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FINAL

DATA EVALUATION REPORT

PROMETRYN

Study Type: Reproductive Toxicity

Prepared for:

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Office of Pesticide Programs
U.S. Environmental Protection Agency
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DATA EVALUATION REPORT

STUDY TYPE: Reproductive toxicity - Rat (83-4)

EPA IDENTIFICATION NUMBERS

TOX CHEM. No.: 097

PC No.: 080805

MRID No.: 414451-01

TEST MATERIAL: 2,4-Bis(isopropylamino)-6-(methylthio)-s-tri-azine

SYNONYMS: Prometryn, Prometryne, Primatol Q. and G-34161

SPONSOR: Agricultural Division, Ciba-Geigy Corporation, Greensboro, NC

STUDY NUMBER: MIN 872222 REPORT NUMBER: 89116

TESTING FACILITY: Pharmaceuticals Division, Ciba-Geigy Corporation, Summit, NJ

TITLE OF REPORT: Prometryn Technical: Two-Generation Reproductive Toxicology Study in Rats

AUTHORS: M.L.A. Giknis and E.T. Yau

REPORT ISSUED: February 9, 1990

CONCLUSIONS: In a two-generation reproduction study, Sprague-Dawley rats were fed prometryn technical in the diet at dosage levels of 0, 10, 750, or 1,500 ppm (during premating for males approximately 0, 0.6, 47.8, and 96.7 mg/kg/day, respectively; for females approximately 0, 0.7, 53.6, and 105.6 mg/kg/day, respectively).

Parental Systemic Toxicity
- NOEL = 10 ppm (for males; 0.6 mg/kg/day; for females, 0.7 mg/kg/day)
- LOEL = 750 ppm (for males, 47.8 mg/kg/day; for females, 53.6 mg/kg/day) based on significantly decreased food consumption, body weight, and body weight gain. Similar effects were observed at the highest dosage level.

Reproductive Toxicity
- NOEL = 10 ppm (0.65 mg/kg/day)
- LOEL = 750 ppm (approximately 50 mg/kg/day) based on significantly decreased pup body weight. A similar effect was observed at the highest dosage level.

CLASSIFICATION: CORE Minimum Data. This study meets the minimum requirements set forth under Guideline Series 83-4 for a two-generation reproductive toxicity study in rats.

A. MATERIALS

Test Compound

Purity:	98.1% (see 104-week oral toxicity/carcinogenicity study in rats #MIN 872225, MRID U19012-01, used same batch #)
Description:	White, off-white powder
Solubility:	Water (33 ppm at 20°) and organic solvents
Batch No.:	FL 870991
Received:	October 30, 1987
Contaminants:	Not reported

Vehicle: Acetone; the test material was dissolved in acetone and premixed with the diet.

Test Animals

Species:	Rat
Strain:	Sprague-Dawley (Crl:CD^{R}BR)
Source:	Charles River Laboratory, Ltd., Kingston, NY
Age:	F_0 males--45 days, study day 0 F_0 females--44 days, study day 0
Weight:	F_0 males--171-256 g, study day 0 F_0 females--141-201 g, study day 0

B. STUDY DESIGN

This study was designed to assess the potential of prometryn technical to cause reproductive toxicity when administered continuously in the diet for two successive generations.

Environmental Conditions: The temperature was maintained at 23°C ± 3° and the humidity was maintained at 50% ± 20%. The light/dark cycle was 14/10 hours. There were approximately 15 air changes per hour.

Mating: After 1 week of acclimatization followed by 11 weeks of dietary treatment, the F_0 females were mated with males from the same group in a ratio of 1:1 until evidence of mating (vaginal plug or presence of sperm in a vaginal smear) was obtained or for a maximum of 3 weeks. The day on which mating was confirmed was designated day 0 of gestation. The F_1 animals were mated in a similar fashion following 14 weeks on the test diet. Sibling matings were avoided.

Group Arrangement: Animals were distributed amongst four groups using computerized random numbers as follows:

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Test Group	Dietary Level (ppm)	Number Assigned per Group F_0 Males	F_0 Females	F_1 Males	F_1 Females
Control	0	30	30	30	30
Low dose	10	30	30	30	30
Mid dose	750	30	30	30	30
High dose	1,500	30	30	30	30

Dosage Selection: A dosage rationale was not provided.

