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CASWELL FILE

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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Propanil; Supplementary Data for 21-Day Dermal Toxicity Study in Rabbits; ID No. 028201

Project No.: 1-2101
Caswell No.: 325
Chemical No.: 028201
MRID No.: 419618-00

TO: Terri Stowe, PM Team #71
Reregistration Branch
Special Review and Reregistration Division (H7508W)

FROM: William Dykstra, Ph.D. William Dykstra 11/15/91
Review Section I, TB-I, IRS
Health Effects Division (H7509C)

THRU: Roger Gardner, Section Head Roger Gardner
Review Section I, TB-I, IRS
Health Effects Division (H7509C) 11-15-91

Requested Action

Review the additional data on 21-Day Dermal Toxicity Study in Rabbits submitted in response to Core-Supplementary classification of original study (MRID# 41777001)

Conclusions and Recommendations

The submitted additional data consisting of individual animal data and EPL pathology report are acceptable and confirm the conclusions of the report. The classification of the 21-day Dermal Toxicity Study in rabbits is upgraded from core-supplementary to core-guideline. The NOEl is 250 mg/kg/day (LDT) and the LEL is 500 mg/kg/day. These findings are detailed in the June 10, 1991 review by W. Dykstra (attached) which provides additional background.

PROP-RAB.WD/LCA

CASWELL FILE

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

008405

JUN 10 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Propanil Reregistration - Propanil Task Force - 21-Day Dermal Toxicity Study in Rabbits with Propanil Technical

Caswell No.: 325
Project No.: 1-0721
Record No.: S391194
MRID No.: 417770-01

FROM: William Dykstra, Ph.D., D.A.B.T. William Dykstra 3/19/9
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Terri Stowe
Registration Branch
Special Review and Reregistration Division (H7508C)

and

Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

THRU: Roger Gardner, Section Head
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

06/04/91

Requested Action

Review 21-Day Dermal Toxicity Study in Rabbits with propanil technical submitted in support of reregistration by Propanil Task Force.

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Conclusions and Recommendations

The study is acceptable as Core-Supplementary and does not support reregistration. The NOEL may be 250 mg/kg/day (the low dose).

The LEL may be the mid dose of 500 mg/kg/day and the effects, at this time, are decreased body weight gain (day 20) and decreased food consumption (days 14-20) in females. Additionally at 1000 mg/kg/day, there was decreased total bilirubin in both sexes at final bleeding.

The EPL Histopathology Report was not included with the study report. Also, individual animal data were not provided.

The study can be upgraded when these deficiencies are resolved.

Reviewed By: William Dykstra, Ph.D., D.A.D.T. William Dykstra 3/19/91
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Roger Gardner, Section Head
Section I, Toxicology Branch I - IRS (H7509C)

008405

DATA EVALUATION REPORT

Study Type: 82-2 - 21-Day Dermal Toxicity in Rabbits TOX Chem No.: 325

Accession No.: N/A MRID No.: 417770-01

Test Material: Propanil Technical (Batch 01)

Synonyms: 3',4'-dichloropropionanilide

Study Number: PH430-PT-001-89

Sponsor: Propanil Task Force

Test Facility: Pharmakon Research International, Inc.

Title of Report: 21-Day Dermal Toxicity Study in Rabbits.

Author: Dennis J. Margitich

Report Issued: March 14, 1990

Conclusions:

The NOEL is 250 mg/kg/day (LDT). The LEL is 500 mg/kg/day and the effects were decreased body weight gain (day 20) and decreased food consumption (days 14-20) in female rabbits. At 1000 mg/kg/day (HDT), in addition to the findings at 500 mg/kg/day, both sexes had decreased total bilirubin at final bleeding.

Classification:

Core-Supplementary (individual data not provided and histopathology report not included in final report).

Special Review Criteria (40 CFR 154.7): N/A

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Review:

21-Day Dermal Toxicity Study in Rabbits (Pharmakon Research International, Inc., Study No. PH430-PT-001-89; March 14, 1990).

Test Material - Propanil technical (Batch 01); grey granular solid; purity not specified; negative control: deionized water placed onto a 2 x 2 gauze.

Animals - New Zealand white (NZW) rabbits, 2.103 to 2.679 kg bw, 27 animals/sex, Hazleton Research Products, Denver, PA; individually caged, fed Purina Certified Rabbit Chow #5322 and fresh tap water ad libitum.

Methods - The animals were treated dermally on the clipped skin of the back. The following regimen was employed:

Group	Males	Females	Dose Level (mg/kg)
I	5	5	0
II	5	5	250
III	5	5	500
IV	5	5	1000

The test material was applied to the shaved intact skin under occlusion for 6 hours per day, 5 days per week, for 3 weeks. Controls received deionized water under the same conditions. Following 6 hours of exposure, the skin was wiped (but not washed) to remove excess material. The skin sites were observed daily prior to dose and prior to terminal sacrifice and scored according to Draize. Animals were observed twice daily for toxic signs and mortality.

