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WASHINGTON, D.C. 20460

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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Executive Summaries for Subchronic Dog Toxicity Study, Chronic/Carcinogenicity Study in Rats, Developmental Rat and Rabbit Toxicity Studies, and Reproductive Toxicity Study in Rats with Propazine.

DP Barcode: D240230 Submission: N/A
PC Code: 080808 Tox Chem No: 184

TO: Catherine Eiden
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FROM: Kit Farwell
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Kit Farwell 10-31-97

THRU: Whang Phang, Senior Scientist
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Whang Phang 10/31/97

Attached are newly-written executive summaries for propazine toxicity studies. These executive summaries were written in preparation for the Hazard ID meeting for propazine on 7/31/97 because the reviews did not include executive summaries and supporting tables.

1. Subchronic Dog Study (1967, MRID 00111680). This study was found unacceptable by the Toxicology Science Advisory Committee because of an insufficient number of animals and lack of toxicity. Registration Division has been notified that a new chronic dog study is required. A new executive summary was written for the Hazard ID meeting (7/31/97) and is attached.

2. Chronic/Carcinogenicity Study in Rats (1981, MRID 00041408). The DER for this study was rewritten for the 1996 Cancer Peer Review Committee. A new executive summary was written for the Hazard ID meeting (7/31/97) and is attached.

3. Developmental Toxicity in Rats (1985, MRID 00150242) and Rangefinding Developmental Toxicity in Rats (1985, MRID 00150241). A new executive summary was written for the Hazard ID meeting (7/31/97) and is attached.

4. Developmental Toxicity in Rabbits (1995, MRID 44153401). A new executive summary was written for the Hazard ID meeting (7/31/97) and is attached.

5. Three-generation Reproduction Study in Rats (1979, MRID 00041409). A new executive summary was written for the Hazard ID meeting (7/31/97) and is attached.

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SUPPLEMENT TO DATA EVALUATION RECORD
Original DER in HED Document # 001376

STUDY TYPE: 82-1(b) Subchronic Dog Feeding Study

DP BARCODE: D240230 SUBMISSION CODE: none
P.C. CODE: 080808 TOX. CHEM. NO.: 184

TEST MATERIAL: Propazine 80W Formulation (83.1% a.i.)
(80% wettable paste, 20% inert)

CITATION: FX Wazeter, et al (1967), Ninety Day Feeding Study in the Beagle Dog. International Research and Development Corporation. Report # 248-002. 11/17/67. MRID 00111680. Unpublished.

SPONSOR: Geigy Agricultural Chemicals

EXECUTIVE SUMMARY: In a subchronic toxicity study (MRID 00111680), Propazine 80W formulation (83.1% a.i.) was administered to 3 Beagle dogs/sex/dose in diet at dose levels of 0, 50, 200, or 1000 ppm (0, 1.25, 5.0, or 25 mg/kg/day) for 90 days. No changes in clinical signs, clinical pathology, or gross or microscopic pathology were attributed to treatment.

Assessment of body weight was difficult because treatment groups had different mean body weights at the start of the study and because there were only 3 animals per sex per dose-group. At termination, male and female high-dose groups had slight weight loss (-4% in both sexes), while controls had slight weight gains (+7% for males and +9% for females) in comparison to pre-test values. This slight effect upon mean body weight was due to weight loss in only 1 male and 1 female from the high-dose group.

This study is classified **UNACCEPTABLE**, **NOT** upgradeable, due to lack of toxicity and insufficient number of test animals. This study does **NOT** satisfy the guideline requirement for an 82-1(b) subchronic oral study in the dog. Requirements for subchronic and chronic dog studies had previously been waived because of this subchronic study with the formulation.

Other deficiencies included no description of dose-selection rationale, use of a formulation rather than technical form, mean group values for test results were not reported, no statistical analysis was performed, analysis of test material purity and stability was not reported, and no ophthalmoscopic exam was performed. Clinical pathology tests not performed included lactate dehydrogenase, cholesterol, creatinine, total protein, albumin, inorganic phosphorous, calcium, sodium, and urinary ketone bodies. No GLP or Quality Assurance statements were provided.

