10-21-91

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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES
October 16, 1991

MEMORANDUM

SUBJECT: Propanil; Review of studies for Reregistration; ID #028201

Caswell No.: 325
Project No.: 1-1447
Case No.: 818688
Submission No.: S397290

FROM: William Dykstra, Ph.D William Dykstra 10/15/91
Review Section I, Toxicology Branch-I
Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Terri Stowe, PM Team #71
Reregistration Branch
SRRD, (H7508W)

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

10-15-91
(for RG)

Requested Action: Review new toxicology studies with propanil for reregistration.

Conclusion and Recommendation:

1. The following results were obtained in the submitted studies:

Study Type	MRID	Result	Classification
81-1	41360801	III	Acceptable
81-2	41360901	IV	Acceptable
81-3	41265901	IV	Acceptable
81-4	41360501	II	Acceptable
81-5	41360601	IV	Acceptable

	40914506 (Sensitizer)		Acceptable
	41360401 (Not a Sensitizer)		Acceptable
85-1	41796401 41796402	Metab-olism	Acceptable

The previous reviews are also included for 81-4, 81-5 and 81-6 (propanil, technical), since they were re-submitted with the newer data.

For technical propanil, the following studies are required:

Acute inhalation - technical
1-yr chronic dog
2-yr chronic/onco - rat
onco - mouse
2-generation rat reproduction

Attachments

Mary/disk 4/818688

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Reviewed by: William Dykstra, Ph.D. William Dykstra 7/30/91
Review Section I, Toxicology Branch I (H7509C)
Secondary Reviewer: Roger Gardner, Section Head
Review Section I, Toxicology Branch I (H7509C) 09-24-91
(for RG)

DATA EVALUATION REPORT

Study Type: 81-1; Acute Oral - Rat TOX Chem No. 325
MRID No.: 413608-01

Accession Number: N/A

Test Material: Propanil; assumed 100% technical

Synonyms: STAM

Study Number: WIL-141001

Sponsor: Propanil Task Force
Liberty, MO

Testing Facility: WIL Research Labs, Inc.
Ashland, Ohio

Title of Report: Acute Oral Toxicity (LD_{50}) Study in Albino Rats with Propanil

Author: Dennis J. Naas

Report Issued: September 5, 1989

Conclusion: 95% C.L.
LD_{50} = 1080 mg/kg (868-1343 mg/kg); Both Sexes. Cumulative mortality was 2/10, 5/10, 8/10 at doses of 750, 1080 and 1555 mg/kg BW. Toxic signs included lethargy, ataxia, cyanosis, prostration, respiratory distress and clear ocular discharge. Necropsy findings in dead rats included mottled lungs, reddened adrenal glands, dark gI contents, red foci on thymus, dark red kidneys, dark areas of stomach. Toxicity Category III

Classification: ~~Core Guideline~~ ACCEPTABLE

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

Review:

Acute Oral Toxicity (LD_{50}) Study in Albino Rats with Propanil (WIL Research Labs Study No. WIL-141001; Sept. 5, 1989).

Test Material: Propanil technical; light purple granular solid; assume 100% purity for acute testing.

Animals: Crl: $CO^{R}BR_{r}$ Sprague-Dawley rats, 15 males and 15 females, young adult (208 to 297 grams at beginning of study) obtained from Charles River Breeding Labs, Inc. Portage, MI, individually caged and fed Purina Certified Rodent Chow® #5002 and tap water.

Methods:

Three groups of 5M and 5F Sprague-Dawley rats were orally gavaged with single doses of test material (1% suspension in aqueous methocel) at a dose volume of 10 ml/kg at doses of 750, 1080, and 1555 mg/kg BW. Dose levels were selected using a progression of 1.44. Animals were fasted 18-20 hours prior to dosing and returned to feed about 3-4 hours after dosing. Observations were 1, 3, 4 hours post-dosing and twice daily for 14 days.

Body weights were recorded on days -1, 0, 7, and 14.

All dead rats and survivors were necropsied.

Results:

1. LD_{50}

	Total Mortality		
Dose (mg/kg)	Males	Female	Total
750	1/5	1/5	2/10
1080	2/5	3/5	5/10
1555	3/5	5/5	8/10

Based on the above data,

	LD_{50} (95% C.L.)	Slope (95% C.L)
Males	1302 (809-2095) mg/kg	1.9 (0.6-6.1)
Females	960 (770-1196) mg/kg	1.3 (1.1-1.6)
Combined	1080 (868-1343) mg/kg	1.5 (1.1-2.2)

Toxicity Category III

2. Body Weight: Unremarkable

3. Toxic Signs: lethargy, ataxia, cyanosis, prostration, respiratory distress, clear ocular discharge.

4. Necropsy: Dead Rats: Mottled lungs, reddened adrenals, dark GI tract contents, red foci on thymus, dark red kidneys, dark area of stomach.

Terminally Sacrificed: No significant changes at necropsy.

Classification: Core-guideline

Addendum: Signed and dated statements of GLP Compliance and Quality Assurance were present and signed by Dennis J. Naas (Study Director, 9/5/89) and Deborah L. Little (9/5/89), respectively.

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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Propanil - Reregistration Response by Propanil Task Force - Acute Toxicity Studies (Guidelines Reference Nos. 81-4, 81-5, and 81-6)

Caswell No.: 325
Record Nos.: 268522, AC660,
ID No.: 0226
Project No.: 0-2042
MRID Nos.: 413605-01, 413606-01, 413604-01

FROM: William Dykstra, Reviewer William Dykstra 11/16/90
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Terri Stowe, PM Team 74
Reregistration Branch
Special Review and Reregistration Division (H7508C)

THRU: Roger Gardner, Section Head 6/10/91 (for RG)
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

6/14/91

Requested Action

Review acute toxicology studies submitted by the Propanil Task Force in support of reregistration of propanil.

Conclusion and Recommendations

The submitted studies are acceptable, ~~as core guideline data~~.

8

The results show that propanil is a moderate eye irritant (Toxicity Category II), a very slight skin irritant (Toxicity Category IV) and is not a dermal sensitizer in guinea pigs.

Reviews of each of these studies are attached.

Attachments

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Reviewed By: William Dykstra William Dykstra 11/16/90
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Roger Gardner, Section Head by direction 6/10/91
Section I, Toxicology Branch I - IRS (H7509C) (for RG)

008130

DATA EVALUATION REPORT

Study Type: Primary Eye Irritation - 81-4 TOX Chem No.: 325

Accession Number: N/A MRID No.: 413605-01

Test Material: Propanil, Batch No. 01, 100% Purity

Study Number: Project No. WIL-141004

Sponsor: Propanil Task Force

Testing Facility: Wil Research Labs
Ashland, OH

Title of Report: Primary Eye Irritation Study in Albino Rabbits with Propanil.

