

DIMETHOATE/035001

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Template version 11/01

DATA EVALUATION RECORD

10/19/04

STUDY TYPE: Reproduction and Fertility Effects Study - [rat] OPPTS 870.3800 [§83-4];
OECD 416.

PC CODE: 035001
TXR#: 0052750

DP BARCODE: D305929
SUBMISSION NO.: None

TEST MATERIAL (PURITY): Dimethoate (Batch # 20522-00; 99.1% a.i.)

SYNONYMS: BAS 152 I; *O, O*-dimethyl *S*-(*N*-methylcarbamoyl-methyl)-phosphorodithioate

CITATION: Mellert, W., Hellwig, J., Gembardt, C., *et al.* (2003) Dimethoate - two-generation reproduction toxicity study in Wistar rats: administration in the diet. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany. Laboratory Project Identification: 70R0466/99118, August 7, 2003. MRID 46181001. Unpublished.

SPONSOR: Dimethoate Task Force, Mannheim, Germany

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study (MRID 46181001), Dimethoate (Batch # 20522-00; 99.1% a.i.) was administered continuously in the diet to Wistar (CrlGlxBrlHan:WI) rats (25 animals/sex/dose) at nominal dose levels of 0, 0.2, 1.0, or 6.5 mg/kg bw/day. The P and F₁ parents were dosed for at least 75 days before they were mated to produce the F_{1a} and F_{2a} litters, then were subsequently remated to produce the F_{1b} and F_{2b} litters. The F_{1a} pups were weaned on postnatal day (PND) 21, and 25 pups/sex/group (1 pup/sex/litter as nearly as possible) were randomly selected as parents of the F₂ generation.

In the parental animals, no treatment-related effects were observed on survival, clinical signs, or food or water consumption.

At 6.5 mg/kg/day, overall (LD 1-21) body weight gains were decreased in the F₁ females during lactation of both the F_{2a} and F_{2b} litters. In P and F₁ parents, erythrocyte cholinesterase activity was decreased during pre-mating and at termination, and brain cholinesterase activity was decreased at termination. In the F₁ males, absolute and relative (to body) prostate weights were

decreased. Focal vacuolization of the epididymides was observed in the P and F₁ males, both compared to controls. Also, the following were observed in the F₁ males compared to controls: i) slight to severe vacuolization of the cauda epididymides; ii) slight to severe reduced secretion of the dorso-lateral prostate gland; and iii) moderate to severe diffuse epithelial atrophy of the dorso-lateral prostate gland. However, reproductive performance was unaffected.

At 1.0 mg/kg/day, decreases (\downarrow 13-20%; $p \leq 0.05-0.002$) were observed in brain cholinesterase activity in both sexes of P and F₁ generations. Decreases (\downarrow 6-10%; $p \leq 0.05-0.02$) in erythrocyte cholinesterase activity were also seen in males of P and F₁ generations during pre-mating and at termination.

At 0.2 mg/kg/day, no compound related effects were seen in the parental animals.

The LOAEL for parental toxicity was 1.0 mg/kg/day, based on decreased erythrocyte (in males) and brain cholinesterase activity (in both sexes). The NOAEL was 0.2 mg/kg/day.

In the offspring, no treatment-related effects were observed on survival, live birth, viability, or lactation indices, on the sex ratio, clinical signs, body weight, sexual maturation, organ weights, or gross pathology.

Body weight gains were decreased in the 6.5 mg/kg/day F_{1a} pups. Brain cholinesterase activity was measured in the controls and 6.5 mg/kg/day groups only. Brain cholinesterase activity in 6.5 mg/kg/day F_{1b} female pups culled on PND 4 was slightly decreased (\downarrow 10%; $p \leq 0.02$). However, no effect was seen in F_{1b} generation PND 4 pups of both sexes and F_{2b} generation PND 4 male pups.

The LOAEL for offspring toxicity was 6.5 mg/kg/day, based on decreased brain cholinesterase activity in female pups culled on PND 4. The NOAEL was not determined.