Dosage Administered: The test material was administered continuously in the diet (Purina® Certified Rodent Chow #5002) for two consecutive generations. The purity of the test material was not reported and it was not stated whether the dosages were adjusted for active ingredient. The stability and homogeneity of the test material in the diet were conducted prior to or concurrent with the conduct of the study. Concentration analyses of all dosage levels were conducted during weeks 1, 5, 9, 11, 17, 18, 25, 33, and 41.

Observations: Observations for mortality were conducted twice a day; cage-side observations for moribundity and overt signs of toxicity were conducted once a day. A more detailed clinical examination was performed weekly. Body weight and food consumption were recorded weekly for all males throughout the study; they were recorded weekly during the premating period for all females, on gestational days (GD) 0, 7, 14, and 21 for all sperm-positive females, on lactational days 0, 7, 14, and 21 for F_0 females with litters, and on lactational days 0, 4, 8, 14, and 21 for F_1 females with litters. Terminal body weight was recorded for all animals.

The following data were recorded for each litter.

- Sex and number of stillborn pups on lactational day 0
- Sex, number of live pups, pup body weight, and pup clinical observations on lactational days 0, 4, 7, 14, and 21
- Gross pup abnormalities on lactational day 0

On lactational day 4, pups were randomly culled to four/sex/litter whenever possible; culled pups were sacrificed and subjected to a gross examination. Pups found dead or moribund were necropsied. Following weaning, 30 male and 30 female F_1 pups were randomly selected as F_1 parental animals. F_2 pups were sacrificed and necropsied after weaning on day 21. Five F_2 pups per sex and group were randomly selected for a detailed gross examination.

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Following weaning, parental F_0 and F_1 animals were sacrificed and subjected to a detailed gross pathological examination including a count of the number of implantation sites in the females. The following tissues from all groups were preserved in fixative and those from the control and high-dose groups were examined histologically.

- Gross lesions
- Seminal vesicles
- Prostate
- Uterus
- Ovaries
- Cervix
- Coagulating gland (males)
- Testes
- Epididymides
- Vagina
- Pituitary

Weights of testis and ovary were recorded.

Statistical Analysis: The following analyses were conducted.

- Parental body weights and body weight change, food consumption, and organ weights--ANOVA followed by Bartlett's test for homogeneity of variance and Dunnett's test for multiple comparisons between groups
- Precoital interval--Chi square test
- Fertility indices (mating, conception, and gestation) and sex ratios--Mantels' trend test
- Postimplantation loss, still birth, and neonatal survival parameters--Mantel's trend test or Chi square test
- Pup body weight--Healy analysis
- Gestation length--Log rank trend test

Compliance

- A signed Statement of No Data Confidentiality Claim, dated February 26, 1990, was provided
- A signed Statement of Compliance with EPA and OECD GLPs, dated February 26, 1990, was provided
- A signed Quality Assurance Statement, dated February 9, 1990, was provided

C. RESULTS

Test Material Analysis: The purity of the test material was not reported. However, in this study, the same batch was used as in an oral toxicity study (see comment on page 2) in which the purity was reported to be 98.1%. Concentrations of the test material in the diets ranged from 93% to 108% of target. Homogeneity analyses revealed concentrations from 93% to 106% of target; stability analyses (conducted at 10, 50, and 50,000 ppm) confirmed that the test material in the diet was stable at room temperature for at least 51 days.

Parental Toxicity

Mortality: No compound-related mortalities were observed. In the F_0 generation, there were three incidental deaths. One female in the control group was sacrificed in a moribund condition on day 75; necropsy revealed mammary gland adenocarcinoma. Two females at 750 ppm were found dead on days 99 and 102. For one of these females, the cause of death was not evident; for the other, it was determined to be bilateral infarction of the kidneys.

In the F_1 generation, there were also three incidental deaths. Two females, one at 10 ppm, the other at 750 ppm, were sacrificed on gestation days 25 and 26, respectively, after having been observed in dystocia. One female at 10 ppm was sacrificed on day 143 because of hind limb paralysis, swollen and bloody vagina, and red nasal discharge.

