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

JUL 2 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES
June 19, 1991

MEMORANDUM

SUBJECT: Propanil; Propanil Task Force; 13-week Range Finding Study; Results Summarized in Letters; Selection of MTD

Caswell No. 325
Project No. 1-0978
ID No. 028201

FROM: William Dykstra, Ph.D. William Dykstra 6/19/91
Review Section I, TB-I, IRS
Health Effects Division, H7509C

TO: Lois Rossi, PM #74
Reregistration Branch
Special Review & Reregistration Division, H7508C

THRU: Roger Gardner, Section Head
Review Section I, TB-I, IRS
Health Effects Division, H7509C Karl P. Baetcke for 6/24/91

Requested Action:

Review letter of 13-week range finding study in rats with propanil which will be used to determine dosages for combined chronic toxicity/oncogenicity study in rats.

Conclusion and Recommendation

1. Based on the results of the attached letter, TB-I does not object to the propanil dietary levels of 0, 200, 600, and 1800 ppm for the chronic toxicity/oncogenicity study in Sprague-Dawley rats. As stated in the letter the MTD should be 1800 ppm (HDT).

Attachment

NPC

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March 4, 1991

Ms. Terri Stowe
Special Review and Reregistration Division
Office of Pesticide Programs (H7508C)
U.S. Environmental Protection Agency
Crystal Station 1
2800 Jefferson Davis Highway
Arlington, VA 22022

Dear Ms. Stowe:

The Propanil Task Force has completed a "13-Week Dose Range-Finding Study in Rats with Propanil" in order to select appropriate dietary concentrations for a combined chronic toxicity/oncogenicity study in rats. We have completed the review of this study and have selected dietary concentrations of 0, 200, 600 and 1800 ppm propanil for this long term study.

Attached to this letter is a criteria document that summarizes the results from the range-finding study and discusses the rationale for the selected doses. This document has been supplied to you for review and comments from EPA toxicologists regarding dose selection. The chronic toxicity/oncogenicity study will initiate at Huntingdon Research Centre on April 4, 1991, thus, an expedited review is needed.

Should you have any questions or comments, please feel free to contact me. If you feel that a meeting may be necessary, we will be able to arrange one at a mutually convenient time. Thank you in advance for your attention to this matter.

Sincerely yours,

Vincent J. Piccirillo, Ph.D., DABT
Toxicologist, Propanil Task Force

cc. Propanil Technical Committee

CRITERIA FOR DOSE SELECTION- COMBINED CHRONIC TOXICITY/ ONCOGENICITY STUDY OF PROPANIL IN RATS

SUMMARY OF RANGE-FINDING RESULTS

Propanil technical was administered via the diet to groups of five male and five female Sprague-Dawley rats for a period of 13 weeks as follows:

Group	Concentration (ppm)	Average Propanil Intake (mg/kg/day)
1	0	0
2	300	25.5
3	1000	84.5
4	2000	167.5
5	4000	341.0

The NOEL in this 13 week study was 300 ppm. The hemoglobin value for the females from this group was lower than control but within historical limits.

Dietary consumption of 1000 ppm produced the following effects:

a. Reduced body weight gain in males (16%) and females (36%) after 13 weeks of treatment.
b. Reduced food consumption (11% for males and females).
c. Impaired efficiency of food utilization (slightly).
d. Decreased red blood cell count, hematocrit and hemoglobin in females.
e. Increased methemoglobin in male rats.
f. Increased bilirubin in females only.
g. Splenic congestion was noted in 2/5 male rats at necropsy.
h. Slightly increased relative spleen weights for females.
i. Histopathology:
   - Liver- Brown pigment deposits in kupffer cells (trace to minimal) in males (5/5) and females (5/5).
   - Kidneys- Brown pigment deposits (hemosiderin) in proximal convoluted tubular epithelium graded as trace or minimal also noted in controls. Incidence and severity considered toxicologically significant for females only from this group.