The reproductive parameters measured were not affected by dimethoate in both P and F₁ generations. **The NOAEL for reproductive effects was 6.5 mg/kg/day (HDT).**

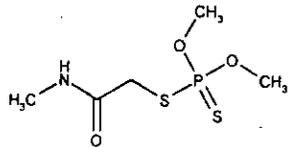
This study is classified as **acceptable/guideline** and satisfies the Guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

COMPLIANCE: Signed and dated Data Confidentiality, GLP, Flagging, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

- 1. Test Material:** Dimethoate
- Description:** White solid
- Batch #:** 20522-00
- Purity:** 99.1% a.i.
- Compound Stability:** Stable in the diet for up to 8 days at room temperature or at freezer conditions
- CAS # of TGA1:** 60-51-5
- Structure:**



- 2. Vehicle:** diet

3. Test animals

- Species:** Rat
- Strain:** Wistar (CrIGlxBrIHan:WI)
- Age at study initiation:** 35±1 days
- Mean weight range on Study Day 1:** 80.6-108.0 g males; 78.0-101.0 g females
- Source:** Charles River Deutschland GmbH, Sulzfeld, Germany
- Housing:** Individually in stainless steel (type DK III) wire mesh cages; females and their litters were housed in Makrolon type M III cages from gestation day 18 through lactation day 21.
- Diet:** Ground Kliba maintenance diet # 3433 (Provimi Kliba SA, Kaiseraugst, Switzerland), *ad libitum*
- Water:** Tap water *ad libitum*
- Environmental conditions:**
- | | |
|--------------------|--------------------------|
| Temperature | 20-24°C |
| Humidity | 30-70% |
| Air changes | 10-15/hr |
| Light cycle | 12 hrs light/12 hrs dark |
- Acclimation period:** Approximately 7 days

B. PROCEDURES AND STUDY DESIGN

- 1. Mating procedure:** In general, each of the male and female animals was paired overnight at a 1:1 ratio for a maximum of 2 weeks. Males were placed in the cage of a female of the same dose group for mating. The following day, a vaginal smear was prepared and examined for the presence of sperm (positive mating). The day on which positive mating was observed was designated as gestation day (GD) 0. Once positive mating occurred, pairing was discontinued. At least 10 days after the first litter was weaned, animals were mated again with different partners from the same dose group as described above.

2. Study schedule: Rats were exposed to the test substance in the diet continuously throughout the study. The P animals were dosed for at least 75 days prior to pairing; thus, the P animals were approximately 15-16 weeks old at mating to produce the F_{1a} litters. The F_{1a} pups were weaned on postnatal day (PND) 21, and 25 pups/sex/group (1 pup/sex/litter, as nearly as possible) were randomly selected from as many different litters as were available to be parents of the F₂ generations. Sibling matings were avoided. When less than 25 litters were available, additional animals were selected on a random basis from the appropriate dose group. At least 10 days after the last F_{1a} pup was weaned, females were mated with different males to produce the F_{1b} litters. The F₁ parents were dosed from weaning for at least 75 days before they were mated; therefore, the F₁ parents were 13-14 weeks old when mated to produce the F_{2a} litters. At least 10 days after the last F_{2a} pup was weaned, females were mated with different males to produce the F_{2b} litters. The F₁ pups not selected to be parents of the F₂ generation and all F₂ pups were killed after standardization (PND 4) or weaning (PND 21).

3. Animal assignment: During acclimation (6 days prior to treatment), all P animals were weighed. P animals were then randomly assigned (stratified by body weight) to the test groups shown in Table 1.

TABLE 1. Animal assignment^a

Test Group	Dose ^b (mg/kg/day)	Animals/group			
		P Males	P Females	F ₁ Males	F ₁ Females
Control	0	25	25	25	25
Low	0.2	25	25	25	25
Mid	1.0	25	25	25	25
High	6.5	25	25	25	25

a Data were obtained from page 34 of the study report.

b Exposure to the test substance was continuous throughout the study.

4. Dose-selection rationale: It was stated that the dose levels summarized in Table 1 were chosen based on the results of a previously performed reproductive toxicity study (Huntingdon Life Science, Ltd. DTF Doc. No. 453-003; not provided). Dimethoate was administered continuously in the diet to Sprague-Dawley rats (number not given) at nominal dose levels of 0, 1, 15, or 65 ppm (equivalent to 0, 0.08, 1.2, and 5.7 mg/kg bw/day). The P animals were dosed for 10 weeks prior to mating, and after delivery of the F_{1a} litters, the P animals were remated to generate F_{1b} litters. A partial third mating was performed with animals that had not been successfully mated at either of the first 2 pairings. The F₁ parents were selected from the F_{1a} litters, and were mated twice to produce F_{2a} and F_{2b} litters.