Clinical Observations: No compound-related clinical signs were observed. Incidental observations consisted of chromodacryorrhea, alopecia, sores, swollen nose, masses, head tilt, and lacrimation. These signs were noted in all dosage groups for both sexes and generations.

Body Weight: Compound-related decreased body weight and weight gain were observed at 1,500 and 750 ppm in both generations and sexes. Summaries of body weight gain from selected time intervals are presented in Tables 1, 2, and 3. Detailed results are presented in the text.

In the F_0 generation males during the premating period, body weight (data not shown) decreased significantly at 1,500 ppm by 4%-7% on days 7 and 21-70 and at 750 ppm by 3%-4% on days 0, 7, 21-35, and 56. For males, body weight remained significantly decreased at 1,500 ppm by 6%-8% during mating and postmating and at 750 ppm by 4% and 5% on days 77 and 84, respectively. Among females during premating, body weight significantly decreased at 1,500 ppm by 7% on day 70. During the entire gestation period, female body weight decreased significantly at 1,500 ppm by 7%-8%; during lactation at 1,500 ppm, it decreased significantly by 9% and 6% on days 0 and 14, respectively. Body weight gain among males (Table 1) decreased significantly at 1,500 ppm by 11%-40% on days 0-7, 14-21, 28-35, 49-56, 63-70, 0-70, and 0-termination and by 11% and 18% at 750 ppm on days 14-21 and 63-70, respectively. Body weight gain among females decreased significantly at 1,500 ppm during premating (Table 1) by 40%, 53%, and 18% on days 0-7, 42-49, and 0-70, respectively, and at 10 ppm by 42% on days 63-70 (considered to be incidental). Body weight gain increased significantly at 1,500 ppm during gestation on days 0-20 (Table 2) and during lactation on days 0-7 and 14-21 (Table 3). The body weight and weight gain decreases observed in males at 1,500 and 750 ppm and in females at 1,500 ppm were considered to be effects of the test compound.

In the F_1 generation males, body weight (data not shown) was significantly decreased at 1,500 and 750 ppm by 6%-9% and 13%-16%, respectively, during the premating, mating, and postmating periods with the exception of days 0-21 at 750 ppm. Among females during premating, it significantly decreased at 1,500 ppm by 6%-11% on days 21-98 and at 750 ppm by 7%-8% on days 49-98. At 1,500 ppm, during the entire gestation period female body weight decreased significantly by 7%-9%;

during lactation, it decreased significantly by 11% on day 0. Body weight gain among males (Table 1) decreased significantly by 11%-44% at 1,500 ppm on days 0-21, 28-42, 70-77, 0-98, and from day 0 to termination and by 10%-18% at 750 ppm on days 0-7, 14-21, 28-35, 0-98, and from day 0 to termination. Body weight gain among females decreased significantly at 1,500 ppm during premating by 14%-48% on days 21-35, 42-49, and 0-98 and at 750 ppm by 48% and 14 % on days 42-49 and 0-98, respectively (Table 1). Body weight gain increased significantly at 1,500 ppm on lactation days 0-8, 14-21, and 0-21 and at 750 ppm on lactation days 0-21 (Tables 3). The body weight and weight gain decreases observed in both sexes at 1,500 and 750 ppm, were considered to be effects of the test compound.

Food Consumption: Compound-related decreases in food consumption were observed at 1,500 and/or 750 ppm in both generations and sexes. Summaries of food consumption (g/day) from selected intervals are presented in Tables 4 and 5. Detailed results are presented in the text.

In the F_0 generation males, during the premating period (Table 4) food consumption decreased significantly at 1,500 ppm by 5-13% on days 0-7, 21-28, 35-56, and 63-70 and at 750 ppm by 5% on days 0-7. Among females, food consumption decreased significantly at 1,500 ppm by 7%-14% on days 0-7 and 28-70 during the premating period (Table 4) and on days 0-7 during the gestation period (Table 5). These decreases were considered to be due to treatment.

