9-26-91

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

008712

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Propetamphos - 52-Week Chronic Dog Study With Technical - Reregistration Submission

Caswell No.: 706A
Project No.: 1-1961
MRID Nos.: 418414-01
418414-02
ID No.: 113601
Submission No.: S400230

FROM: William Dykstra, Ph.D. William Dykstra 9/9/91
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THRU: Roger Gardner, Section Head
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

9-26-91 (for RG)

Requested Action

Review 1-year chronic dietary study in dogs with technical propetamphos.

1 of 15

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Conclusion and Recommendation

The study is acceptable as core-minimum data. The DER for the study is attached. The NOEL is the low dose of 4.0 ppm.

Attachment

Reviewed By: William Dykstra, Ph.D. William Dykstra 9/9/91
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Roger Gardner, Section Head
Section I, Toxicology Branch I - IRS (H7509C) 9/26/91
(for RG)

DATA EVALUATION REPORT

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Study Type: 83-1; Chronic Toxicity - Nonrodent, Dog

TOX Chem No.: 706A

Accession No.: N/A

MRID Nos.: 418414-01, 418414-02

Test Material: SAN 52.139 I Technical; 90.8% purity

Synonyms: Propetamphos, Safrotin

Study No.: 226912

Sponsor: Sandoz AG, Switzerland

Testing Facility: RCC Research and Consulting Company AG/Switzerland

Title of Report: 52-Week Oral Toxicity Study With San 52.139 I Technical Grade in the Dog

Author: T.R. Allen

Report Issued: February 25, 1991

Conclusions

The NOEL is 4.0 ppm. The LEL is 20 ppm (mid-dose) and the effects are plasma and RBC cholinesterase depression in males and females and increased absolute and relative (to brain) liver weight in males. Additional findings were observed at 100 ppm (HDT). These additional findings were inhibition of brain cholinesterase in males, decreased food consumption in high-dose males and females, death of high-dose male dog #14 on day 227 (week 33) in extremis, decreased body weight gain in high-dose males, mild to moderate anemia in high-dose males and females, hepatotoxic effects in high-dose males and females seen as increased levels of SGOT, SGPT, glutamate dehydrogenase, alkaline phosphatase, gamma-glutamyl transaminase and ornithine-carbamyl

transferase, concentrated urine in high-dose male dog #14, thickened mucosa in 4/4 males and 3/4 females at the high-dose, and minimal to moderate hepatocellular necrosis in 2/4 high-dose male dogs.

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Classification: Core-minimum

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

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A. Materials:

1. Test Compound - Can 52.139 I tech.; Description: Clear, yellow liquid; Batch No.: 6329; Purity: 90.8 percent; Contaminants: List in CBI appendix.

2. Test Animals - Species: Dog; Strain: Beagle, purebred; Age: 7 to 9 months; Weight: Males - 7.6 to 10.5 kg, Females - 7.1 to 10.2 kg; Source: KFM Kleintier Farm, Switzerland.

B. Study Design:

1. Animal Assignment - Animals were assigned randomly to the following test groups:

Test* Group	Dose in Diet (ppm)	Main Study 12 Months Male	Female
1 Control	0	4	4
2 Low (LDT)	4	4	4
3 Mid (MDT)	20	4	4
4 High (HDT)	100	4	4

*Dose levels were correctly chosen on the basis of an 8-week Range-Finding Study in Dogs (MRID No. 418414-01)

2. Diet Preparation - Diet was prepared every 2 weeks and stored at room temperature. Samples of treated food were analyzed for stability and concentration every 3 months.

Results - The test material was stable in the dog diet at room temperature for at least 21 days. Mean concentrations were found in the range of 88.6 percent to 103.6 percent of nominal concentration.

Homogeneity ranged from -6 percent to +6 percent of the mean concentration.

3. Animals received food (Kliba 335 Diet) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: For body weights, organ weights, and clinical pathology data, one-way analysis of variance, followed by t-test, or Dunnett's test, or Steel's test at $p < 0.05$ level of significance.