The LOAEL for parental toxicity was 15 ppm (equivalent to 1.2 mg/kg/day) based on reduced plasma, brain and erythrocyte cholinesterase activity, body weight gain, and water consumption. The LOAEL for offspring toxicity was 65 ppm (equivalent to 5.7 mg/kg/day), based on reduced

brain cholinesterase activity in the male pups and retarded body weight gain and delay in a physical landmark (startle response) in the F_{1a} and F_{2a} litters. The LOAEL for reproductive performance was 65 ppm (equivalent to 5.7 mg/kg/day), based on reduced reproductive performance, including fertility.

Based on these results, 0.2 mg/kg/day was selected as the expected NOAEL, 1.0 mg/kg/day was selected as an intermediate dose, and 6.5 mg/kg/day was selected to cause treatment-related effects without mortality in the parental animals.

5. Dosage preparation and analysis: Dosing formulations were prepared weekly; however, storage conditions were not provided. The test compound was weighed, dissolved in approximately 20 g of acetone using an ultrasonic bath, and mixed with a small amount of feed. This premix was then diluted with an appropriate amount of feed to obtain the desired dietary concentration. Homogeneity (top, middle, and bottom) and concentration were verified on all dose levels weekly during the first 4 weeks, and then every 3-4 weeks thereafter. Prior to the study, stability was verified in a 1 ppm dietary formulation, using either acetone or water as a carrier, and following storage for up to 8 days at either ambient temperature or freezer temperature (not specified).

Results

Homogeneity (% coefficient of variation)

0.2 mg/kg = 0.3-11.6%

1.0 mg/kg = 0.3-11.2%

6.5 mg/kg = 0.1-6.0%

Stability (range of % of initial concentration)

stored 8 days at room temperature: 93.4-94.1%

stored 8 days at freezer temperature: 104.0-115.1%

Concentration (range of % of nominal concentration)

0.2 mg/kg = 88.6-107.3%

1.0 mg/kg = 87.1-109.9%

6.5 mg/kg = 81.7-106.7%

The analytical data indicated that the mixing procedure was adequate and the variation between nominal and actual dosage to the study animals was acceptable.

6. Dosage administration: All doses were administered continuously in the diet throughout the study. Dietary concentrations were adjusted weekly based on body weight and food consumption from the previous week, with the following exceptions: i) during mating, the last pre-mating concentration was used for both sexes; ii) during gestation and post-weaning, females

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were given the last pre-mating concentration; and iii) during lactation, females were given 50% of the last pre-mating concentration. Males were exposed to the female dietary concentration during cohabitation.

C. OBSERVATIONS

1. Parental animals: All animals were observed at least twice daily for mortality and morbidity; clinical signs of toxicity were recorded daily. Body weights were measured 6 days prior to study initiation, on Study Day 1, and then weekly until termination. Females were weighed weekly until mating was detected; on GD 0, 7, 14, and 20; and on lactation days (LD) 1, 4, 7, 14, and 21. Females that did not show signs of positive mating or that did not have a litter were weighed at the same time as the males. Food consumption (g/rat/day) was recorded weekly (each time for a period of 6 days) throughout the study for the males, and during Weeks 0-10 for the females. Additionally, food consumption by the females was determined during GD 0-7, 7-14, and 14-20, and on LD 1-4, 4-7, and 7-14. It was stated that food consumption was not determined after LD 14 as the pups were thought to be consuming a considerable amount of feed. Water consumption (g/rat/day) was recorded weekly (each time for a period of 3 days) during Weeks 0-10 for males and females. Additionally, water consumption was determined during GD 0-1, 6-7, 13-14, and 19-20, and during LD 1-2, 4-5, 7-8, and 14-15 for the females. Estrous cycle length and normality were determined for all females for both P and F₁ generations for a minimum of 3 weeks prior to pairing until evidence of positive mating was observed. Sperm enumeration (0 and 6.5 mg/kg/day), morphology (0 and 6.5 mg/kg/day), and motility (all doses) were evaluated when the males were killed. Serum and erythrocyte cholinesterase activities were measured in the P generation during acclimation (base line), in all P and F₁ parents prior to mating, and in all surviving P and F₁ parents at the end of treatment.