In the F_1 generation males, during the premating period (Table 4), food consumption consistently decreased significantly at 1,500 and 750 ppm by 5%-16% with the exception of days 0-7 at 750 ppm. Among females, food consumption decreased significantly at 1,500 ppm by 9-16% on days 14-21, 28-77, and 84-98 during the premating period (Table 4) and by 9% on days 0-7 during the gestation period (Table 5). In addition, for females during premating, food consumption decreased significantly at 750 ppm on days 28-63 and 91-98 by 9-13% and at 10 ppm on days 91-98 by 8% (Table 4). The decreases observed at 1,500 ppm in both sexes and at 750 ppm in males were considered to be due to treatment, while those noted at 10 ppm were incidental.

Test Material Intake:

	Dose levels (ppm) 0	10	750	1,500
Dose levels (mg/kg/day)				
F_0 generation,				
Premating Males	0	0.63	47.49	93.13
Females	0	0.70	52.81	101.72
Gestation Females	0	0.61	46.33	93.59
F_1 generation,				
Premating Males	0	0.65	48.18	100.24
Females	0	0.72	54.63	109.04
Gestation Females	0	0.61	46.18	92.62

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Gross and Microscopic Pathology: No compound-related gross or histologic findings were observed for any sex or generation.

In the F_0 generation, no differences were observed between groups in absolute and relative (to body weight) testis and ovary weights.

In the F_1 generation, relative testis weight was significantly increased at 1,500 ppm. However, this was considered to be a secondary effect of the decreased body weight at that dosage level.

Reproductive Toxicity

The effects of dietary administration of the test material on reproductive parameters are summarized in Tables 6 and 7. Compound-related effects were observed in pup body weight in both generations at 1,500 ppm and in F_1 offspring at 750 ppm.

In the F_1 offspring, body weight significantly decreased at 1,500 ppm during the entire lactation period and at 750 ppm on lactation days 14 and 21.

In the F_2 offspring, body weight significantly decreased at 1,500 ppm on lactation days 4, 14, and 21. Mean litter size on day 0 was significantly decreased at 10 ppm and significantly increased at 1,500 and 750 ppm; these differences, however, were considered to be incidental since they were not dosage related or observed across generations.

No compound-related clinical observations or gross findings were noted in pups from any litter or generation.

C. REVIEWERS' DISCUSSION/CONCLUSIONS

Test Material Analyses: The purity of the test compound was not reported in this study but was stated in another study that used the same batch as this study. Therefore, this was not considered to be a reporting deficiency. Concentrations, stability, and homogeneity of the test compound in the diet were within ±10% of target values.

Parental Toxicity: Compound-related toxicity was observed at 1,500 and 750 ppm in both sexes and generations. It was manifested as significantly decreased body weight, body weight gain, and food consumption. The effects were most pronounced in the F_1 generation for all animals during premating at both dosage levels. Sometimes, but not always, there appeared to be an association between decreased food consumption and decreased weight gain. The reviewers recommend that the study authors calculate and analyze food efficiency to clarify this relationship. Body weight may have decreased as a secondary effect owing to a palatability problem with the test diet as opposed to a direct effect of the test compound. Regardless of cause, however, decreased body weight may impact negatively upon fertility and the developing embryo/fetus. Therefore, it is considered to be a compound-related effect. Mortality, clinical observations, and gross and microscopic pathology were not affected by the test compound.

Based on these results, the parental toxicity NOEL and LOEL were 10 and 750 ppm, respectively.

Reproductive Toxicity: Compound-related reproductive toxicity was observed at 1,500 and 750 ppm. It was manifested as significantly decreased body weight in the F_1 offspring at 1,500 and 750 ppm during the entire lactation period and in the F_2 offspring at 1,500 ppm during most of the lactation period. These weight decreases may impact negatively upon other organ systems that are developing postnatally (i.e., neuro-and immune systems). Therefore, they are considered to be reproductive effects even if they occur secondarily owing to the decreased body weight in the dams. Fertility indices, precoital interval, length of gestation, and offspring survival parameters were not affected by the test compound.

Based on these results the NOEL and LOEL for reproductive toxicity were 10 and 750 ppm, respectively.