Author: Dennis J. Naas

Report Issued: September 5, 1989

Conclusions:

100 mg of finely ground test material was instilled into the right eye of each of six female New Zealand White (NZW) rabbits. Draize scores were made at 1, 24, 48, and 72 hours and 4, 7, and 14 days. Conjunctivitis occurred in 6/6 which cleared by day 14. Iritis was present in 6/6 which cleared by day 14. Corneal opacity occurred in 3/6 which cleared by 4 days. Average maximum Draize score of 23.8 at 24 hours. Toxicity Category II.

Classification: Core-Guideline

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

Review:

Primary Eye Irritation Study in Albino Rabbits with Propanil (WIL Project No. WIL-141004; September 5, 1989; MRID No. 413605-01).

Test Material - Propanil, assumed 100% purity; Batch No. 01; Supplied by Propanil Task Force.

Animals - NZW rabbits, six females, young adult (2127 to 3043 g bwt), individually housed, Purina Certified Rabbit Chow #5322 and tap water ad libitum.

Methods - 100 mg of finely ground test material was instilled into the conjunctival sac of the right eye of each of six female rabbits. The eyelids were closed for 1 second. The eyes remained unwashed. The left eye of each animal served as a control. Observations were made at 1, 24, 48, and 72 hours and at 4, 7, and 14 days. In addition, both eyes of all rabbits were further examined at 72 hours and 7 and 14 days with sodium fluorescein and ultraviolet light.

Results - There were no mortalities. Body weight was essentially unchanged during the study period. The left eyes of all rabbits were free of irritation.

All right eyes had conjunctivitis which cleared in 7 days for 3/6 and by day 14 in the remaining 3/6. Iritis was present in 3/6 eyes which cleared by 48 and 72 hours and day 14. Corneal opacity was present in 3/6 eyes which cleared by 72 hours, 4 days, and 72 hours in the three rabbits. Average maximum Draize score at 24 hours was 23.8; Toxicity Category II, classification is considered appropriate.

Addendum - A Quality Assurance Statement was signed on August 5, 1989 by Deborah L. Little, Supervisor of Quality Assurance.

A table of primary eye irritation scores provided by the registrant in the report is shown below.

Table 1. Primary Eye Irritation Study In Albino Rabbits With Propanil

Project No: WIL-141004
Sponsor: Propanil Task Force

Individual Ocular Irritation Scores

Group: 100 mg/Right Eye, Unwashed				Examination Intervals						
Animal	Sex	Tissue		1 H	24 H	48 H	72 H*	4 D	7 D*	14 D*
8483	F	Cornea	(O-A)	0 0	0 0	0 0	0 0	0 0	0 0	
		Iris		0	0	0	0	0	0	
		Conjunctiva	(R-C-D)	2 2 1	2 1 0	1 1 0	1 0 0	1 0 0	0 0 0	
8490	F	Cornea	(O-A)	0 0	2 3	2 1	0 0	0 0	0 0	0 0
		Iris		0	1	1	0	0	0	0
		Conjunctiva	(R-C-D)	2 3 2	3 3 2	2 2 0	2 1 0	1 0 0	1 1 0	0 0 0
8497	F	Cornea	(O-A)	2 3	2 3	2 2	1 2	0 0	0 0	0 0
		Iris		1	1	0	0	0	0	0
		Conjunctiva	(R-C-D)	2 2 2	2 2 2	1 1 0	1 1 0	1 0 0	1 0 0	0 0 0
8499	F	Cornea	(O-A)	0 0	0 0	0 0	0 0	0 0	0 0	
		Iris		0	0	0	0	0	0	
		Conjunctiva	(R-C-D)	2 2 2	2 1 0	2 1 0	1 0 0	1 0 0	0 0 0	
8505	F	Cornea	(O-A)	0 0	0 0	0 0	0 0	0 0	0 0	
		Iris		0	0	0	0	0	0	
		Conjunctiva	(R-C-D)	2 2 2	2 1 0	2 0 0	1 0 0	0 0 0	0 0 0	
8507	F	Cornea	(O-A)	1 1	2 1	1 1	0 0	0 0	0 0	0 0
		Iris		1	1	1	1	1	1	0
		Conjunctiva	(R-C-D)	2 3 2	3 2 1	2 1 0	2 0 0	1 0 0	0 0 0	0 0 0
Total				119.	143.	77.	35.	17.	11.	0.
Mean				19.8	23.8	12.8	5.8	2.8	1.8	0.0

* = Fluorescein Solution Applied; O = Opacity; A = Area; R = Redness; C = Chemosis; D = Discharge; H = Hours; and D = Days.

Classification: Core-Guideline

008122

Reviewed By: William Dykstra William Dykstra 11/30/90
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Roger Gardner, Section Head
Section I, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT 008430

Study Type: Primary Dermal Irritation - 81-5 TOX Chem No.: 325

Accession Number: N/A MRID No.: 413606-01

Test Material: Propanil, 100% Purity, Batch 01

Synonyms: None

Study Number: Project No. WIL-141003

Sponsor: Propanil Task Force

Testing Facility: Wil Research Labs
Ashland, OH

Title of Report: Primary Dermal Irritation Study in Albino Rabbits with Propanil.

Author: Dennis J. Naas

Report Issued: September 5, 1989

Conclusions:

0.5 g of finely ground, moistened, test material was applied under occlusion for 4 hours to shaved, intact skin of six rabbits (4F and 2M). Scoring according to Draize at 4-5, 24, 48, and 72 hours showed very slight erythema in four rabbits and very slight edema in one rabbit at 4-5 hours which cleared by 24 hours. P.I.S. = 0.2/4.0; Toxicity Category IV.

Classification: Core-Guideline

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

Review:

Primary Dermal Irritation Study in Albino Rabbits with Propanil (WIL Project No. WIL-141003; September 5, 1989; MRID No. 413606-01).

Test Material - Propanil, 100% purity; Batch No. 01; provided by Propanil Task Force.

Animals - New Zealand White rabbits - two males and four females, 2463 to 3086 g bwt at study initiation; individually housed; tap water and Purina Rabbit Chow #5322 ad libitum.

Methods - 0.5 g of finely ground test material, moistened, was applied directly to the shaved, intact skin of each of six rabbits at one intact site per rabbit. The test material was occluded and the animals wore plastic restraint collars. The test material remained in contact with the rabbit's skin for 4 hours. At the end of 4 hours, the collars and bandages were removed and the sites wiped with wet disposable paper towels. Sites were scored according to Draize for erythema, edema, and any other dermal findings at 4-5, 24, 48, and 72 hours after dosing.

Results - There were very slight erythema in four rabbits and very slight edema on one rabbit at the initial 4-5 hour observation period which had disappeared by 24 hours. Primary irritation index was 0.2/4.0. Toxicity Category IV.

There were no mortalities and body weight was not remarkably changed during the study period.

Addendum - A Quality Assurance Unit statement was signed on September 5, 1989 by Deborah L. Little, Supervisor of Quality Assurance.

The following table from the report shows individual results.

