug/ml in this case, it is unnecessary to repeat the test with a higher concentration of the middle dose under the nonactivated system.

Recommendation: The nonactivated study is upgraded to acceptable. Azinphos-Methyl was not mutagenic in cultured human lymphocytes at concentrations up to 100 ug/ml without metabolic activation.