D. CLASSIFICATION: CORE Minimum Data

Table 1. Mean Body Weight Gain (g ± S.D.) During the Premating Period for Rats Fed Prometryn Technical for Two Successive Generations[a]

Study Days	Dietary Level (ppm) 0	10	750	1,500
Number of animals/group	30	30	30	30
F_0 Males				
0 - 7	53.0 ± 10.0	52.5 ± 10.8	51.3 ± 10.8	41.6 ± 5.6*
14 - 21	45.3 ± [illegible].9	44.2 ± 5.8	40.4 ± 3.5*	38.2 ± 5.6*
28 - 35	33.4 ±	35.1 ± 6.6	32.2 ± 4.3	29.7 ± 4.5*
49 - 56	25.8 ± 6.9	23.2 ± 7.1	22.2 ± 6.3	20.9 ± 5.2*
63 - 70	24.5 ± 7.2	20.6 ± 8.1	20.1 ± 5.0*	14.6 ± 6.4*
0 - 70	326.2 ± 37.2	330.9 ± 35.3	310.8 ± 31.3	288.5 ± 35.0*
F_0 Females				
0 - 7	22.2 ± 8.4	21.3 ± 8.6	17.9 ± 6.7	13.3 ± 7.0*
14 - 21	12.8 ± 5.4	15.7 ± 7.7	15.6 ± 5.6	13.8 ± 4.8
28 - 35	10.0 ± 5.7	12.7 ± 6.1	13.3 ± 6.3	13.3 ± 6.9
49 - 56	9.5 ± 7.3	7.8 ± 7.0	7.7 ± 6.3	7.1 ± 4.3
63 - 70	10.0 ± 6.5	5.8 ± 7.8*	8.4 ± 6.0	8.1 ± 5.5
0 - 70	131.3 ± 32.4	130.2 ± 29.3	128.9 ± 26.6	107.1 ± 17.8*
F_1 Males				
0 - 7	65.3 ± 11.7	65.6 ± 5.8	57.2 ± 7.9*	55.1 ± 4.6*
14 - 21	55.6 ± 10.2	54.6 ± 11.5	48.1 ± 9.0*	45.6 ± 9.3* (29)[b]
28 - 35	43.5 ± 9.4	40.3 ± 7.5	35.8 ± 5.1*	32.4 ± 5.1*
49 - 56	23.8 ± 16.4	23.3 ± 3.3	19.7 ± 6.6	19.3 ± 5.0
63 - 70	16.3 ± 7.1	17.1 ± 5.2	17.0 ± 6.3	15.9 ± 5.4
91 - 98	17.1 ± 10.7	19.4 ± 5.8	19.5 ± 6.7	14.1 ± 3.5*
0 - 98	462.5 ± 77.2	465.1 ± 49.3	410.3 ± 41.4*	385.6 ± 31.5*
F_1 Females				
0 - 7	31.3 ± 8.4	32.2 ± 8.8	28.4 ± 5.7	31.1 ± 6.2
14 - 21	22.4 ± 8.5	19.6 ± 8.0	18.5 ± 8.9	18.2 ± 5.9
28 - 35	18.2 ± 9.2	19.1 ± 8.7	14.0 ± 5.6	13.5 ± 3.5*
49 - 56	9.2 ± 6.9	6.6 ± 6.0	8.3 ± 4.3	8.0 ± 4.6
63 - 70	8.7 ± 7.0	12.8 ± 5.8*	6.7 ± 8.6	6.8 ± 4.2
91 - 98	5.6 ± 6.9	3.4 ± 7.2	6.9 ± 5.1	5.1 ± 3.7
0 - 98	190.5 ± 39.2	184.2 ± 36.9	164.1 ± 25.0*	163.4 ± 16.9*

[a] Data were extracted from Study No. MIN 872222, Tables 6.5.1, 6.5.2, 6.13.1, and 6.13.2.

[b] Number of animals included in calculation

* Significantly different from control ($p \leq 0.05$)

Table 2. Mean Body Weight Gain (g ± S.D.) During Gestation for Rats Fed Prometryn Technical for Two Successive Generations[a]