Table 1. Primary Dermal Irritation in Albino Rabbits

Project No.: WIL-141003
Submission Propanil Task Force

Individual Dermal Scores

			INTACT					INTACT			
			Erythema		Edema			Erythema		Edema	
Animal	Sex	Site	4-5 H	24 H	4-5 H	24 H	Site	48 H	72 H	48 H	72 H
8401	M	A	1	0	0	0	A	0	0	0	0
8403	M	A	1	0	0	0	A	0	0	0	0
8406	F	A	0	0	0	0	A	0	0	0	0
8408	F	A	1	0	0	0	A	0	0	0	0
8412	F	A	1	0	1	0	A	0	0	0	0
8422	F	A	0	0	0	0	A	0	0	0	0
		Total	4	0	1	0	Total	0	0	0	0

PII Calculated Using Test Periods 4-5 H, 24 H, 48 H, 72 H.
Primary Irritation Index (PII) = (4 + 0 + 0 + 0 / 24) + (1 + 0 + 0 + 0 / 24)
(PII) = 4 / 24) + (1 / 24)
(PII) = 0.2 + 0.0
(PII) = 0.2 = Slightly Irritating

H = Hours; M = Male; and F = Female.

Classification: Core-Guideline

008722

Reviewed By: William Dykstra William Dykstra 11/16/90
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Roger Gardner, Section Head
Section I, Toxicology Branch I - IRS (H7509C)

008430

DATA EVALUATION REPORT

Study Type: Dermal Sensitization - 81-6 TOX Chem No.: 325

Accession Number: N/A MRID No.: 413604-01

Test Material: Propanil, 100% Purity, Batch 01

Synonyms: None

Study Number: Project No. WIL-141005

Sponsor: Propanil Task Force

Testing Facility: Wil Research Labs
Ashland, OH

Title of Report: Skin Sensitization Study in Albino Guinea Pigs with Propanil.

Author: Dennis J. Naas

Report Issued: September 5, 1989

Conclusions:

Propanil was tested in a modified Buehler method for topical skin sensitization in Hartley Albino guinea pigs. There was a primary irritation phase to select the concentrations of propanil solution for the induction (25% propanil solution) and challenge phases (2.5% propanil solution). There were nine induction doses over a 3-week period. After 14 days from the last induction dose, challenge doses to the propanil group, a naive control group, and a positive control group, DNCB, were performed. Propanil was not a skin sensitizer in comparison to the naive controls. The positive control group produced skin sensitization in all animals.

Classification: Core-Guideline

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

Review:

Skin Sensitization Study in Albino Guinea Pigs with Propanil (WIL Project No. WIL-141005; September 5, 1989; MRID No. 413604-01).

Test Material - Propanil, technical 100% purity; Batch No. 01; provided by Propanil Task Force; positive control was 0.1 percent w/v dinitrochlorobenzene in 80 percent ethanol.

Animals - Hartley Albino guinea pigs, 12 males and 12 females, Murphy Breeding Laboratories, Inc., Plainfield, IN, 314 to 399 g, young adults, individually caged, Purina Guinea Pig Chow #5025 and tap water ad libitum.

Experimental Design:

1. Primary Irritation Phase - Test material was prepared for dosing as w/v solutions in acetone at concentrations of 1.0, 2.5, 5, 10, and 25 percent.

2. Induction - The 25 percent w/v solution of propanil in acetone was chosen for induction. The positive control was 0.1 percent w/v solution in 80 percent ethanol with dinitrochlorobenzene.

3. Challenge Phase - Test material was 2.5 percent w/v solution in acetone. Positive control was 0.1 percent dinitrochlorobenzene.

4. Test Material Administration - Direct topical occluded application to shaved, intact skin. This route of administration is the modified Buehler method.

   a. Primary Irritation Phase - 0.4 mL/site. There were three test sites per guinea pig. The period of exposure was 6 hours.

   b. Induction Phase - The 25 percent w/v prepared test material and positive control materials were applied occluded at 0.4 mL/site. Induction doses were applied to the same site on the left flank of all test and positive control group animals. Test and positive control group animals each received nine induction doses spaced 2 or 3 days apart over a period of 3 weeks. All induction exposures were 6 hours, after which bandages were removed and the sites washed with wet disposable paper towels.

      All naive control animals remained untreated during the induction phase.

c. Challenge Phase - 14 days after the last induction, the test and naive control group animals were dosed with 0.4 mL/site of a 2.5 percent w/v solution of propanil in acetone on the right flank. Positive control animals were dosed with a 0.1% w/v dinitrochlorobenzene in 80 percent ethanol at 0.4 mL/site on the right flank.

Dermal Observations - All sites were examined and graded in accordance with the score scale at 24 and 48 hours (score scale 0, ±, 1, 2, 3, 4, = no reaction, slight patchy erythema, slight confluent or moderate patchy erythema, moderate erythema, severe erythema (with or without edema).

Results:

1. Mortality - Naive control group I female 04001171 was sacrificed on study day 7. This study animal was replaced. No other deaths occurred.

2. Body Weight - No remarkable weight changes.

3. Dermal Observations

a. Primary Irritation Phase - 25 percent propanil acetone solution was lowest concentration that induced consistent, very slight to slight reactions.

The 25 percent propanil solution was the highest concentration that produced no irritation and was selected for challenge dose.

b. Challenge Phase - One test group animal (propanil) and two naive control animals produced slightly patchy erythema (scores of ±) observed at 24 hours. All other test sites in the propanil test group or naive control were negative. In the positive control group, grade 2 or 3 persisted through 48 hours in all animals. The table below shows the results.

(Report Table 8)

"Table 8. Skin Sensitization Study in Albino Guinea Pigs with Propanil

Project No.: WIL-141005
Sponsor: Propanil Task Force

Incidence of Dermal Responses at Challenge

Group	Material	Interval	Dermal Scores 0	±	1	2	3	Number of Animals	Irritation Severity Index
Test	2.5% w/v Propanil in acetone	24 H	11	1	0	0	0	12	0.04
		48 H	12	0	0	0	0	12	0.0
Naive Control-I	2.5% w/v Propanil in acetone	24 H	4	2	0	0	0	6	0.17
		48 H	6	0	0	0	0	6	0.0
Positive Control	0.1% DNCB	24 H	0	0	0	1	5	6	2.8
		48 H	0	0	0	5	1	6	2.2

H = Hours.
DNCB = Dinitrochlorobenzene.

Conclusion - Propanil is not a skin sensitizer in this experimental design. The positive control, dinitrochlorobenzene, produced positive skin sensitivity results.

Addendum - A Quality Assurance Unit statement was signed on September 5, 1989 by Deborah L. Little, Supervisor of Quality Assurance.

