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

SEP 28 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Prometryn: Recommended Doses to be Used in a Rat Chronic Toxicity Study

Tox. Chem. No. 97

TO: Robert J. Taylor
Product Manager #25
Registration Division (TS-767c)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

John E Whalan 9-28-87

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
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and
William Burnam, Deputy Chief
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Hazard Evaluation Division (TS-769c)

Budd 9/28/87

WSB 9/25/87

Ciba-Geigy and representatives from EPA met on September 8, 1987 to discuss dose selection for an upcoming chronic prometryn feeding study in rats. The following persons were in attendance:

Dr. Warner Phelps	Ciba-Geigy Corporation
Dr. George McCormick	Ciba-Geigy Corporation
Dr. Thomas J. Parshley	Ciba-Geigy Corporation
Joanne Miller	EPA Registration Division
William Burnam	EPA Toxicology Branch
Edwin R. Budd	EPA Toxicology Branch
John E. Whalan	EPA Toxicology Branch

Prior to the meeting, the Registrant submitted body weight and food consumption data for a 90-day prometryn feeding study in rats. No further prometryn data were provided. At the meeting, Drs. McCormick and Parshley described the toxicity profile found in the 90-day study. The doses used in this study were 50, 500, 1000, and 5000 ppm in the feed. By far the most profound effects seen were marked anorexia and decreased body weight gain at the 5000 ppm dose, especially in the males. There were no clinical signs or gross pathologic lesions. In the opinion of the Registrants, the "slight" changes in clinical pathology and organ weights, were not significant. Histopathologic evaluation had not yet begun. There were no obvious target organs.

There was also some discussion on the findings in the chronic studies of two analogs - ametryn and terbutryn. It was the opinion of the Toxicology Branch that there were insufficient data provided at the meeting with which to make a definitive suggestion of chronic doses. It was clear, however, that the Registrant's suggested doses of 0, 10, 50, 375, and 750 ppm were too low. Accordingly, the Toxicology Branch proposed doses of 0, 10, 150, 750, and 1500 ppm, with the caveat that the Registrant revise these doses based on their further evaluation as data become available.

The Registrant explained that the rats were already in-house, and the study was scheduled to begin on September 24, 1987. For this reason they requested that the Toxicology Branch continue in the dose selection process, and offered to submit further information. Toxicology Branch requested histopathology data from the 90-day prometryn study, and as much substantiating data as possible from that study and the two chronic analog studies.

A package of data was received a few days later. This information, as well as agency files on ametryn and terbutryn, were evaluated by John Whalan and discussed with Ed Budd. The available data were not complete, but there was sufficient information with which to propose doses. These doses were relayed by telephone to Dr. Phelps on September 21, 1987.

These three analogs all cause significant decreases in weight gain as the major toxic sign. Of the three analogs, prometryn seems to be the least toxic. Although an MTD can be based on a variety of toxicologic manifestations, the prometryn MTD will be based solely on body weight effects.

Over the course of 90 days, prometryn caused profound effects on body weight at 5000 ppm in males and females, and minimal effects in males at 1000 ppm. While a dose of 5000 ppm would probably be too high for a chronic study, a dose of 1000 ppm would probably be too low. The latter would be expected to elicit body weight effects in males, but possibly not in females. A maximum dose of 1500 or 2000 ppm would likely cause significant decreases in body weight gain in both sexes without being excessive. Little other toxicity is expected unless prometryn proves to be oncogenic.

Therefore, the suggested doses are 0, 10, 150, 750, and 1500 ppm. The Registrant wants to change the 150 ppm dose to 100 ppm; the Toxicology Branch concurs since this will have minimal effect on the study. Thus, the agreed upon chronic doses are 0, 10, 100, 750, and 1500 ppm. The ultimate responsibility for dose selection and modification rests with the Registrant. The EPA cannot assure the success of the study because of its limited access to data, and its inability to monitor studies.