Gestational Days	Dietary Level (ppm) 0	10	750	1,500
F_0 Generation - F_1 Litters				
Number of dams/group	29	24	29	29
0 - 7	27.1 ± 9.9	33.4 ± 9.3	22.7 ± 7.2	24.8 ± 11.9
7 - 14	27.5 ± 8.4	31.2 ± 7.8	30.3 ± 6.4	28.7 ± 6.4
14 - 20	69.2 ± 15.1	75.6 ± 13.5	66.6 ± 18.2 (28)[b]	63.8 ± 15.7
0 - 20	123.8 ± 18.5	140.3 ± 18.1[*]	124.0 ± 25.5 (28)[b]	117.3 ± 22.1
F_1 Generation - F_2 Litters				
Number of dams/group	21	23	28	24
0 - 7	26.9 ± 9.1	*26.4 ± 5.1	25.4 ± 9.7	21.9 ± 11.4
7 - 14	24.5 ± 8.1	27.7 ± 6.8	27.6 ± 9.1	27.5 ± 9.7
14 - 20	66.2 ± 20.5	60.9 ± 25.0	70.4 ± 15.1	64.6 ± 14.0
0 - 20	117.6 ± 30.3	115.0 ± 32.2	123.4 ± 18.9	114.0 ± 15.8

[a]Data were extracted from Study No. MIN 872222, Tables 6.5.3 and 6.13.3.

[b]Number of dams included in calculation

[*]Significantly different from control ($p \leq 0.05$)

Table 3. Mean Body Weight Gain (g ± S.D.) During Lactation for Rats Fed Prometryn Technical for Two Successive Generations[a]

Gestational Days	Dietary Level (ppm) 0	10	750	1,500
F_0 Generation - F_1 Litters				
Number of dams/group	29	26	27	29
0 - 7	6.2 ± 17.7	7.4 ± 17.0	11.4 ± 15.4	20.6 ± 14.7*
7 - 14	13.2 ± 12.9	15.8 ± 7.9	12.5 ± 9.8	7.3 ± 14.0
14 - 21	-15.9 ± 11.6	-20.5 ± 11.5	-8.6 ± 9.9	4.5 ± 15.8*
0 - 21	3.5 ± 21.2	2.6 ± 18.6	15.3 ± 17.5	32.4 ± 17.2*
F_1 Generation - F_2 Litters				
Number of dams/group	21	20	27	24
0 - 8	-1.6 ± 14.9	-5.8 ± 16.6	8.3 ± 23.6	19.4 ± 13.3*
8 - 14	14.6 ± 17.3	12.7 ± 25.8	14.6 ± 23.2	12.0 ± 21.0
14 - 21	-7.7 ± 19.9	-10.0 ± 19.9	0.5 ± 22.2	14.1 ± 18.1*
0 - 21	5.3 ± 23.5	-3.1 ± 21.2	23.4 ± 22.5*	45.5 ± 18.2*

[a]Data were extracted from Study No. MIN 872222, Tables 6.5.4 and 6.13.4.

*Significantly different from control ($p \leq 0.05$)

Table 4. Mean Food Consumption (g/day ± S.D.) During the Premating Period for Rats Fed Prometryn Technical for Two Successive Generations[a]