Classification: Core-Guideline

008722

Reviewed by: William Dykstra, Ph.D. William Dykstra 7/29/91
Review Section I, Toxicology Branch I (H7509C)
Secondary Reviewer: Roger Gardner, Section Head
Review Section I, Toxicology Branch I (H7509C) 9/25/91
C.fin RG)

DATA EVALUATION REPORT

Study Type: 81-2 Acute Dermal Rabbit TOX Chem No. 325
MRID No.: 413609-01

Accession Number: N/A

Test Material: Propanil technical; 100% purity

Synonyms: STAM

Study Number: WIL-141002

Sponsor: Propanil Task Force
Liberty, MO

Testing Facility: WIL Research Labs, Inc.
Ashland, Ohio

Title of Report: Acute Dermal Toxicity (LD_{50}) Study in Albino Rabbits with Propanil

Author: Dennis J. Naas

Report Issued: September 5, 1989

Conclusion: LD_{50} > 2000 mg/kg (Both Sexes) Limit Dose No deaths
Toxicity Category IV
5M + 5F NZW rabbits received on shaved intact skin a single dermally applied dose of 2000 mg/kg BW of test material under semi-occlusive dressing for 24 hours. No deaths. Slight erythema and edema. No body weight changes. No remarkable lesions at necropsy. Toxicity Category IV Limit Dose

Classification: ~~Core Guideline~~ ACCEPTABLE

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

Review:

Acute Dermal Toxicity (LD_{50}) Study in Albino Rabbits with Propanil (With Research Labs no. WIL-141002; Sept. 5, 1989).

Note: A GLP Compliance Statement signed by Dennis J. Naas (Study Director, 9/5/89) and Quality Assurance Statement signed by Deborah L. Little (9/5/89) were present in the report.

Test Material: Propanil technical; assumed 100% purity; light purple granular solid.

Animals: Five male and five female NZW rabbits, young adults (2200-2456 grams at initiation), individually caged and fed Purina Certified Rabbit Chow #5322 and tap water.

Experimental Design:

The fur on the rabbit's trunk was clipped free of hair and remained unbraided.

Five male and five female NZW rabbits received a dermally applied dose of 2000 mg/kg BW of test material, moistened with two milliliters of deionized water, on the intact, fur clipped trunk (5-10% body surface) under semi-occlusive dressing for 24 hours. The rabbits wore collars during exposure and following treatment the test material was removed. Observations were 1.0, 3.0 and 4.0 hours post-dose and once daily for 14 days. Body weight was recorded on day 0, 7, and 14.

Results: No deaths
LD_{50} > 2000 mg/kg (Both sexes). This is the limit dose for the study.

Toxicsigns: none reported

Skin Reactions: slight erythema and edema up to day 5.

Body Weight: No remarkable changes

Necropsy: No remarkable lesions

Classification: Core-guideline
Toxicity Category IV: limit dose

008722

Reviewed by: William Dykstra, Ph.D. William Dykstra 7/30/91
Review Section I, Toxicology Branch I (H7509C)
Secondary Reviewer: Roger Gardner, Section Head
Review Section I, Toxicology Branch I (H7509C) 09-25-91

DATA EVALUATION REPORT

Study Type: 81-3; Acute Inhalation - Rat TOX Chem No. 325
MRID No.: 412659-01

Accession Number: N/A

Test Material: Propanil; 60 DF; Batch # F01A202

Synonyms: STAM

Study Number: 6120-89

Sponsor: Terra International, Inc.

Testing Facility: Stillmeadow, Inc.
Houston, Texas

Title of Report: Acute Inhalation Toxicity Study in Rats

Author: Mark S. Holbert

Report Issued: May 30, 1989

Conclusion: Groups of 5M and 5F Sprague- Dawley rats were exposed to aerosolized concentrations of 2.45, 5.33, and 10.5 mg/L of propanil 60DF for 4 hours. Mortality was 0, 20 and 100%, respectively, for the three doses for both sexes.

LL_{50} = 6.181 mg/L (5.297 - 7.213 mg/L) Both sexes

Toxicity Category IV

Classification: Core-Guideline

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

Review:

Acute Inhalation Toxicity Study in Rats (Stillmeadow Report No. 6120-89; May 30, 1989)

Note: GLP Compliance Statement signed by Mark S. Holbert (Study Director) and Quality Assurance Statement signed by James P. Gregory (8/30/89) were present.

Test Material:

10.5 mg/L Exposure Level

Propanil 60DF (powdered) Batch #F01A202 1; beige powder

2.45 and 5.33 mg/L Exposure Level

Propanil 60F Micronized Experimental Sample Batch # F01A2181; beige powder

Animals: HSD: (SD) BR; Harlan Sprague-Dawley rats, 15 males and 15 females, (nulliparous), 175-296 gms, young adult, 1-3 per cage, fed Purina Formulab Chow #5008 and tap water, available ad libitum except during exposure period.

Experimental Designs:

Five males and 5 females for each of three exposure periods were selected for testing. A maximum of 10 animals were exposed during any given exposure period to an aerosol generated from the undiluted test material (fine powder) for a period of 4 hours. During the exposure period, the animals were housed in a 200 L Stainless Steel dynamic flow inhalation chamber. The aerosol was generated by passing a stream of dry, filtered air through four glass flasks containing the test material. The concentrated aerosol was then diluted with dry and filtered air and drawn into the exposure chamber. Air flow was recorded at 30 minute intervals during the exposure period. Temperature and humidity were determined every 30 minutes.

Gravimetric determination was of test material was determined twice per hour (taken from the breathing zone of the animals) and nominally at the end of each period. Particle size determinations were made using an Andersen cascade impactor.

Observations were for 14 days.

Results:

Dose Level (mg/L)	Number Dead/Number Treated Males	Females	Percent Mortality
2.45	0/5	0/5	0/10
5.33	1/5	1/5	2/10
10.5	5/5	5/5	10/10

95% C.F.

LC_{50} = 6.18/mg/L (5.297 - 7.213 mg/L)

Body Weight: Survivors gained weight

Toxic Signs: decreased activity, ataxia chromodacryorrhea, diarrhea, dilated pupils, gasping, lacrimation, moribund, nasa discharge, piloerection, polyuria, ptosis, salivation and respiratory gargle

Necropsy: (External and Internal): chromodacryorrhea, ~~achromatin~~ nasal discharge, distended GI tract, discolored and mottled lungs, discolored liver and kidneys, swollen kidneys, withdrawn testes

Particle Size Distribution

Test Material: PROPANIL 60 DF MICRONIZED
Concentration: 2.45 mg/L
1 Hour Distribution

Stage	Size Range (um)	ECD** (um)	Amount Collected (mg)	% in Size Range	Cumulative % Less Than Size Range
Preseparator***	>=10.0	10.0	18.3	9.88	
0	9.0 - 10.0	9.0	4.2	2.54	87.36
1	5.8 - 9.0	5.8	33.0	20.01	67.35
2	4.7 - 5.8	4.7	27.9	16.91	50.43
3	3.3 - 4.7	3.3	42.6	25.83	24.60
4	2.1 - 3.3	2.1	20.7	12.55	12.24
5	1.1 - 2.1	1.1	14.6	8.85	3.39
6	0.7 - 1.1	0.7	3.8	2.30	1.09
7	0.4 - 0.7	0.4	1.3	0.78	0.30
Backup Filter	0.0 - 0.4	0.0	0.5	0.30	0.00

Calculated CHI^2 = 10.191 with 6 Degrees of Freedom.
Values of T and CHI^2 for P=.05 are: T = 2.45 CHI^2 = 12.6
GOOD FITTING CURVE

Particle Size (Microns)	% of Particles Collected
<= 1.44	3
<= 2.23	16
<= 4.58	50
<= 8.99	84
<= 14.04	95

Mass Median Aerodynamic Diameter = 4.304 um
Geometric Standard Deviation = 1.996

* - Finney, D.J.: PROBIT ANALYSIS. 3rd ed., Chapters 3 and 4, 1971. Cambridge University Press.
** - Effective cutoff diameter.
*** - Preseparator weights determined directly.