2. Litter observations: The following litter parameters (X) were observed (Table 2).

TABLE 2. F₁/F₂ litter observations^a

Observation	Postnatal Day						
	Day 0	Day 1	Day 4 ^b	Day 4 ^c	Day 7	Day 14	Day 21
Number of live pups	X	X	X	X	X	X	X
Number of dead pups	X	X	X	X	X	X	X
Pup weight		X	X	X	X	X	X
External alterations	X	X	X	X	X	X	X
Clinical signs	X	X	X	X	X	X	X
Sex of each pup (M/F)	X						X

a Data were obtained from pages 49-50 of the study report.

b Before standardization (culling)

c After standardization (culling)

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On post-natal day (PND) 4, litters of 9 or more pups were standardized by random selection to a

maximum of 8 pups/litter (4 pups/sex/litter, as nearly as possible). Preputial separation was evaluated in the males daily beginning on PND 40; vaginal patency was evaluated in the females daily beginning on PND 27. Body weights were recorded when criteria were reached.

3. Postmortem observations

1) Parental animals: All adults, including those killed for humane reasons, were anesthetized with CO₂ and exsanguinated by decapitation. Animals were then subjected to a complete macroscopic examination. P animals were killed after weaning of the F_{1b} pups, and it was stated that the F₁ parents were killed some weeks after the F_{2b} pups were weaned. Estrous cycle stages were determined in all adult females at termination. Brain samples were taken at necropsy from all P and F₁ parents and brain cholinesterase activity was determined. The following tissues were collected for histological examination (X) and fixed in 4% buffered formalin (except for the ovaries, epididymides, and testes, which were fixed in Bouin's solution). Additionally, the (XX) tissues were weighed.

XX	Liver	XX	Cervix ^a	XX	Pituitary gland
XX	Kidney	XX	Ovaries	XX	Adrenal gland
XX	Epididymides	XX	Seminal vesicles ^b	XX	Spleen
XX	Testes	XX	Coagulating glands ^b	XX	Thyroid gland ^c
XX	Uterus ^a	XX	Prostate gland	XX	Parathyroid gland ^c
XX	Oviducts ^a	XX	Brain	X	All gross lesions

a Uterus was weighed with cervix and oviducts

b Seminal vesicles were weighed with coagulating glands

c Thyroid and parathyroids were weighed together

Microscopic examination was performed on all tissues in the control and 6.5 mg/kg/day groups. The epididymides, seminal vesicles, coagulating gland, and prostate gland also were examined in all males in the 0.2 and 1.0 mg/kg/day groups. The vagina, cervix, uterus, ovaries, oviducts, testes, pituitary gland, and adrenal gland were examined in animals with suspected impaired fertility in the 0.2 and 1.0 mg/kg/day. The pituitary gland in the 0.2 and 1.0 mg/kg/day groups and the thyroid and parathyroid glands from all dose groups were examined in the F₁ female parents. Additionally, a differential ovarian follicle count was performed on the ovaries of the control and 6.5 mg/kg/day F₁ females.

2) Offspring: All pups with scheduled terminations (i.e., culled on PND 4 or killed on PND 21) were killed by CO₂ asphyxiation, and, along with decedents or stillborn pups, were examined externally, eviscerated, and their organs assessed macroscopically. If there were notable findings or abnormal clinical observations, pups were further examined by skeletal staining using a modification of Dawson's method and/or processing of the head by Wilson's method, if deemed necessary. Pups were not examined microscopically. On PND 4, brain tissue was sampled and weighed from 1 pup/sex/litter from all of the F₁ and F₂ litters. Brain cholinesterase activity was measured in the controls and 6.5 mg/kg/day groups from the F_{1b} and F_{2b} pups. On PND 21, 1 pup/sex/litter was randomly selected from all of the F₁ and F₂ litters, and the brain, spleen, and thymus were weighed.

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D. DATA ANALYSIS

1. **Statistical analyses:** Data were subjected to the following statistical procedures:

Parameter	Statistical test
Water and food consumption (parental animals), body weight and body weight gains (all animals), estrous cycle duration, number of mating days, duration of gestation, number of pups delivered per litter, time to sexual maturation	Two-sided Dunnett's test
Male and female mating and fertility indices; gestation, viability, and lactation indices; females with live born, stillborn, and all stillborn pups; live birth index, pups stillborn, pups died, pups cannibalized, pups sacrificed moribund, number of litters with affected pups at necropsy, sexual maturation data, males with >4% abnormal sperm	Fisher's exact test
Proportions of affected pups per litter with necropsy observations	One-sided Wilcoxon's test
Total spermatids/g testis, total sperm/g cauda epididymides, % motility	One sided Wilcoxon's test with Bonferoni-Holm Adjustment
Pup organ weights (absolute and relative to body)	One-way Kruskal-Wallis test followed by two-sided Wilcoxon's test if significance found
Parental cholinesterase activity	One-way Kruskal-Wallis test followed by two-sided Mann-Whitney U test if significance found
Pup cholinesterase activity (control and 6.5 mg/kg/day)	Mann-Whitney U test

Significance was denoted at $p \leq 0.05$ and $p \leq 0.01$, except for analysis of cholinesterase activity, where significance was denoted at $p \leq 0.05$, $p \leq 0.02$, and $p \leq 0.002$.

