CASWELL FILE

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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

SUBJECT: Dimethoate 241/75: Registrant's Reply to the Previous TB Review Comments Concerning the Micronucleus Test with Dimethoate. CASWELL NO. 358

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THRU: David Ritter, Acting Section Head
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Review of the Registrant's Response to the Previous TB Review Comments Concerning the Micronucleus Test with Dimethoate (6/28/85 J. Chen).

Registrant's Response

It is our understanding that the EPA Health Effects Test Guideline EPA 560/6-83-001 supercedes EPA 560/6-82-001. EPA 560/6-83-001 states that either a single dose or three doses may be used. Because the test was done in 1984, the 1983 guideline was used. The statements of the EPA Health Effects Test Guideline EPA 560/6-83-001 are as follows:

"For an initial assessment, one dose of the test substance may be used, the dose being the maximum tolerated dose or that producing some indication of the cytotoxicity, e.g. a change in the ratio of polychromatic to normochromatic erythrocytes. Additional dose levels may be used. For determination of dose response, at least three dose levels should be used."

Based on the above, we belive that the micronucleus test meets current EPA on OECD Guidelines (No. 474) and that test is technically sound. Therefore, on behalf of the Dimethoate Task Force, we request EPA to reconsider its rejection of the study.

Reviewer's Comments

The provided reason for using a single dose of test substance with a double treatments instead of using three doses of test substance with double treatments in the mouse micronucleus test according to the protocol recommended by the EPA Health Effects Gudieline EPA 560/6-83-001 is considered acceptable.

However, following this guideline closely, the decision that a compound is negative in the mouse micronucleus test must result from the testing at the highest tolerated dose level that producing some indication of the cytotoxicity, e.g. the presence of cytotoxicity of the test compound in the bone marrow of treated animals (the ratio of polychromatic to normochromatic erythrocytes should be clearly below that of the animals in the negative control group). Based on the results of single injection (55 mg/kg of Dimethoate) of this study submitted previously, there was no change (e.g., reduction) in the ratio of PCE/NCE found in the treated groups in compare with the negative control group (e.g., Ratio of PCE/NCE: control group, 1.46$\pm$0.41; teated group sampled at 6 hrs, 1.50 $\pm$ 0.62; treated group sampled at 30 hrs, 1.69 $\pm$ 0.49; treated group sampled at 48 hrs, 1.44 $\pm$ 0.52; treated group sampled at 72 hrs, 1.98 $\pm$ 0.80). The compound, Dimethoate, at the dose (55 mg/kg) of single injection clearly exhibited no inhibition of erythropoiesis in the bone marrow of treated animals in terms of the cytotoxicity. Therefore, it is unclear that the highest tolerated dose of Dimethoate was actually used in the mouse micronucleus test. The "multiple-dose schedule of 2 doses of 55 mg/kg each 24-hr apart, however, did produce a marginal but statistically significant decrease in the PCE/NCE ratio of treated animals, again with no evidence of an effect on micronucleus induction.

Recommendation

The study is upgraded to acceptable.

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