Dose (mg/L)

2.45 Chamber flow rate = 77.2 Liters/min
5.33 Chamber flow rate = 77.2 Liters/min
.0.5 Chamber flow rate = 61.9 Liters/min

Test Material: PROPANIL 4O DF M'CHROMIZED
Concentration: 5.33 mg/L
1 Hour Distribution

Stage	Size Range (um)	ECD** (um)	Amount Collected (mg)	% in Size Range	Cumulative % Less Than Size Range
Presepparator***	>=10.0	10.0	22.4	10.39	
0	9.0 - 10.0	9.0	9.7	4.50	83.09
1	5.8 - 9.0	5.8	65.2	30.26	54.83
2	4.7 - 5.8	4.7	14.8	6.87	47.95
3	3.3 - 4.7	3.3	33.1	25.58	22.37
4	2.1 - 3.3	2.1	24.8	11.51	10.86
5	1.1 - 2.1	1.1	14.9	6.91	3.94
6	0.7 - 1.1	0.7	6.5	3.01	0.92
7	0.4 - 0.7	0.4	1.6	0.74	0.18
Backup Filter	0.0 - 0.4	0.0	0.4	0.18	0.00

Calculated CHI* = 8.387 with 6 Degrees of Freedom.
Values of T and CHI* for P=.05 are: T = 2.45 CHI* = 12.6
GOOD FITTING CURVE

Particle Size (Microns)	% of Particles Collected
<= 1.48	5
<= 2.37	16
<= 4.96	50
<= 10.36	84
<= 16.65	95

Mass Median Aerodynamic Diameter = 4.965 um
Geometric Standard Deviation = 2.086

* - Finney, D.J.: PROBIT ANALYSIS, 3rd ed., Chapters 3 and 4, 1971, Cambridge University Press.
** - Effective cutoff diameter.
*** - Presepparator weights determined directly.

Test Material: PROPANIL 4O DF POWDERED
Concentration: 10.33 mg/L
1 1/4 Hour Distribution

Stage	Size Range (um)	ECD** (um)	Amount Collected (mg)	% in Size Range	Cumulative % Less Than Size Range
Presepparator***	>=9.0	10.0	10.1	8.72	
0	9.0 - 10.0	9.0	5.5	4.75	86.51
1	5.8 - 9.0	5.8	17.7	15.29	71.21
2	4.7 - 5.8	4.7	11.8	10.19	61.01
3	3.3 - 4.7	3.3	24.9	21.52	39.49
4	2.1 - 3.3	2.1	24.5	21.17	18.32
5	1.1 - 2.1	1.1	13.8	11.92	6.39
6	0.7 - 1.1	0.7	4.5	3.88	2.50
7	0.4 - 0.7	0.4	1.6	1.38	1.12
Backup Filter	0.0 - 0.4	0.0	1.3	1.12	0.00

Calculated CHI* = 4.868 with 6 Degrees of Freedom.
Values of T and CHI* for P=.05 are: T = 2.45 CHI* = 12.6
GOOD FITTING CURVE

Particle Size (Microns)	% of Particles Collected
<= 1.00	5
<= 1.70	16
<= 3.84	50
<= 8.49	84
<= 14.70	95

Mass Median Aerodynamic Diameter = 3.848 um
Geometric Standard Deviation = 2.258

* - Finney, D.J.: PROBIT ANALYSIS, 3rd ed., Chapters 3 and 4, 1971, Cambridge University Press.
** - Effective cutoff diameter.
*** - Presepparator weights determined directly.

AI-RAT.WD/LCA

008722

Reviewed by: William Dykstra, Ph.D. William Dykstra 7/31/91
Review Section I, Toxicology Branch I (H7509C)
Secondary Reviewer: Roger Gardner, Section Head
Review Section I, Toxicology Branch I (H7509C) 09/25/91
(for RG)

DATA EVALUATION REPORT

Study Type: 81-6; Dermal Sensitization - Guinea Pigs
TOX Chem No. 325
MRID No.: 409145-06

Accession Number: N/A

Test Material: 60 DF; 60% a.i. Dry Flowable; FD-1-73

Synonyms: Propanil 60DF

Study Number: 5415-88

Sponsor: Riverside/Terra Corporation
Memphis, TN

Testing Facility: Stillmeadow, Inc.

Title of Report: Dermal Sensitization Study in Guinea Pigs

Author: J. O. Kahn, Ph.D.

Report Issued: August 18, 1988

Conclusion: A sensitizing reaction was produced by 50 mg of Propanil 60DF moistened with 0.05 ml of deionized water (group A) in the challenged guinea pigs. A positive control group (group B) treated with 0.05% W/V solution of 2,4-DNCB in ethanol also produced positive results.

Classification: ~~Core-Guideline~~ ACCEPTABLE

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

Review:

Dermal Sensitization study in Guinea Pigs (81-6) (Stillmeadow Study No. 5415-88; August 18, 1988)

Test Material: Propanil 60DF; 60% a.i. Dry Flowable; FD-1-73 5-25-88

Positive Control: 0.05% W/V of 2,4-dinitrochlorobenzene in ethanol

Experimental Animals: Young adult Hartley-Albino guinea pigs, 20 males, 285-345 gm, obtained from Harland Sprague-Dawley Inc., Houston, TX; Five per cage fed Purina Guinea Pig Chow and tap water ad libitum.

Experimental Design:

Ten males were selected for each of two treatment group. The animals were prepared by clipping the back of the trunk free of hair as necessary and on the days prior to treatments 2 through 10 and the challenge and rechallenge treatments.

Group I - 50 mg test material; highest non-irritating
Group II - positive control; 0.05 ml of DNCB

Individual body weights were recorded on study days 0, 35 and 39. The animals were treated on study days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, 36 and 50. The animals were treated one each of the first 10 treatment days by introducing 0.5 ml of the positive control or 50 mg of test material moistened with 0.05 ml of deionized water beneath a gauze pad which was secured by a piece of adhesive. The adhesive coverlet patches were placed laterally from the midline of the back on the left front quadrant of the exposure area. The entire trunk of each animal was then wrapped with polyethylene film. Each animal was placed in a restrainer for 6 hours. The same test site location was used on each animal on all treatment days At the end of the 6 hour treatment period, the wrapping and patches were removed and the animals were returned to their cages.

On Day 36, all animals were treated in an identical manner as on the previous 10 treatment days with the addition that a second patch was placed on the right rear quadrant. On Day 50, the second patch was placed on the right front quadrant of each animal.

Observations for skin reactions were made 24 hours after each treatment for each test site. Additionally, observations were made 48 hours after treatments 1 and 10 and the challenge treatments on Day 36 and rechallenge on Day 50.

