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

SEP 28 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Prometryn. Minutes of a Meeting with Registrants to Discuss the Selection of Doses to be Used in a Chronic Rat Feeding 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 9-15-87

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

Budd 9/16/87

Whalan 9/27/87

Ciba-Geigy requested a meeting with the Toxicology Branch to discuss dose selection for an upcoming chronic prometryn feeding study in rats. This was in accordance with Dr. Farber's request that, "whenever possible [Registrants] meet with toxicologists in the Office of Pesticide Programs to reach some concurrence on the doses to be tested in the study before the initiation of the study." The meeting was held on September 8, 1987, with the following persons 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

The Registrant had previously 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. Histopathology has not yet been completed, so they could not comment on those findings. There were no obvious target organs.

The Registrant was prepared to base the MTD on the body weight changes, even though the anorexia and reduced body weight gain were probably due to food palatability problems. They were under the mistaken impression that the MTD used to select doses for chronic studies was based solely on body weight changes. John Whalan explained that clinical signs, clinical pathology, gross pathology, organ weights, and histopathology can also be used as criteria for defining the MTD.

Ed Budd stated that the target organs are likely to be the liver and kidney (based on a chronic dog study performed in 1965). He felt that the histopathology evaluations should be completed for those two organs before setting an MTD. Bill Burnam expanded this request to include all organs since we do not know for certain which organs may be the targets of prometryn.

The Registrants presented body weight effects from chronic rat studies for two analogs - ametryn and terbutryn. On these studies, they based the MTD on body weight effects. They could not provide any further information. A chronic mouse study was also performed using prometryn, but the Registrant did not have any data to discuss (this study is not yet ready for submission to the Agency). The mouse studies, and the analog chronic studies may have provided valuable information on target organs.

The Registrant had proposed using chronic rat doses of 750, 375, 50, and 10 ppm. The lowest dose was based on residue levels. Bill Burnam felt that the proposed maximum dose for the rat chronic study (750 ppm) was too low. Ed Budd and John Whalan concurred. We also agreed that there was no way to ascertain with the limited data provided what the target organs were, or what doses were necessary to elicit a toxic response.

John Whalan suggested that more realistic doses might be 1500, 750, 150, and 10 ppm. The highest dose would be expected to have significant impact on weight gain, no compound-related mortality, and minimal effect on other toxic parameters. These doses were suggested with the caveat that the Registrant modify them after further evaluation of the 90-day prometryn rat study, the chronic prometryn study in mice, and the chronic analog studies.

John Whalan said that although we are willing to discuss the proposed doses, we cannot set firm doses without full access to the data. The ultimate responsibility for dose selection rests with the Registrant. Bill Burnam challenged this. He said that we are now able to set doses, and if those doses do not achieve the desired toxic levels (i.e. excessive mortality or no toxicity) we will accept the study anyhow. Ed Budd asked if this is now Branch policy, and said that this needs further discussion. John Whalan said that this policy would open the Agency to legal action if any study fails to suit the needs of a Registrant. Further, he would refuse on scientific grounds to assign firm doses without visiting Ciba-Geigy and extensively reviewing the data. Even then, the assigned doses would be accompanied with the warning that there is no way to assure the success of the study based on those doses.

The meeting closed with the Registrant agreeing to complete the histopathology on the 90-day rat study, and further evaluate the chronic analog studies. There is a need to establish (publish) a Branch policy on dose selection which hitherto has been the domain of the Registrant.

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