Body weights were recorded at initiation, weekly, and at terminal necropsy. Food consumption was determined on days 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20. Animals were sacrificed at the end of the experiment by intravenous sodium pentabarbitol administration.

Blood was collected before treatment and at terminal necropsy for hematology and clinical analysis from all animals. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)		Total plasma protein (TP)
X	Hemoglobin (HGB)	X	Leukocyte differential count
X	Leukocyte count (WBC)		Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)		Mean corpuscular HGB conc. (MCHC)
X	Platelet count		Mean corpuscular volume (MCV)

b. Clinical Chemistry

X	Electrolytes:	X	Other:
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorus	X	Cholesterol
X	Potassium	X	Globulins
	Enzymes:	X	Glucose
	Alkaline phosphatase	X	Total Bilirubin
	Cholinesterase	X	Total Protein
	Creatinine phosphokinase		Triglycerides
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (also SGPT)		
X	Serum aspartate aminotransferase (also SGOT)		

Sacrifice and Pathology - All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X	Digestive system	X	Cardiovasc./Hemat.	X	Neurologic
	Tongue		Aorta		Brain
	Salivary glands		Heart		Periph. nerve
	Esophagus		Bone marrow		Spinal cord (3 levels)
	Stomach		Lymph nodes		Pituitary
	Duodenum		Spleen		Eyes (optic n.)
	Jejunum		Thymus		Glandular
	Ileum		Urogenital		Adrenals
	Cecum	XX	Kidneys		Lachrymal gland
	Colon		Urinary bladder		Mammary gland
	Rectum	XX	Testes		Parathyroids
XX	Liver		Epididymides		Thyroids
	Gallbladder		Prostate		Other
	Pancreas		Seminal vesicle		Bone
	Respiratory		Ovaries		Skeletal muscle
	Trachea		Uterus	X	Skin (treated and untreated)
	Lung			X	All gross lesions and masses

A full histopathological evaluation was carried out on the treated and untreated skin sites, liver, and kidneys from all terminal animals in the control and high-dose groups and all rabbits that died during the study. Due to hepatic coccidiosis and the protozoan, Encepthalitozoon cuniculi, observed in the study, the liver and kidney of all animals were evaluated by the pathologist. In addition, the treated and untreated skin sites were also examined as a possible target organ. At the sponsor's request the testes were not evaluated unless a gross lesion was

detected. Gross lesions were evaluated from all animals except when noted.

Statistics - Raw data were collected and evaluated statistically. Evaluation of equality of means was made by the one-way analysis of variance using the F distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine significant differences from control means. The levels of significance were $p < 0.05$ and 0.01.

Quality Assurance Report - A Quality Assurance Unit Statement was signed by Leslie T. Pinnell, M.S., on March 14, 1990. Additionally, a GLP compliance statement was signed by the study director, Dennis J. Margitich, B.S., on March 14, 1990.

Results:

1. Toxic Signs - There was no compound-related erythema or edema at any dose level in any treated rabbit in comparison with controls.

   In males, decreased activity, dyspnea, flaccid body tone, diarrhea, abnormal gait, and abnormal stance were observed in one rabbit (#9764) at 500 mg/kg/day beginning on day 15 through day 19, when the rabbit was found dead. Since these findings, including death, were not observed at 1000 mg/kg/day (HDT), the findings were not dose-related and were not considered compound-related.

   In females, abnormal gait, abnormal stance, decreased activity, diarrhea, and flaccid body tone appeared on day 12 in one female low-dose rabbit (#9759) and continued until day 14, when the rabbit was found dead. Also on day 14, one high-dose rabbit (#9780) showed decreased activity, abnormal gait, and abnormal stance, and was found dead on day 15.

   Female #9769, from the 500 mg/kg/day (mid-dose) group, displayed absence of feces on day 19 and diarrhea on day 21. Female #9776 from the high-dose group displayed abnormal stance, abnormal gait, decreased activity, flaccid body tone, and diarrhea from days 14 through 21.

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The clinical signs observed in the three rabbits that died (1 male and 2 females) as well as the two rabbits that did not die can be tallied as followed:

	Females	Males
High Dose	2	0
Mid Dose	1	1
Low Dose	1	0
Control	0	0

It appears that the findings in males, since they are not dose-related, are not compound-related. Similarly, in females, the toxic signs were comparable to those observed in males, but more frequent. These findings in females, therefore, are considered nonspecific and not compound-related.

The causes of death in the three deceased rabbits could not be determined and are considered coincidental and not compound-related.

2. Body Weight - There were no statistically significant differences in body weight and body weight gain in treated male and female rabbits in comparison with controls. However, there was a dose-related suppressed body weight gain in all treated female groups when compared with controls on day 20 (44, 27, 8, -2 g for the control, low-, mid-, and high-dose female groups, respectively). The decreased body weight gain can be associated with the decreased food consumption for the mid- and high-dose female groups beginning on day 14.