5. Quality assurance was performed and the statement was dated and signed by K. Schneider on February 26, 1991.

C. Methods and Results:

1. Observations - Animals were inspected twice daily for signs of toxicity and mortality.

Results

Mortality (survival) - One high-dose male dog (Dog #14) was found collapsed on day 227 (week 33). The dog was killed in extremis. Prior to collapse, dog #14 had reduced food consumption, decreased body weight, and dark, liquid feces. Other toxic signs in high-dose dogs (both sexes) were diarrhea and vomiting, and only 2/4 high-dose females showed estrus changes compared with all females from all other treated groups. Dogs in the 4 and 20 ppm groups did not have toxic signs.

2. Body Weight - They were weighed pretest for 1 week, then weekly for 52 weeks.

Results - There were no compound-related effects in body weight gain in the 4 and 20 ppm male and female dogs in comparison to controls. In the high-dose males, dog #14 showed decreased weight gain during most of the study after week 8 until its death in week 33. High-dose female dogs were comparable to controls.

3. Food Consumption and Compound Intake - Consumption was determined and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Results - Food Consumption -

Food efficiency -

Compound intake -

Food consumption was decreased up to 17 percent in high-dose males and up to 33 percent in high-dose females during the first 3 months of the study. During weeks 20 to 27, all treated females consumed up to 15 percent less food than controls, but the differences were not dose-related and are not considered compound-related. Food consumption of dogs at 4 and 20 ppm were comparable to controls.

Compound intake averaged 0.13, 0.59, and 3.03 mg/kg/day in males and 0.14, 0.67, and 3.39 mg/kg/day in females.

4. Ophthalmological examinations were performed at pretest, 13, 26, and 51 weeks on all animals.

Results - There were no compound-related ophthalmic findings at any examination in treated dogs in comparison to controls.

5. Blood was collected before treatment and at 4, 13, 26, and 51 weeks for hematology and clinical analysis from all animals. The CHECKED (X) parameters were examined.

a. Hematology

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

*Recommended by Subdivision F (Oct. 1982) guidelines for chronic studies.

Results - There were no compound-related effects at 4 and 20 ppm in both sexes.

In high-dose dogs, the following results were found:

4 weeks

Males: no significant effects

Females: no significant effects

13 weeks

Males: statistically significantly lower RBC, hematocrit, and increased MCV. Increased reticulocytes (differences up to 15%).

Conclusion: slight anemia is beginning.

Females: no statistically significant changes, but RBC, hemoglobin, and hematocrit were decreased in comparison to controls. Increased reticulocytes in comparison to controls.

Conclusion: less anemia than males.

26 weeks

Males: statistically significantly decreased RBC, hemoglobin, hematocrit; increased reticulocytes (significant anemia).

Females: similar lowered values; reticulocytes were statistically significantly increased (anemic response).

51 weeks

Males: Highly statistically significantly increased reticulocytes and increased platelets (compensatory response to anemia).

Females: Normal values for all parameters.

b. Clinical Chemistry

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

*Recommended by Subdivision F (Oct. 1982) guidelines for chronic studies.

Results - There were no compound-related effects at 4 and 20 ppm in both sexes.

In high-dose dogs, the following hepatotoxic results were found in both sexes.

Values above the highest control value at the same time point are underlined. (No comparative data are available for male #14 in the week of its death, week 33.)

As can be seen from the data, the hepatotoxic effects of high-dose females disappeared by week 51.