SELECTED MEAN GROUP BODY WEIGHTS (kg)

DOSE GROUP (ppm)	MALES WEEK					FEMALES WEEK				
	0	1	5	9	13	0	1	5	9	13
0	10.0	10.1	10.3	10.4	10.7	8.5	8.5	9.0	9.3	9.3
% pre-test	100%	101%	103%	104%	107%	100%	100%	106%	109%	109%
50	7.9	8.4	8.5	8.6	8.7	7.9	8.0	8.7	8.8	8.9
200	8.6	8.6	8.5	8.8	8.5	6.2	6.5	6.9	7.2	7.2
1000	9.0	8.7	8.7	8.6	8.6	7.1	6.7	6.7	6.9	6.8
% pre-test	100%	97%	97%	96%	96%	100%	94%	94%	97%	96%
% Control	90%	86%	84%	83%	80%	84%	79%	74%	74%	73%

Calculated by reviewer from Table 1 of study report (MRID 0011680), Individual Weekly Body Weights, kg.

SUPPLEMENT TO DATA EVALUATION RECORD 012391

STUDY TYPE: 83-5 Combined Chronic Toxicity/Carcinogenicity Study

DP BARCODE: D240230
P.C. CODE: 080808

SUBMISSION CODE: none
TOX. CHEM. NO.: 184

TEST MATERIAL: Propazine Technical (% a.i. not specified)

CITATION: DC Jessup (1981), Two Year Oral Chronic Toxicity Study in Rats. International Research and Development Corp. Report IRDC 382-007. 4/18/91. MRID 00041408. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 00041408), propazine (% purity not specified) was administered to 60 sex/dose Sprague-Dawley rats in diet at dose levels of 0, 3, 100, or 1000 ppm (0, 0.1, 5.2, or 51 mg/kg/day males; 0, 0.2, 6.4, or 68 mg/kg/day females) for 2 years. An additional 10/sex were added to control and high-dose groups for interim sacrifice at 12 months (5/sex) and after a 4 week recovery period (5/sex).

No consistent changes in hematology, clinical chemistry, or urinalysis were seen. Clinical observations showed a significant increase in palpable masses in high-dose females (presumably in the breast area). At termination, mean body weight for the high-dose group was decreased in comparison to controls (-13.1% males and -11.4% females). Body weights for low- and mid-dose groups of both sexes were decreased approximately 4-6% in comparison to controls. Food consumption was comparable between groups.

The NOEL for systemic toxicity is 100 ppm (5.2 mg/kg/day males and 6.4 mg/kg/day females) and the LOEL is 1000 ppm (51 mg/kg/day males and 68 mg/kg/day females) based upon decreased body weight.

Mammary gland tumors (adenocarcinomas and adenomas) were increased in low- and high-dose female groups (3 and 1000 ppm) when compared to controls and were considered compound related. Other tumor types were comparable between control and treatment groups of both sexes.

Dosing was considered adequate based upon body weight decrements in excess of 10% in male and female high-dose groups. This carcinogenicity study in the rat is **Acceptable/Guideline** and **does satisfy** guideline requirements for an 83-1(a) chronic toxicity and an 83-2(a) carcinogenicity study.

SUPPLEMENT TO DATA EVALUATION RECORD
Original DER in HED Document 5226

STUDY TYPE: 83-3(a) Developmental Rat Study

DP BARCODE: D240230
P.C. CODE: 080808

SUBMISSION CODE: none
TOX. CHEM. NO.: 184

TEST MATERIAL: Propazine Technical (99.1%)

CITATION: C. Salamon (1985), Teratology Study in Albino Rats with Propazine Technical. American Biogenics. Study 450-1788. 5/8/85. MRID 00150242 (main study), and MRID 00150241 (pilot study).

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00150242), propazine (99.1%) was administered to 25/dose female Sprague-Dawley rats by gavage at doses of 0, 10, 100, or 500 mg/kg/day from gestation days 6 through 15.

Salivation, described as "clear", was reported in 15 of the pregnant females in the 500 mg/kg/day group; salivation also occurred in 2/7 females in the rangefinding study at the HDT of 1000 mg/kg/day. Maternal body weights were decreased in the 100 mg/kg/day group (-7% compared to controls on day 13 of gestation) and in the 500 mg/kg/day group (-14% on day 13). The decreased body weights were accompanied by decreased food consumption in the 100 mg/kg/day group (-18% on day 6) and the 500 mg/kg/day (-40% on day 6). **The maternal NOEL is 10 mg/kg/day and the maternal LOEL is 100 mg/kg/day based upon decreased body weights and food consumption.**

The litter incidences of corpora lutea, implantation sites, resorptions, and viable and dead fetuses were similar between dose groups. Statistically significant decreases in fetal body weights occurred in the 500 mg/kg/day group (-6% compared to controls for males and females). The 100 mg/kg/day group had increased litter incidence in comparison to controls of incomplete ossification of interparietals. In addition, the 500 mg/kg/day group had increased litter incidence of 14th rib, non-ossified hyoid, and incomplete ossification of frontals/parietals, occipitals/interparietals, hyoid, and sacral vertebra(e). **The developmental NOEL is 10 mg/kg/day and the developmental LOEL is 100 mg/kg/day based on decreased ossification.**

This study is classified ACCEPTABLE/GUIDELINE and satisfies the 83-3(a) guideline requirement for a developmental study in the rat.