Grams (Food Consumption)

	(mg/kg/day) 0	250	500	1000
Day 14	164	166	149	128
Day 16	167	164	132	119
Day 18	188	156	125	118
Day 20	225	190	143	150

On the basis of the decreased body weight gain at the mid- and high-dose levels, the low dose of 250 mg/kg/day is considered the NOEL in females. In males, the NOEL for body weight and body weight gain is 1000 mg/kg/day.

3. Food Consumption - There were no statistically significant differences between controls and treated male and female rabbits in food consumption during the experiment. However, the trend towards decreased food consumption in mid- and high-dose treated females from days 14 to 20 is considered compound-related. The NOEL for food consumption is the low dose of 250 mg/kg/day in females and 1000 mg/kg/day in males.

4. Gross Findings - There were no compound-related gross findings in males and females. Incidental findings included, in males, 1/4 in mid dose in brain, 1/4 in low dose in liver, and 1/4 in low dose in testes. In females, incidental findings included 1/4 in mid dose in stomach, 1/5 in control in treated skin, and 1/5, 1/4, 3/5, and 1/4 in livers of control, low-, mid-, and high-dose groups, respectively. Due to absence of dose-response in the liver findings and due to the different findings in each dose group, the liver results were not considered compound-related in females.

5. Histopathology - EPL histopathology report, mentioned in the text of the study report, was not appended to the study report. This EPL Histopathology report is required to be submitted.

   Based on the study author's narrative, there were no compound-related histopathological lesions in the skin, liver, or kidneys of treated male and female rabbits in comparison with controls.

6. Organ Weights - There were no compound-related effects in absolute or relative (to body weight) organ weights in treated male and female rabbits in comparison with controls.

7. Clinical Chemistry

   Males - There were no compound-related or statistically significant differences in treated male groups in comparison with controls in creatinine, BUN, SGPT, SGOT, Na, K, cholesterol, total protein, albumin, and phosphorus. At terminal sampling, chloride values of the mid- and high-dose groups were statistically, significantly increased in comparison with controls, mid-dose calcium levels were significantly increased, mid-dose A/G ratios were significantly increased, high-dose total bilirubin were significantly increased. The mid-dose clinical chemistry increases (A/G ratio, Ca^{++} and glucose) were not dose-related and are not considered compound-related. The significantly increased chloride and decreased bilirubin did not appear to be related to any liver or

kidney findings and were, therefore, not considered toxicologically significant. However, decreased total bilirubin was also seen in high-dose females.

Females - There were no compound-related or statistically significant differences in treated female groups in comparison with controls in creatinine, BUN, SGPT, Na, K, Cl, cholesterol, total protein, albumin, calcium, phosphorus, and A/G ratio. At terminal sampling, low- and mid-dose glucose were increased, mid-dose SGOT was decreased, and high-dose total bilirubin was decreased. The glucose and SGOT findings were not dose-related and were not considered compound-related (additionally, decreases in SGOT or SGPT are not toxicologically significant). The decreased total bilirubin in high-dose females did not correlate to a liver finding or detected health status problem of the rabbits, but in light of the occurrence of decreased bilirubin in males at the high dose, the finding is considered to be compound-related.

NOEL = 500 mg/kg/day

LEL = 1000 mg/kg/day - decreased total bilirubin in both sexes.

8. Hematology

Males - There were no statistically significant or compound-related effects in RBC, hematocrit, WBC, hemoglobin, and differential WBC (except eosinophils). At terminal sampling, the mid- and high-dose platelet values were significantly increased in comparison to controls. The values of the mid- and high-dose groups (457.8 and 457.2 x $10^3/mm^3$ for the mid- and high-dose groups, respectively, in comparison with 307.4 for controls) were within normal limits, were not related to the health status of the rabbits, and did not appear to be of toxicological significance. Also, a significant increase was seen for eosinophils in mid- and high-dose groups which appeared to be dose-related (0.11 and 0.12 for mid- and high-dose groups, respectively). These values, however, are not higher than the baseline values (0.14, 0.14, 0.11, and 0.09 for control, low-, mid-, and high-dose groups, respectively), and are within the normal range for rabbits. They are not considered toxicologically significant.

Females - There were no statistically significant or compound-related hematological findings in any parameter in female treated rabbits in comparison with controls.

Morphological Observations - Morphological findings of the differential blood smear did not reveal any compound-related effects (according to the text of the report). However, pictures or other data were lacking.

Tox Chem No. 325 File Last Updated _____ Current Date 11/12/91

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
82-2; 21-day dermal toxicity study in rabbits (Pharmacon No. PH 430-PT-001-89; March 14, 1990	propanil tech (batch 01)	419618-00	Additional individual animal data and E-PL Histopathology report changes classification from Core-supplementary to Core-guideline NOEL is 250 mg/kg/day		guideline

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