(High-Dose Males)

	ASAT ukat/l	ALAT ukat/l	GLDH nkat/l	ALP ukat/l	G-GT nkat/l	OCT nkat/l
M14						
Pre	0.36	0.35	72.7	5.26	29.60	39.84
w 4	0.36	0.39	105.3	5.39	14.26	82.18
w 13	0.63	2.95	1401.8	6.56	140.38	562.11
w 26	0.31	0.62	250.4	1.99	24.44	129.86
w 33	1.52	1.26	439.4	4.14	52.58	60.01
w 51	----------	----------	dead	----------	----------	----------
M15						
Pre	0.53	0.24	58.5	3.70	30.25	54.68
w 4	0.46	0.38	65.6	3.56	25.48	51.68
w 13	0.56	0.46	60.7	2.27	35.85	45.18
w 26	1.24	5.38	2258.4	6.78	120.21	1410.62
w 51	0.53	0.83	115.4	3.04	36.78	66.18

(High-Dose Females)

	ASAT ukat/l	ALAT ukat/l	GLDH nkat/l	ALP ukat/l	G-GT nkat/l	OCT nkat/l
F29						
Pre	0.55	0.51	77.2	4.67	27.18	48.01
w 4	0.53	3.22	135.5	10.96	180.80	49.34
w 13	0.70	0.72	131.3	3.32	32.96	81.52
w 26	0.55	0.40	63.0	4.86	22.23	30.51
w 51	0.63	0.54	47.8	4.01	43.82	38.51
F30						
Pre	0.60	0.44	81.4	5.33	39.66	39.84
w 4	0.51	0.67	93.4	5.64	40.79	49.34
w 13	0.57	0.57	147.4	4.69	51.51	59.85
w 26	0.44	0.76	193.7	3.39	73.52	89.68
w 51	0.54	0.70	125.4	4.76	76.0	60.01
F31						
Pre	0.47	0.47	50.8	4.57	28.63	54.68
w 4	0.51	0.46	42.9	2.31	32.94	61.01
w 13	0.65	0.53	76.1	1.82	31.52	45.18
w 26	0.62	1.07	185.7	2.41	54.40	88.18
w 51	0.49	0.46	61.3	4.97	57.88	35.51

* ASAT = SGOT
ALAT = SGPT
GLDH = glutamate dehydrogenase
ALP = alkaline phosphatase
G-GT = gamma-glutamyl transaminase
OCT = ornithine-carbamyl transferase

Unexpected high values compared with the normal range for some of these enzymes were seen in two control females in week 51:

	ALAT	GLDH	ALP	G-GT	OCT
F17	1.00			76.85	151.03
F18	6.02	739.2	15.82	433.48	154.03

No unusually high values were seen in the control males. Occasionally, a high value was seen in some dogs at 4 and 20 ppm, but no consistent treatment-related pattern was evident.

Additionally, hepatotoxicity was seen in high-dose males #14, #15, and #16 as statistically significantly decreased total protein in weeks 4, 13, and 26 and decreased albumin in weeks 4 and 13.

Cholinesterase Inhibition

Statistically significant decreases in plasma and RBC but not brain cholinesterase occurred in high-dose females. In males, plasma and RBC cholinesterase were significantly inhibited at the mid- and high dose, and brain cholinesterase was inhibited significantly at the high dose. Additionally, mid-dose values of both sexes of plasma and RBC cholinesterase were decreased (not significantly) greater than 20% of control values.

Mean values are shown below.

Males

Cholinesterase Activity

		BuCHE-PL umol-SH/ml	(% dec.)	ACHE-ERY umol-SH/ml	(% dec.)	ACHE-BRAIN umol-SH/g	(% dec.)
Pretest							
1	(0 PPM)	6.33		2.24		--	
2	(4 PPM)	6.01		2.33		--	
3	(20 PPM)	5.52	13	1.92	14	--	
4	(100 PPM)	6.22		1.95		--	
4 Weeks							
1	(0 PPM)	6.01		2.05		--	
2	(4 PPM)	5.47	9	2.12		--	
3	(20 PPM)	3.70**	38	1.30	37	--	
4	(100 PPM)	2.73**	55	0.38**	81	--	
13 Weeks							
1	(0 PPM)	6.49		2.39		--	
2	(4 PPM)	6.11	6	2.44		--	
3	(20 PPM)	4.13**	36	1.26*	47	--	
4	(100 PPM)	2.73**	58	0.51**	79	--	
26 Weeks							
1	(0 PPM)	6.22		2.03		--	
2	(4 PPM)	5.58	10	1.99	2	--	
3	(20 PPM)	3.97**	36	1.11*	45	--	
4	(100 PPM)	2.31**	63	0.40**	60	--	
51 Weeks							
1	(0 PPM)	6.48		2.20		4.42	
2	(4 PPM)	5.83	10	2.12	4	4.55	
3	(20 PPM)	3.93**	39	1.20	45	4.60	
4	(100 PPM)	2.46**	62	0.45**	78	3.49*	21