Study Days	Dietary Level (ppm) 0	10	750	1,500
Number of animals/group	30	30	30	30
F_0 Males				
0 - 7	23.7 ± 2.2	22.8 ± 2.0	22.4 ± 1.3*	20.5 ± 1.8*
14 - 21	24.1 ± 2.1	24.3 ± 1.8 (29)[b]	23.8 ± 1.6	23.5 ± 2.1*
28 - 35	24.6 ± 2.1 (28)[b]	25.1 ± 2.1	24.0 ± 1.7	23.4 ± 2.1*
49 - 56	25.8 ± 2.8	25.7 ± 2.2	24.6 ± 1.8	23.8 ± 2.5*
63 - 70	26.0 ± 2.3	25.8 ± 2.6	24.7 ± 1.8	24.3 ± 2.5*
F_0 Females				
0 - 7	16.1 ± 1.8	15.9 ± 1.5	15.4 ± 1.3	13.9 ± 1.2*
14 - 21	16.9 ± 2.2	16.7 ± 2.0	17.1 ± 1.5	16.2 ± 2.7*
28 - 35	16.9 ± 2.1	17.3 ± 2.1	17.4 ± 1.8 (29)[b]	15.5 ± 1.1* (29)[b]
49 - 56	17.9 ± 2.6	17.3 ± 2.2 *	17.1 ± 2.5	15.6 ± 1.1*
63 - 70	17.6 ± 2.3	16.9 ± 2.0	17.1 ± 1.9	15.9 ± 1.1*
F_1 Males				
0 - 7	23.8 ± 3.5	24.4 ± 2.6	22.7 ± 2.3	21.2 ± 2.2*
14 - 21	29.0 ± 2.9	29.3 ± 2.7	27.1 ± 2.2*	25.7 ± 1.9*
28 - 35	30.0 ± 2.8	29.9 ± 2.9	27.2 ± 2.2*	25.5 ± 1.8*
49 - 56	30.7 ± 3.6	29.9 ± 2.7	27.1 ± 2.1*	25.9 ± 2.0*
63 - 70	30.7 ± 2.8	30.6 ± 2.7	27.5 ± 2.5*	26.5 ± 2.1*
91 - 98	29.2 ± 4.5	29.5 ± 2.7 (28)[b]	26.3 ± 2.3*	24.7 ± 1.9*
F_1 Females				
0 - 7	17.3 ± 1.9	17.8 ± 2.0	17.0 ± 2.0	16.6 ± 1.2*
14 - 21	19.7 ± 2.0	19.1 ± 2.2	19.2 ± 3.1	17.8 ± 1.2*
28 - 35	21.3 ± 2.4	21.2 ± 3.1	19.2 ± 2.3*	18.1 ± 1.1*
49 - 56	20.4 ± 2.0 (29)[b]	20.4 ± 2.6	18.2 ± 2.5* (29)[b]	17.8 ± 1.1*
63 - 70	21.0 ± 2.7	20.9 ± 2.4	19.5 ± 4.1	18.6 ± 1.0*
91 - 98	20.1 ± 2.8	18.4 ± 2.1*	18.3 ± 2.6*	17.3 ± 1.3*

[a]Data were extracted from Study No. MIN 872222, Tables 6.2.1, 6.2.2, 6.10.1, and 6.10.2.

[b]Number of animals included in calculation

*Significantly different from control ($p \leq 0.05$)

Table 5. Mean Food Consumption (g/day ± S.D.) During Gestation for Rats Fed Prometryn Technical for Two Successive Generations[a]

Gestational Days	Dietary Level (ppm) 0	10	750	1,500
F_0 Generation - F_1 Litters				
Number of dams/group	29	24	29	29
0 - 7	21.2 ± 2.2	21.2 ± 2.0	20.6 ± 2.2	19.2 ± 2.2*
7 - 14	21.6 ± 2.8	21.6 ± 2.9	21.9 ± 1.9	20.8 ± 1.4
14 - 20	22.9 ± 2.8	23.4 ± 2.0	22.5 ± 3.5 (28)[b]	21.5 ± 3.2
F_1 Generation - F_2 Litters				
Number of dams/group	21	23	28	24
0 - 7	21.9 ± 2.7	21.4 ± 1.9	* 20.4 ± 2.8	20.0 ± 1.6*
7 - 14	23.1 ± 2.7	23.4 ± 2.3	22.6 ± 2.8	21.5 ± 1.5
14 - 20	25.3 ± 2.8	25.7 ± 2.4	24.9 ± 3.5	23.5 ± 1.7

[a]Data were extracted from Study No. MIN 872222, Tables 6.2.3 and 6.10.3.

[b]Number of dams included in calculation

*Significantly different from control ($p \leq 0.05$)

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Table 6. Summary of Effects of Dietary Administration of Prometryn Technical on F_1 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm)			
	0	10	750	1,500
No. matings (F_0 parents)	30	30	30	30
Mating index (%)[b]	100	100	100	100
No. pregnancies	29	26	29	29
Fertility index (%)[c]	100	86.7	96.7	96.7
Gestation index (%)[d]	100	100	96.6	100
Gestation length (days)	23.1	23.3	23.1	23.0
Total no. stillborn pups	9	8	3	11
Total no. viable litters	29	26	28	29
Total no. live pups[e]				
Day 0	412	385	427	442
Day 4 precull	410	364	422	429
Day 21	230	201	231	223
Mean no. live pups/litter				
Day 0	14.2	14.8	15.3	15.2
Day 4 precull	14.1	14.0	15.3	14.8
Day 21	7.9	7.7	7.9	7.8
Live birth index (%)[f]	97.9	98.0	99.3	97.6
Viability index (%)[g]	99.4	94.6	95.1	97.1
Lactation index (%)[h]	99.1	99.0	99.5	99.6
Mean pup body weight (g)				
Day 0, males	6.3 (28)[i]	6.4 (26)	6.2 (28)	6.0* (28)
females	6.0 (28)	6.1 (26)	5.8 (28)	5.7* (28)
7, males	15.7 (29)	16.0 (26)	14.9 (27)	14.6* (29)
females	15.3 (29)	15.2 (26)	14.4 (27)	13.9* (29)
21, males	55.0 (29)	56.0 (26)	51.4 (27)	48.5* (29)
females	52.9 (29)	53.3 (26)	49.3* (27)	47.0* (29)
Sex ratio (% males, day 0)	54.1	47.5	49.9	52.0