RANGEFINDING STUDY: In a rangefinding developmental toxicity study (MRID 00150241), propazine (99.1%) was administered to female Sprague-Dawley rats (7/dose) by gavage at doses of 0, 300, 600, 800, or 1000 mg/kg/day from gestation days 6 through 15. One pregnant female in each of the 600, 800, and 1000 mg/kg/day groups died; cause of death not determined. Significant body weight decrements occurred in each of the treatment groups. Clinical signs (crusty muzzle, listless, staggering, red or yellow staining, vocalizing, salivation) occurred in the 600, 800, and/or 1000 mg/kg/day groups. The number of pregnant animals, and mean number of corpora lutea, implantation sites, and viable fetuses was similar between control and treatment groups. The mean number of early resorptions was increased in the 1000 mg/kg/day group in comparison to controls (control, 1.0; 1000 mg/kg, 3.8). Mean fetal weights were significantly decreased in each treatment group. Skeletal and visceral examinations were not made in this rangefinding study.

Maternal Body Weight (g)

GESTATION DAY	DOSE in mg/kg/day (# of Dams)			
	Control (25)	10.0 (25)	100.0 (25)	500.0 (25)
0	238	242	237	237
6	271	272	269	266
13	298	295	278**	255**
20	382	276	360**	340**
GRAVID UTERINE WT (g)	81.3	79.3	74.0	73.8
NET FINAL WT	300	296	286**	266**

Data extracted from Table 3 of study report (MRID 00150242).
Net Final Wt = BW - gravid uterine wt
**Statistically significant at 99% confidence level.

Maternal Food Consumption (g)

GESTATION DAY	DOSE in mg/kg/day			
	Control	10.0	100.0	500.0
0	19.6	20.7	20.7	20.3
6	16.4	14.9	11.8**	9.9**
13	17.9	16.2	14.7**	12.5**
19	23.2	22.8	24.6	25.3

Data extracted from Table 4 of study report (MRID 00150242).
**Statistically significant at 99% confidence level.

SUPPLEMENT TO DATA EVALUATION RECORD
Original DER in HED Document 012214

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STUDY TYPE: Prenatal Developmental Study - Rabbit
OPPTS 870.3700 (83-3b)

DP BARCODE: D240230
P.C. CODE: 080808

SUBMISSION CODE: none
TOX. CHEM. NO.: 184

TEST MATERIAL: Propazine Technical (98% a.i.)

CITATION: Knapp, J. F. (1995) A developmental toxicity study of propazine technical in rabbits. WIL Research Laboratories, Inc., Ashland, Ohio, 44805. Laboratory Study No. WIL-157005, October 11, 1995. MRID 44153401.

SPONSOR: Griffin Corporation, Valdosta, Georgia 31603

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44153401), propazine technical (98% a.i., Lot #309027C) was administered to 20 New Zealand White rabbits/dose level by gavage in corn oil at dose levels of 0, 2, 10 or 50 mg/kg/day from day 6 through 19 of gestation.

Decreased defecation was observed in the 50 mg/kg/day group. Body weight gain was decreased by 65% in the 50 mg/kg/day group during the treatment period (gestation days 6-19). Food consumption was decreased by 28% in the 50 mg/kg/day group during the treatment period. **The maternal LOEL is 50 mg/kg/day, based on decreased defecation and decreased body weight gain and food consumption during the treatment period. The maternal NOEL is 10 mg/kg/day.**

Live litter size, mean fetal weight, fetal sex ratios, mean number of corpora lutea and implantation sites and postimplantation loss were unaffected by treatment. There were no treatment related effects in developmental parameters. **The developmental LOEL is > 50 mg/kg/day and the developmental NOEL is ≥ 50 mg/kg/day.**

This developmental toxicity study in the rabbit is classified **ACCEPTABLE** and **does satisfy** the guideline requirement for a developmental toxicity study (OPPTS 870.3700; 83-3b) in rabbits.