The 2000 and 4000 ppm dietary concentrations produced pronounced effects on body weight gain. Food consumption was approximately 80% of control at both dietary concentrations. Males and females showed decreases in erythropoietic parameters, increased bilirubin values, and increased methemoglobin concentrations. Dose-related splenic enlargement and congestion were seen in males and females. Urinalysis revealed discolored urine from animals in both groups. Female rats from the 4000 ppm group showed decreased urinary protein and specific gravity. As noted at 1000 ppm, deposits of brown colored pigment (hemosiderin) were seen in hepatic Kupffer cells and in the proximal convoluted tubular epithelium of the kidneys. The incidence and severity of these findings showed a dosed-related response. Microscopically, minimal centrilobular hepatocytic enlargement was seen in 4/5 male rats receiving 2000 ppm and in 5/5 males and 3/5 females receiving 4000 ppm.

The greatest concern is in regards to the body weight, hematological and urinalysis effects noted at the 2000 and 4000 ppm levels. The impact of these changes on survival must be considered in selection of the high dose for the chronic study. It is noteworthy that similar effects were noted in previous rat studies.

Approximately 1961, a 13-week subchronic study in Wistar rats was conducted. Borderline effects on body weight gain were seen at 1000 ppm with more marked reductions at 3300 and 10000 ppm. Also at 1000 ppm, increased relative spleen weight was noted in females and decreased hemoglobin concentration was noted in males. Effects on food consumption and hematological parameters were seen at 3300 ppm and higher. The NOEL was 330 ppm.

In a previous two-year chronic study with Wistar rats, the following were seen at a treatment level of 1600 ppm:

a. Increased mortality was noted after 20 months of treatment for males.
b. Decreased body weight gain was seen in males and females; approximately 15-20% at 13 and 52 weeks.
c. Decreased hematocrit and hemoglobin concentration in females at the 3, 6, 12, and 24 month intervals.
d. Increased relative spleen weight in males and females
e. Increased relative liver weight in females, increased testes weights in males

The 400 ppm levels was considered the Lowest Effect Level (LEL) on the basis of increased relative spleen weight in females. The body weight gains was approximately 10% lower than control for males and female. The NOEL was 100 ppm.

DOSE SELECTION

On the basis of the above data, we have selected Propanil dietary levels of 0, 200, 600 and 1800 ppm for the chronic toxicity/oncogenicity study.

The 200 ppm dose level is expected to be a NOEL. In the recent 13-week study, the hemoglobin value for the females receiving 300 ppm was lower than the concurrent control group but well within historical control range. This finding probably represents a random occurrence but because of the hematological findings at the higher doses, a treatment related effect cannot be ruled out.

The 600 ppm dose is expected to be the Lowest Effect Level. It is expected that this dietary concentration will produce a minimal effect on body weight gain (10 to 20%) with essentially no effect on food consumption. It is expected that this level will also define the lower limit for the hematological, clinical and microscopic pathological changes.

The 1800 ppm level is expected to be a Maximum Tolerated Dose level. It is expected to produce significant toxicity as noted at 2000 ppm in the rangefinding study and at 1600 ppm in the previous chronic study. A concentration of 2000 ppm produced a 30 to 40% decrease in body weight gain. This decrease could not be attributed solely to lower food consumption. An apparent effect on efficiency of food utilization was noted in both the current range-finding study as well as the previous two year study. Substantial depression of body weight gain raises questions regarding the impact that may be produced on survivability. The liver is a demonstrated target organ for propanil and possible effects on cellular metabolism are suggested. Additionally, propanil ingestion at 1000 ppm and greater produces hemolysis as indicated by several parameters (decreased hematocrit, RBC count and hemoglobin concentration, increased bilirubin, hemosiderin deposition in the liver and kidneys, splenic congestion). The previous two year study showed decreased survival of male rats receiving 1600 ppm during the last few months of the study.

Thus, the 1800 ppm level is considered as dietary level that sufficiently challenges the rats without compromising the results of the study.