[a] Data were extracted from Study No. MIN 872222, Tables 6.6.3, 6.6.4, 6.8.1, 6.8.3.1, 6.8.3.2, and 6.8.3.3 and individual animal data.

[b] Mating index: No. sperm-positive females expressed as % of total No. mated females

[c] Fertility index: No. females delivering a litter expressed as % of No. sperm-positive females

[d] Gestation index: No. females delivering a live litter expressed as % of No. pregnant females

[e] Calculated by the reviewers

[f] Live birth index: Percentage of pups surviving one day

[g] Viability index: Percentage of pups surviving four days (precull)

[h] Lactation index: Percentage of pups surviving 21 days based on No. pups on day 4 postcull

[i] Number of litters included in calculation

* Significantly different from control ($p \leq 0.05$)

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Table 7. Summary of Effects of Dietary Administration of Prometryn Technical on F_2 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	10	750	1,500
No. matings (F_1 parents)	30	30	30	30
Mating index (%)[b]	[illegible]	93.3	100	100
No. pregnancies	22	23	28	24
Fertility index (%)[c]	88.[illegible]	82.1	93.3	80.0
Gestation index (%)[d]	95.[illegible]	87.0	96.4	100
Gestation length (days)	23.4	23.3	23.3	23.2
Total no. stillborn pups	4	5	10	5
Total no. viable litters	21	20	27	24
Total no. live pups[e]				
Day 0	265	238	384	356
Day 4 precull	264	229	370	340
Day 21	148	136	212	186
Mean no. live pups/litter				
Day 0	12.6	11.9*	14.2*	14.8*
Day 4 precull	12.6	12.1	13.7	14.2
Day 21	7.4	7.2	7.9	7.8
Live birth index (%)[f]	98.5	97.9	97.5	98.6
Viability index (%)[g]	99.7	96.2	96.9	95.5
Lactation index (%)[h]	99.4	97.1	100	98.9
Mean pup body weight (g)				
Day 0, males	6.5 (18)[i]	6.7 (20)	6.2 (27)	6.1 (24)
females	6.2 (18)	6.3 (20)	5.9 (27)	5.8 (24)
8, males	16.7 (19)	16.5 (19)	16.6 (27)	15.3 (24)
females	16.5 (19)	16.1 (19)	16.0 (27)	14.9* (24)
21, males	49.6 (19)	50.2 (19)	47.9 (27)	44.5* (24)
females	48.1 (19)	48.7 (19)	46.1 (27)	43.2* (24)
Sex ratio (% males, day 0)	47.6	47.1	50.8	46.9

[a]Data were extracted from Study No. MIN 872222, Tables 6.14.2, 6.14.3, 6.14.4, 6.16.1, 6.16.3.1, 6.16.3.2, and 6.16.3.3. and individual animal data.

[b]Mating index: No. sperm-positive females expressed as % of total No. mated females

[c]Fertility index: No. females delivering a litter expressed as % of No. sperm-positive females

[d]Gestation index: No. females delivering a live litter expressed as % of No. pregnant females

[e]Calculated by the reviewers

[f]Live birth index: Percentage of pups surviving one day

[g]Viability index: Percentage of pups surviving four days (precull)

[h]Lactation index: Percentage of pups surviving 21 days based on No. pups on day 4-postcull

[i]Number of litters included in calculation

*Significantly different from control (p≤0.05)