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

MAR 13 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: George LaRocca (PM#15)
Registration Division (TS-767C)

FROM: George Z. Ghali, Ph.D.
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Hazard Evaluation Division (TS-769C)

G. Ghali 2/29/84

THRU: Christine F. Chaisson, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Christine F. Chaisson 3/8/84

3/13/84

SUBJECT: EPA Reg. No. 3125-183; Di-syston; Micronucleus test in the mouse (IBT replacement). Caswell No. 341; Access. No.: 250895.

Registrant: Mobay Chemical Corporation, St. Louis, Missouri.

Action Requested:

Review and evaluation of a micronucleus test in the mouse.

Conclusions and Recommendations:

1. The test chemical did not exhibit mutagenic effects under the test conditions.

2. The registrant is required to provide an explanation for the lack of cholinergic signs in the test animals at a dose level approaching the LD_{50} value.

3. The test is classified as supplementary data until the above issue (#2) is addressed by the registrant.

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Data Evaluation

Test Type: Mutagenicity; micronucleus test in the mouse.

Test Chemical: S 276, batch 79/R/225/49, Contains 50% of the active ingredient Di-syston.

Testing Laboratory: Bayer A G, Institute of Toxicology, Wuppertal, W. Germany. Report No.: 10451 dated 12/23/81.

Protocol:

Four groups of five male and five female NMRI (SPF Han) mice weighing 25-34 grams (8-12 weeks old) were used. The animals were dosed twice at 24 hours intervals. The test substance was suspended in 0.5% Cremophor and administered orally at dose levels of 0.6, 12 mg/kg. The positive control Trenimon (alkylating agent, Bayer, batch 079809) was dissolved in demineralized water and administered intraperitoneally at 0.125 mg/kg. the dose volume was kept uniformally at 10 ml/kg body weight. The animals were sacrificed six hours after the second treatment. According to the author, "the smears were prepared and reproduced according to Schmid (1, 2). One thousand polychromatic to normochromatic erythrocytes were counted per animal, and incidence of these cells with micronuclei was established. The slides were scanned meanderwise. The ratio of polychromatic to normochromatic erythrocytes was also established to omit animals with pathological bone marrow depression (not induced by the tes chemical). The results were statstically evaluated with the Nemeniy non-parametric ranking test using probability error of less than 5% ($p<0.05$)."

According to the author the dosage levels were selected based on a pilot study, in which groups of five male and five female mice were treated orally in a manner similar to the main study with 2.5, 5.0 or 10 mg/kg (based on the pure test substance). the animals were dosed twice at 24 hours intervals. The author stated that the highest dose level (10 mg/kg) was tolerated without symptoms.

Results:

The author stated that the highest dose levels in both the pilot study and the main study were tolerated with no symptoms.

The test chemical did not increase the number of micronucleated polychromatic erythrocytes twhen compared to the negative control under the test conditions. The incidence of cells with micronuclei were 2.0 and 1.6% respectively in the low and high dosage groups of the treatment, compared to 1.9 and 58.0% in the negative and positive controls respectively.

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Discussion:

On a few occasions the author stated that "the mice showed no symptoms of damage after the oral administration of the test chemical S 276 in doses of up to 2 x 12 mg/kg". The author further stated that "the animals behaved normally and their motor activity remained unaffected". On the other hand, literature data indicate that the dose levels tested in this study, if not higher than the LD_{50} values for rodents, they are at least approaching these values . The author, however, did not make any comments as to why no toxicity signs were observed.

Core Classification:

Supplementary data

References:

1. Schmid, W., The Micronucleus Test. Nutation Res., 31, 9-15, 1975.

2. Schmid, W., Der Mikrokerntest. Deutsche Forschungsgemeinschaft. Kommision fur Mutagenitatsfragen. Mitteilung III, 53-61, 1975.