Results:

Body Weight: All animals gained weight during the study.

Skin Reactions: Average scores are shown below:

	Hours After Day of Treatment											Challenge				Rechallenge			
	LF											LF		RR		LF		RF	
	Day 1		3	6	8	10	13	15	17	20	22	36		36		50		50	
Group	24	48	24	24	24	24	24	24	24	24	24 48	24	48	24	48	24	48	24	48
I (Positive Control)	0.0	0.0 (0.0)	0.2	1.3	3.0	3.5	4.5	4.6	4.8	5.1	6.2 5.8 (6.0)	3.7	3.4 (3.6)	1.3	1.3 (1.3)	3.7	3.2 (3.5)	2.9	2.5 (2.7)
II (Test Group)	0.0	0.0 (0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0 0.0 (0.0)	0.2	0.5 (0.4)	0.5	1.5 (1.0)	1.8	1.4 (1.6)	1.9	1.5 (1.7)

LF - Left Front Test Site
RR - Right Rear Test Site
RF - Right Front Test Site

Discussion: The average skin reaction scores for the positive control group (Group I) were 0.0 for day 1, and 1.3 for the first virgin challenge site and 3.6 for the original test site for the challenge treatment (day 36). The average scores were 2.7 for the second virgin challenge site and 3.5 for the original test site at rechallenge on day 50. Therefore, DNCB was a sensitizing agent in guinea pigs.

For the test material treated animals (Group II), the average skin reaction scores were 0.0 for day 1, 1.0 for the first virgin challenge site and 0.4 for the original test site for the challenge treatment. The average scores were 1.7 for the second virgin challenge site and 1.6 for the original test site at rechallenge on day 50.

Therefore, the test material, Propanil 60DF, produced a sensitizing reaction in guinea pigs.

Addendum: A statement of Quality Assurance and a GLP Compliance Statement were signed by James F. Gregory (8/18/88) and by Janice G. Kuhn (Study Director), respectively.

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008722

Reviewed by: William Dykstra, Ph.D. William Dykstra 8/13/91
Review Section I, Toxicology Branch I (H7509C)
Secondary Reviewer: Roger Gardner, Section Head
Review Section I, Toxicology Branch I (H7509C) 9-25-91 (for RG)

DATA EVALUATION REPORT

Study Type: 81-6; Delayed Contact Hypersensitivity - Guinea Pigs
TOX Chem No. 325
MRID No.: 408719-06

Accession Number: N/A

Test Material: V-087-93-PILRUN-I - light tan liquid

Synonyms: Propanil 4 Flowable

Study Number: PH424-CC-001-88

Sponsor: Cedar Chemical Corp.
Memphis, TN

Testing Facility: Pharmakon Research International, Co.
Waverly, PA

Title of Report: Delayed Contact Hypersensitivity in Guinea Pigs

Author: S. Armandi and V. Ciofalo

Report Issued: October 24, 1988

Conclusion: The test material when induced and challenged at a 0.5% concentration caused delayed hypersensitivity in guinea pigs. When rechallenged at a 0.1% concentration, the test material did not cause delayed contact hypersensitivity in guinea pigs. Therefore, Propanil 4 Flowable is a delayed contact hypersensitizing agent in guinea pigs.

Classification: ~~Core-Guideline~~ ACCEPTABLE

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

Review: Delayed Contact Hypersensitivity in Guinea Pigs (Pharmakon Study No. PH424-CC-001-88; Oct. 24, 1988).

Test Material: V-087-93-PILRUN-1; light tan liquid (Propanil 4 Flowable)

Positive control: DNCB, 0.3%
Negative control: 80% ethanol

Animals: Hartley Guinea Pigs, male and female, 300-700 grams initially, purchased from Bukberg Lab Animal, Tomkins Cove, N.Y. MA, 5 per cage, fed Wayne Guinea Pig Diet* and water, ad libitum.

Experimental Design:

Frequency of Administration	Animals	Dose
Three (3) Inductions	20 Experimental	0.5% test mat.
Three (3) Inductions	5 Positive cont.	0.3% DNCB
Three (3) Inductions	10 neg. cont.	80% ETOH
One (1) Challenge	20 exp. animal	0.5% test mat.
One (1) Challenge	5 post. cont.	0.3% DNCB
One (1)Challenge	10 neg. cont.	80% ethanol
One (1) Challenge	4* naive animals	0.5% test mat.
One (1) re-Challenge	20 exp. animals	0.1% test mat.
One (1) re-Challenge	4* naive animals	0.1% test mat.

* Four animals from the negative control were used as naive control animals for rechallenge.

The left shoulder of each animal was clipped free of hair just prior to 1st, 2nd, and 3rd applications (10% of body surface). The appropriate material was applied under occlusive patch and wrap for 6 hours. The treated sites were examined after each dosing day and scored at 24 and 48 hours The procedure was performed once a week for three weeks, a total of three six-hour inductions. Fourteen days after last induction, the animals were challenged on a naive sit on the left side. Seven days after the primary challenge, the experimental group and a group of four naive pigs were rechallenged on the right side with 01% concentration of test material. Hair was removed by Neet Cream Hair Remover from both left and right sides.

Results:

~~PLACE TABLE HERE~~

The results show that the positive control (0.3 DNCB) and test material (0.5%) produced a delayed sensitizing effect of 5/5 and 5/20, respectively, at 24 and 48 hours. After challenge (ethanol was negative), but the diluted test material (0.1%) did not produce a delayed sensitizing effect when applied as 0.1% dose at rechallege in comparison to naive controls (also received 0.1% test material).

Delayed Contact Hypersensitivity in Guinea Pigs
Incidence and Severity of Responses at Challenge and Rechallenge

PH 4.4-CC-001-88

	Challence			
	Naive Site			
	24 hours		48 hours	
Test Article	Incidence	Severity	Incidence	Severity
V-087-93-PILBUN-1 (0.5%)	5/20	0.6	4/20	0.4
Naive Animals V-087-93-PILBUN-1 (0.5%)	0/4	0.0	0/4	0.0
DNCB (0.3%)	5/5	2.6	5/5	2.6
Ethanol (80%)	0/10	0.1	0/10	0.0

	Rechallence	
	Naive Site	
Test Article		
V-087-93-PILBUN-1 (0.1%)	1/20	0.3	1/20	0.3
Naive Animals V-087-93-PILBUN-1 (0.1%)	0/4	0.0	0/4	0.0

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008722

Reviewed by: William Dykstra, Ph.D. William Dykstra 8/13/91
Review Section I, Toxicology Branch I (H7509C)
Secondary Reviewer: Roger Gardner, Section Head
Review Section I, Toxicology Branch I (H7509C)

9-25-91
(for RG)

DATA EVALUATION REPORT

Study Type: 85-1; Metabolism - Rat TOX Chem No. 325
MRID No.: 417964-02
417964-00

Accession Number: N/A

Test Material: C^{14} Propanil (99% radiochemical purity)

Synonyms: STAM

Study Number: 88072

Sponsor: Propanil task Force
Liberty, MO

Testing Facility: XenoBiotic Labs, Inc.
Princeton, NJ

Title of Report: Metabolism of C^{14} Propanil in Rats

Author: Dr. Wu, Ph.D.