*/**: Dunnett-test based on pooled variance significant at 5 percent or 1 percent level

Females
Cholinesterase Activity

	BuCHE-PL umol-SH/ml	(% dec.)	ACHE-ERY umol-SH/ml	(% dec.)	ACHE-BRAIN umol-SH/g	(% dec.)
Pretest						
1 (0 PPM)	5.26		2.48		--	
2 (4 PPM)	5.74		2.14	14	--	
3 (20 PPM)	5.90		2.95		--	
4 (100 PPM)	6.81		2.91		--	
4 Weeks						
1 (0 PPM)	4.83		2.48		--	
2 (4 PPM)	5.26		2.12	15	--	
3 (20 PPM)	4.08	15	1.82	27	--	
4 (100 PPM)	3.70	23	0.51**	79	--	
13 Weeks						
1 (0 PPM)	6.01		2.65		--	
2 (4 PPM)	5.85		2.35	11	--	
3 (20 PPM)	4.77	21	1.73	35	--	
4 (100 PPM)	3.11**	48	0.60**	77	--	
26 Weeks						
1 (0 PPM)	5.85		2.33		--	
2 (4 PPM)	6.76		2.01	14	--	
3 (20 PPM)	5.04	14	1.70	28	--	
4 (100 PPM)	3.22*	45	0.61**	74	--	
51 Weeks						
1 (0 PPM)	6.47		2.45		4.31	
2 (4 PPM)	8.04		2.12	13	4.98	
3 (20 PPM)	5.79	11	1.74	29	5.06	
4 (100 PPM)	3.31	49	0.59**	76	3.53	18

*/**: Dunnett-test based on pooled variance significant at 5 percent or 1 percent level

6. Urinalysis - Urine was collected from fasted animals at 4, 13, 26, and 51 weeks. The CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen

*Recommended by Subdivision F (Oct. 1982) guidelines for chronic studies.

Results - High-dose male dog #14 had concentrated urine prior to death at week 33.

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

*Recommended by Subdivision F (Oct. 1982) guidelines for chronic studies.

Results

a. Organ Weight - Absolute liver weights and liver/brain weight ratios were increased in mid- and high-dose male dogs to a statistically significant degree in comparison to controls.

Males		Males	
Dose (ppm)	Liver (grams)	Dose (ppm)	Liver/Brain(%)
0	277.1	0	339.3
4	293.2	4	342.3
20	342.9*	20	425.2*
100	389.9**	100	494.6**

* $p < 0.05$
** $p < 0.01$

Other organ weights in treated dogs were comparable to controls.

b. Gross Pathology - Thickened mucosa (duodenum and/or jejunum) of the intestine was observed at the high dose in 4/4 males (including dog which died) and 3/4 females. However, no histopathological lesions were present in these grossly observed findings.

Additionally, male #14 had liquid, black-brown contents in the intestine, enlarged lymph nodes, and small irregular surfaced liver and dry sternum bone (cut surface).

c. Microscopic Pathology

1) Nonneoplastic

Males 100 ppm

Dog #14 - large gastric ulcer, atrophy of fatty tissue, histiocytosis of lymph nodes, thymic and bone marrow atrophy, moderate hepatocellular necrosis

Dog #15 - minimal focal hepatocellular necrosis

There were no compound-related microscopic lesions in organs of dogs treated at 4 and 20 ppm.

Females

No compound-related effects at any dose level

2) Neoplastic

No tumors were observed in any control or treated dogs.