2. Indices

Reproductive indices: The following reproductive/viability indices were calculated by the performing laboratory from breeding and parturition records of animals in the study:

Male mating (%) = # of males with confirmed mating (females with vaginal sperm or that gave birth to a litter or with fetuses *in utero*)/# of males placed with females x 100

Male fertility (%) = # of males proving their fertility (female giving birth to a litter or with pups/fetuses *in utero*)/# of males placed with females x 100

Female mating (%) = # of females mated (females with vaginal sperm or that gave birth to a litter or with fetuses *in utero*)/# of females placed with males x 100

Female fertility (%) = # of females pregnant (females that gave birth to a litter or with pups/fetuses *in utero*)/# of females mated (females with vaginal sperm or that gave birth to a litter or with fetuses *in utero*) x 100

Gestation index (%) = # of females with live pups on the day of birth/total # of females pregnant (females that gave birth to a litter or with fetuses *in utero*) x 100

Offspring viability indices: The following viability indices were calculated by the performing laboratory from lactation records of litters in the study:

Live birth index (%) = # of pups live born at birth/total # of pups born x 100

Viability (%) = # of live pups on PND 4 (pre-culling)/# of live pups on the day of birth x 100

Lactation (%) = # of live pups on PND 21/# of live pups on PND 4 (post culling) x 100

3. Historical control data: Historical control data were provided, consisting of 20-25 studies (including the current study) performed between April, 2000 and February 2003 in Wistar rats from the same supplier. Routes of administration used included diet, gavage, and drinking water. Summary tables of maternal body weights during gestation and lactation, reproduction and litter data, pup weights, pup necropsy observations, pup organ weights, and parental sperm evaluations were provided.

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality and clinical signs: There were no unscheduled deaths in the P generation parents. In the F₁ parents, two males (Weeks 6 and 21) and one female (Week 26) in the 1.0 mg/kg/day group and one 6.5 mg/kg/day male (Week 9) were found dead. Additionally, one 6.5 mg/kg/day female was found in moribund condition and was killed during Week 27. Clinical, gross pathology, and histopathology examinations revealed none of these deaths were considered treatment-related. No clinical signs of toxicity were observed in the P or F₁ parents. One 0.2 mg/kg/day F₁ female exhibited chromodacryorrhea, poor general state, red crusts on the nose, and piloerection during gestation of the F_{2b} litter; and one 6.5 mg/kg/day F₁ female did not nurse her F_{2b} pups properly, but these findings were not considered treatment-related as they occurred during only one littering.

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2. **Body weight and food consumption:** Body weight and food consumption data are presented in Tables 3a, b, c, and d. No effects of treatment were observed on body weights or body weight gains in the males of either generation throughout the study. No effects of treatment were noted on body weights or body weight gains in the females of either generation during pre-mating or gestation, or in the P females during lactation. In the 6.5 mg/kg/day F₁ females Table 3d), overall (LD 1-21) body weight gains were decreased during lactation of both the F_{2a} (↓18%; not significant [NS]) and F_{2b} (↓60%; p≤0.05) litters. All other alterations (p≤0.05) in body weight and body weight gains were sporadic and not dose-dependent.

No treatment-related effect was observed on food consumption in either the P or F₁ generations. Differences (p≤0.05) in food consumption were observed; however, these increases were sporadic, minor, and not dose-dependent.

TABLE 3a. Selected mean (±SD) body weights (g), body weight gains (g), and food consumption (g/rat/day) - P and F₁ generation males^a

Observation/study day		Dose Group (mg/kg/day)			
		0	0.2	1.0	6.5
P Generation					
Body weight	Week 0	95.8±7.36	95.4±7.19	94.9±5.67	94.3±6.48
Body weight	Week 29	431.2±41.00	435.7±31.47	436.4±39.80	429.1±40.88
Body weight gain	Week 0-29	335.4±38.77	340.4±30.11	341.5±39.89	334.8±41.19
Food consumption ^b	Week 0-29	22.3±1.62	22.2±1.63	22.2±1.65	22.3±1.60
F₁ Generation					
Body weight	Week 0	66.4±9.16	67.1±10.08	67.9±8.27	66.2±10.82
Body weight	Week 28	461.4±36.60	463.2±34.71	472.2±30.65	445.1±49.97
Body weight gain	Week 0-28	394.9±32.68	396.2±33.04	403.3±30.68	379.0±47.35
Food consumption ^b	Week 0-28	23.3±2.17	23.4±2.15	24.0±2.17	23.3±2.05

a Data were obtained from pages 158-160, 168-173, 257-259, and 267-272 of the study report.

b It was stated that overall food consumption was calculated as a mean of means, and the performing laboratory did not statistically analyze these data.