Report Issued: January 31, 1991

Conclusion: The mean radioactivity balance was between 90.26-98.70%. Most of the radioactivity was isolated in the urine (78.44-90.04%) and much less in feces (1.72-12.91%).

By intravenous route, there was a sex difference, with females excreting 10.58% in feces and males only 1.72%.

Thirteen major metabolites, mostly in urine, were identified.

There were sex differences in metabolites with M12 being present as 5.9-7.71% in males and only 0-3.11% in females. M12 was a fecal metabolite.

Classification: ~~Core Guideline~~ ACCEPTABLE

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

Review: Metabolism of C^{14} Propanil in Rats (XenoBiotic Labs, Inc., Study No. 88072, Jan. 31 1991).

Note: GLP Compliance Statement was signed by Diana Wu (Study Director, 5/31/91) and Quality Assurance Statement was signed by Jo Anne L. Reynolds (5/31/90) for material balance study (Volume 1) and by Diana Wu (1/31/91) and JoAnne L. Reynolds (1/31/91) for metabolite identification study (Volume 2).

Test Material: C^{14} propanil (specific activity of 19.39 u Ci/g, (radiochemical purity of 99.09%) and nonradiolabeled propanil (technical grade, lot # C048204E, received from Cedar Chemical Co.) were used in the study.

Animals: Male and female CRL:CD(SD) BR rats (6-10 weeks old, weighing 150-220 g) were obtained from Charles River Breeding Laboratories, Kingston, NY. After acclimation, rats were placed in individual metabolism cages and powdered Certified Rodent Chow #5002 (Ralston Purina Company) was provided. Rats were fasted from approximately 18 hours before to 6 hours after dosing. At other times, food was available ad libitum. Water was available ad libitum throughout the study.

Experimental Design:

1. Dosing Groups

Rats were divided into five groups. Each group was administered with either the test compound or the vehicle alone according to the following assignments:

Control Group: two rats/sex, dosed orally with dosing vehicle (1% aqueous carboxymethyl cellulose, (CMC) only.

Group A: single oral low dose (SOLD), five rats/sex were given a single dose of ~2.5 mg/kg ^{14}C-propanil by gavage.

Group B: multiple oral low dose (MOLD), five rats/sex were dosed orally with nonradiolabled propanil at 2.5 mg/kg daily for 14 days. On day 15, each rat was given a single dose of ~2.5 mg/kg ^{14}C-propanil by gavage.

Group C: single oral high dose (SOHD), five male and six female rats were given a single dose of ~300 mg/kg ^{14}C-propanil by gavage.

Group D: Intravenous (IV) dose, six male and five female rats were dosed with ~0.7 mg/kg of ^{14}C-propanil in normal saline (0.9% saline) by IV injection. This dose was determined by solubility in saline.

2. Sample Collection

Urine and feces samples were collected at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-36 hours, 36-48 hours, and daily thereafter for 7 days. Urine was collected into containers surrounded by X-cold blocks. Cages were rinsed with water at 24- and 48-hour sample collections. At study termination, cages were thoroughly rinsed with methanol/water MeOH/H_2O (50/50). Urine and cage rinses were assayed immediately by liquid scintillation counting (LSC). Feces were stored in the freezer until analyzed.

At study termination, rats were anesthetized and exsanguinated by cardiac puncture. Blood (~5 ml) was collected into heparinized syringe and stored in refrigerator until analyzed for total radioactivity. The following tissues wee then excised from the animal and stored in the freezer until analyzed: bone, brain, fat, heart, liver, kidneys, lung, muscle, pancreas, reproductive organs,skin, and spleen. The residual carcasses were also stored in the freezer until analyzed.

All frozen samples were analyzed within 3 months, except tissue and carcass samples of repeat Group A females which were analyzed after 6 months.

In order to isolate and identify the metabolites, the urine and feces samples were pooled and combined according to the dosing level and sex.

Metabolites in urine and feces were isolated purified, and identified by procedures including solvent partition, solid phase extraction, high performance liquid chromatography (HPLC), thin-layer chromatography (TLC), gas chromatography/mass spectrometry (GC/MS), fast atom bombardment/mass spectrometry (FAB/MS), thermospray/liquid chromatography/mass spectrometry (TSP/LC/MS), desorption chemical ionization/mass spectrometry (DCI/MS), and direct insertion probe/mass spectrometry (DIP/MS).

Reference metabolites used as standards were obtained from Aldrich Chemical Company, Inc., Sigma® Chemical Company, Rohm and Haas Company, Ecochem Research, Inc., the National Center for Toxicological Research (NCTR), and from University of Tennessee (UT). Co-chromatography was used for positive confirmation of respective metabolites.

Results

A. Radioactivity Balance

Total Percent ^{14}C Recovery
Group A (Single Oral Low Dose, 2.5 mg/kg)

Animal No.	Sex	Urine*	Feces	Tissues	Carcass	Total
161	M	81.66	6.81	0.12	0.20	88.79
163	M	88.20	11.43	0.08	0.13	99.84
164	M	84.74	8.31	0.10	0.20	93.35
165	M	93.02	5.73	0.09	0.22	99.06
166	M	87.80	11.78	0.09	0.14	99.81
Mean		87.08	8.81	0.10	0.18	96.17
SD		4.24	2.71	0.02	0.04	4.94
209**	F	70.39	11.59	0.11	0.34	82.43
210**	F	82.89	11.04	0.15	0.21	94.29
211**	F	80.85	12.72	0.09	0.14	93.80
213**	F	84.97	9.63	0.20	0.34	95.14
214**	F	73.08	12.11	0.12	0.33	85.64
Mean		78.44	11.42	0.13	0.27	90.26
SD		6.36	1.18	0.04	0.09	5.81

* Urine is the sum of urine and cage rinse.

** Group A females were repeated due to the low recovery in the original female group (Nos. 168, 170, 171. 173, and 174).

Total Percent ^{14}C Recovery
Group B (Multiple Oral Low Dose, 2.5 mg/kg)

Animal No.	Sex	Urine*	Feces	Tissues	Carcass	Total
142	M	81.79	11.63	0.14	0.40	93.96
144	M	83.37	6.37	0.09	0.14	89.97
145	M	85.03	19.00	0.09	0.19	104.31
146	M	79.17	11.63	0.09	0.29	91.18
147	M	80.15	11.96	0.09	0.32	92.52
Mean		81.90	12.12	0.10	0.27	94.39
SD		2.37	4.50	0.02	0.20	5.74
152	F	78.72	11.62	0.13	0.52	90.99
154	F	83.37	10.04	0.11	0.31	93.83
155	F	85.00	10.06	0.11	0.14	95.31
156	F	81.19	9.94	0.26	0.57	91.96
157	F	82.74	11.26	0.15	0.26	94.41
Mean		82.20	10.58	0.15	0.36	93.30
SD		2.38	0.79	0.06	0.18	1.78

* Urine is the sum of urine and cage rinse.