SUPPLEMENT TO DATA EVALUATION RECORD
Original DER in HED Document # 000575.

STUDY TYPE: 3-Generation Reproduction Study in the Rat. 83-4.

DP BARCODE: D240230 SUBMISSION CODE: none
P.C. CODE: 080808 TOX. CHEM. NO.: 184

TEST MATERIAL: Propazine Technical (% a.i. not reported).

CITATION: DC Jessup, et al (1979), Three Generation Reproduction Study in Rats. International Research and Development Corp. (Mattawan, MI). Report 382-010, 11/8/79. MRID 00041409. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY: In a 3-generation reproductive study (MRID 00041409), technical propazine (% a.i. unspecified) was administered in diet to 10 males and 20 females/group Charles River CD rats at concentrations of 0, 3, 100, or 1000 ppm (0, 0.15, 5, or 50 mg/kg/day). There were 2 litters per generation.

Parental toxicity was manifested as significant body weight decrements for males and females in comparison to controls for the high-dose group of 1000 ppm. Weight decrements at termination were greater for males (-12 to -18%) than for females (-7 to -8%). Statistical significance for body weight decrements in females was reported at termination and also after approximately 10 weeks of treatment in each generation.

Offspring toxicity was manifested as body weight decrements of approximately -10% on gestation day 21 in male and female pups of the F1b, F2a, F2b, F3a, and F3b generations of the 1000 ppm dose group.

Parental organ weights showed inconsistent effects at the high-dose group in comparison to controls with no histological correlates and were not considered treatment related effects.

The parental/offspring NOEL is 100 ppm (5 mg/kg/day) and the parental/offspring LOEL is 1000 ppm (50 mg/kg/day) based on body weight decrements in males and females.

No reproductivity toxicity occurred. Male and female fertility, gestation length, pup viability, and pup survival were similar in all groups.

The reproductive NOEL is ≥ 1000 ppm (50 mg/kg/day) and the reproductive LOEL is > 1000 ppm (50 mg/kg/day).

A QA statement was provided. The following deficiencies were noted. The concentration, stability, homogeneity of test material were not reported, pup weights were not reported on day 14, mating was 1 male to 2 females, and rats were 100 days old rather than 8 weeks old at start of study. **This study is classified Acceptable/Guideline and satisfies the 83-4 Guideline requirement for a multi-generation reproduction study in the rat.**

SELECTED MEAN PARENTAL BODY WEIGHTS (grams)

GROUP	WEEK OF STUDY	DOSE GROUP			
		0 ppm	3 ppm	100 ppm	1000 ppm
F0 Males	0	139	139	139	139
	10	451	450	446	403
	33	605	596	583	535
F0 Females	0	120	120	120	120
	10	251	246	250	228**
	33	329	327	330	304*
F1 Males	33	264	270	259	246
	41	491	468	474	435
	63	637	601	620	561*
F1 Females	33	182	171	186	167
	41	269	258	268	242**
	63	339	320	337	314*
F2 Males	63	205	202	225	194
	72	450	433	451	402
	95	621	603	611	537
F2 Females	63	148	151	169**	133
	72	261	250	270	233**
	95	331	328	337	303*

Prepared by reviewer from Tables 1, 2, 10, 11, 19, and 20 of study report (MRID 00041409).
* $p<0.05$ or ** $p<0.01$ significantly different from control group.

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MEAN PUP BODY WEIGHTS (grams)
ON POSTPARTUM DAY 21

GROUP	DOSE GROUP			
	0 ppm	3 ppm	100 ppm	1000 ppm
F1a Males	50.0	51.3	54.9	48.3
F1a Females	48.2	47.8	51.8	46.0
F1b Males	53.2	52.3	54.7	48.4*
F1b Females	51.3	50.1	50.5	46.5*
F2a Males	45.2	47.1	44.1	40.2*
F2a Females	43.3	44.8	41.8	38.3*
F2b Males	47.4	44.8	47.9	41.4**
F2b Females	44.2	?	41.8	39.6**
F3a Males	43.9	44.1	42.0	38.7*
F3a Females	41.3	42.1	40.6	37.5*
F3b Males	49.5	50.0	50.1	44.9*
F3b Females	47.7	47.5	49.0	43.2*

Prepared by reviewer from Tables 6-9, 15-18, 24-27 in the study report (MRID 00041409).
? = illegible entry on study report.
* $p<0.05$ ** $p<0.01$

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cc: Kit Farwell (RRB1), Catherine Eiden (RCAB), Caswell File
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