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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ID. No. 003125-00347, Triadimenol Mouse Oncogenicity Protocol

Tox. Chem. No.: 127201
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FROM: Melba S. Morrow, D.V.M. MSM 4/24/96
Review Section II, Toxicology Branch I
Health Effects Division (H7509C)

TO: Cynthia Giles-Parker/Tobi Snyder
Team 22
Registration Division (H7505C)

THRU: Joycelyn E. Stewart, Ph.D. JES 4/30/96 KFH 5/2/96
Head, Section II
Toxicology Branch I
Health Effects Division (H7509C)

Registrant: Bayer
Chemical: Triadimenol (Baytan, KWG 0519)

CONCLUSIONS:

The protocol for conducting the mouse oncogenicity study with triadimenol conforms generally to the Subdivision F Guidelines, 83-2. It is recommended that the dosing be modified to include a high dose that will provide clear signs of toxicity, without excessive deaths.

We recommend the high dose be increased because the effects observed at 1500 ppm in the 90-day study in CD-1 mice are marginal, appear to be adaptive responses or are of unknown toxicological relevance. The reported effect on body weights (9% decrease in males) at 1500 ppm, is not biologically significant. Elevations in hepatic enzymes, protein and albumen at 1500 ppm are probably related to the adaptive changes (hypertrophy and homogeneous cytoplasm) seen in the liver. Histopathology of the liver at 1500 ppm revealed effects (cytoplasmic vacuolation, lipid storage and single cell necrosis) of unknown severity in only 1/10 males and

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3/10 females when compared to the incidence at 4500 ppm of 8/10 males and 9/10 females.

Additionally, in the 2 year study in CF1/W74 mice administered dietary levels of triadimenol up to 2000 ppm, histological changes were reported in the liver and the thyroid. At this dose level there were also alterations in body weights and changes in clinical pathology that were indicative of liver damage but the extent and severity of the findings in this study were not provided. From the information provided on this study, excessive toxicity was not apparent.

ACTION REQUESTED:

Registration Division has requested a review of the protocol for a mouse oncogenicity study. As per instructions from Karl Baetcke, Chief, Toxicology Branch I, comments were to be limited to those pertaining to dose selection, only.

BACKGROUND:

The registrant has provided a protocol for a new oncogenicity study in mice as per request by California EPA.

Two studies were conducted previously in two different strains of mice. In the first study, CF1/W74 mice received triadimenol at dietary levels of 0, 125, 500 or 2000 ppm for 24 months. In this study, body weight decreases were reported at 500 and 2000 ppm (percents not specified). Additionally, at 2000 ppm, there were cystic changes in the thyroid and nodular hyperplasia in the liver. Histological changes in the liver could be correlated to elevations in ALT, AST and AP and to decreases in plasma cholesterol (extent of clinical chemistry alterations, not specified). The NOEL for this study was determined to be 125 ppm.

In a 90-day dose selection study in CD1 mice (10/sex/dose level), triadimenol was administered at dietary dose levels of 0, 160, 500, 1500 or 4500 ppm. The results were as follows:

At 4500 ppm, 1/10 males died during the first week of the study. Piloerection and squatting were observed in males and a 9% decrease in body weight was observed in females. Decreased hematocrit and increased MCHC were reported in females and in males, the leukocyte counts were decreased. Liver enzymes were elevated and there was a reported decrease in plasma proteins. Histopathological findings included hypertrophy of liver cells, cytoplasmic vacuolation, lipid storage and single cell necrosis in 8/10 males and 9/10 females. Liver weights were also increased at this level (absolute and relative) in both sexes and cytochrome P-450 concentration was also significantly increased in both sexes.

At 1500 ppm, no deaths and no clinical signs of toxicity were reported. A 9% decrease in body weight was reported for males and a decrease in the number of leukocytes was reported for this sex

only. Liver enzymes and triglyceride concentration in the liver were elevated in both sexes and total protein and bilirubin were decreased in both sexes. Cholesterol was decreased at this dose level, but in males, only. Microscopic liver lesions similar to those found at 4500 ppm were present in 1/10 males and in 3/10 females. Liver weights were increased in both sexes, but only the relative organ weight in females was considered statistically significant and cytochrome P-450 concentrations were elevated in both sexes.

At 500 ppm, liver enzymes were elevated in both sexes and bilirubin was decreased in males, only. Liver histology revealed cellular hypertrophy and homogeneous cytoplasm in males, only.

At 160 ppm, increases in glutamate dehydrogenase were reported and P-450 concentrations in the liver were elevated.

DISCUSSION:

Toxicology Branch I suggests that the 1500 ppm proposed high dose be increased in order to produce toxicological effects that can not be interpreted as being adaptive or inconclusive. Support for increasing the dose is found in the 2 year study in which the compound did not appear excessively toxic at 2000 ppm in another strain of mice.