Total Percent ^{14}C Recovery
Group C. (Single Oral High Dose, 300 mg/kg)

Animal No.	Sex	Urine*	Feces	Tissues	Carcass	Total
184	M	83.54	11.95	0.09	0.46	96.04
185	M	83.51	11.99	0.09	0.15	95.74
187	M	82.86	15.57	0.08	0.13	98.64
188	M	89.96	12.02	0.10	0.43	102.51
189	M	87.04	13.04	0.9	0.41	100.58
Mean		85.38	12.91	0.09	0.32	98.70
SD		3.04	1.55	0.01	0.16	2.91
198	F	79.87	11.70	-	-	91.47
199	F	91.32	9.94	0.15	0.34	101.75
203	F	88.43	7.85	0.13	0.36	96.77
205	F	85.41	14.80	0.07	0.50	100.78
207	F	81.40	11.56	0.10	0.74	93.80
208	F	81.13	16.03	0.09	0.95	98.20
Mean		84.59	11.96	0.11	0.58	97.13
SD		4.59	3.03	0.03	0.26	3.98

* Urine is the sum of urine and cage rinse.

Tissue and carcass of rat No. 198 wre not analyzed for ^{14}C content.

Total Percent ^{14}C Recovery
Group D (IV Dose, 0.7 mg/kg)

Animal No.	Sex	Urine*	Feces	Tissues	Carcass	Total
176	M	89.77	2.40	0.06	0.16	92.29
177	M	89.54	1.84	0.08	0.69	92.15
179	M	91.14	1.47	0.07	0.31	92.99
180	M	91.05	1.48	0.06	0.05	91.64
182	M	90.13	1.256	0.06	0.01	91.46
183	M	88.60	1.84	0.12	0.52	91.08
Mean		90.04	1.72	0.08	0.29	92.10
SD		0.06	0.41	0.02	0.27	0.72
191	F	88.17	10.05	0.18	0.37	98.77
192	F	84.51	10.60	0.14	2.09	97.34
193	F	82.87	12.14	0.17	0.50	95.68
194	F	88.50	10.07	0.10	0.20	98.87
195	F	84.26	10.02	0.17	0.40	94.85
Mean		85.66	10.58	0.15	0.71	97.10
SD		2.52	0.91	0.03	0.78	1.81

* Urine is the sum of urine and cage rinse.

The mean radioactivity material balance recovery ranged from 90.26% (females, group A) to 98.70% (males, group C) of the total dose administered. Most of the radioactivity was excreted from the urine and ranged from 78.44% to 90.04% of the total dose. A lesser amount was excreted in the feces and ranged from 1.72% to 12.91% of the total dose.

Most of the radioactivity was eliminated within 24 hours in Groups A, B, and D, whereas Group C took 48 hours to eliminate 90% of the radioactivity.

By the intravenous route, Group D, females excreted 10.58% in feces while males excreted 1.72% in feces of the total dose. Therefore, there appears to be a route and sex difference in excretion.

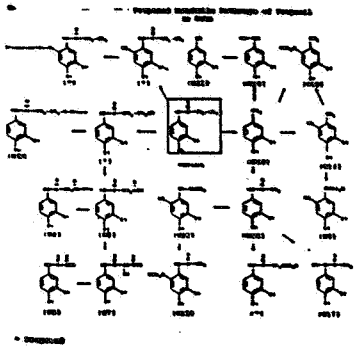
Total radioactivity remaining in the carcass ranged 0.18% to 0.71% of the total dose. The residue levels ranged in tissues from 0 to 0.092 ppm, with the liver having the highest residue for Groups A, B, and D. As expected, group D, which received a much higher dose, had higher tissue levels.

B. Metabolite Identification

The majority of metabolites were eliminated in the urine (74.65-87.34%) and feces (1.40-10.25%) within the first 24 hours post dosing, except for Group C, which continued to produce metabolites to the second and third day.

Metabolites were isolated either in the free polar or non-polar form or conjugated as sulfates and glucuronates. A total of 13 products, including parent, were identified.

As presented in the text of the report, the metabolite pathway is proposed.



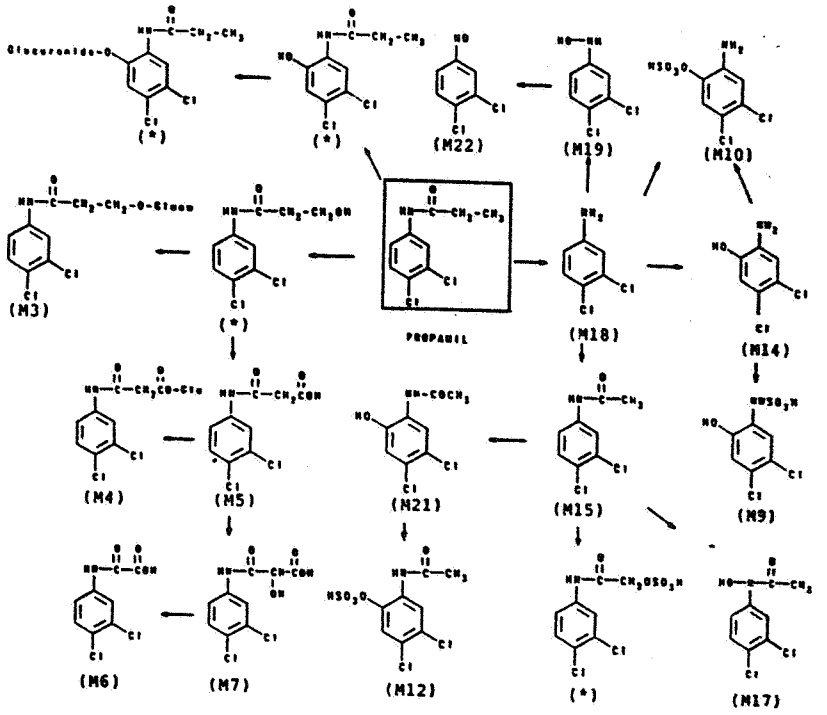
The quantitative rage of metabolites excreted at all dose levels included the following major metabolites: M5/M6/M7 (16.95-44.41% in males and 16.88-43.75% in females), M10 (7.61-25.42% in males and 10.51-20.85% in females), M4 (0.17-14.36% in males and 1.33-11.36% in females), M9 (1.91-4.64% in males and 1.89-4.94% in females, M3 (328-5.04% in males and .17-3.85% in females, and M25 (.28-5.35% in males and 3.12-8.27% in females).

Metabolite M12, a fecal metabolite, was detected in higher percentages in the male rats (5.9-7.71%), but appeared to be a minor product in the female rats (0-3.11%).

The majority of the metabolites were found in the urine, which was the major route of excretion.

The metabolites found in the feces were all minor (<-1%), except M12 and M13 from the male rat feces, which amounted to 4.14% and 1.91%, respectively.

Proposed Metabolic Pathways of Propanil in Rats



* Proposed

META-RAT.WD/LCA