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TABLE 3b. Selected mean (\pm SD) body weights (g), body weight gains (g), and food consumption (g/rat/day) - P and F₁ generation pre-mating females^a

Observation/study day		Dose Group (mg/kg/day)			
		0	0.2	1.0	6.5
P Generation					
Body weight	Week 0	89.8 \pm 5.34	88.9 \pm 5.14	89.2 \pm 4.65	88.4 \pm 5.45
Body weight	Week 10	212.9 \pm 18.20	216.3 \pm 17.73	219.3 \pm 16.55	210.1 \pm 17.73
Body weight gain	Week 0-10	123.1 \pm 15.32	127.5 \pm 17.19	130.0 \pm 15.55	121.7 \pm 14.76
Food consumption ^b	Week 0-10	16.7 \pm 0.41	17.0 \pm 0.45	17.2 \pm 0.61	16.7 \pm 0.44
F₁ Generation					
Body weight	Week 0	61.6 \pm 7.71	62.0 \pm 7.79	63.6 \pm 7.77	62.8 \pm 9.28
Body weight	Week 10	211.2 \pm 24.18	217.9 \pm 16.47	219.2 \pm 17.14	209.6 \pm 16.06
Body weight gain	Week 0-10	149.6 \pm 21.59	155.8 \pm 15.55	155.6 \pm 16.49	146.8 \pm 15.16
Food consumption ^b	Week 0-10	17.6 \pm 1.40	18.1 \pm 1.42	18.3 \pm 1.46	17.6 \pm 1.26

a Data were obtained from pages 161, 174-175, 260, and 273-274 of the study report.

b It was stated that overall food consumption was calculated as a mean of means, and the performing laboratory did not statistically analyze these data.

TABLE 3c. Mean (\pm SD) body weights (g), body weight gains (g), and food consumption (g/rat/day) - P and F₁ generation females during gestation^a

Observation/gestation day		Dose Group (mg/kg/day)			
		0	0.2	1.0	6.5
P Generation - F_{1a} litter					
Body weight	GD 0	214.2 \pm 14.77	215.6 \pm 18.55	218.9 \pm 16.67	209.9 \pm 18.27
Body weight	GD 7	239.0 \pm 17.44	238.3 \pm 19.83	242.7 \pm 18.40	232.1 \pm 18.97
Body weight	GD 14	261.9 \pm 20.16	261.8 \pm 21.65	267.0 \pm 20.10	255.0 \pm 20.23
Body weight	GD 20	309.2 \pm 23.09	310.6 \pm 27.80	317.8 \pm 26.86	304.5 \pm 23.18
Body weight gain	GD 0-20	95.0 \pm 12.71	95.0 \pm 15.54	99.0 \pm 15.59	94.6 \pm 9.56
Food consumption ^b	GD 0-20	22.0 \pm 1.33	21.5 \pm 1.24	22.4 \pm 1.30	21.9 \pm 1.28
P Generation - F_{1b} litter					
Body weight	GD 0	244.0 \pm 20.32	247.6 \pm 18.65	250.6 \pm 15.33	241.4 \pm 20.65
Body weight	GD 7	261.7 \pm 23.70	264.4 \pm 21.33	270.2 \pm 16.32	258.5 \pm 23.22
Body weight	GD 14	285.5 \pm 26.53	287.2 \pm 23.35	295.1 \pm 19.99	279.9 \pm 23.51
Body weight	GD 20	340.0 \pm 30.89	339.0 \pm 24.78	354.9 \pm 29.01	330.7 \pm 27.64
Body weight gain	GD 0-20	96.0 \pm 16.17	91.4 \pm 11.24	104.2 \pm 19.19	89.4 \pm 17.76
Food consumption ^b	GD 0-20	22.3 \pm 1.08	22.3 \pm 1.17	23.7 \pm 0.99	22.7 \pm 1.05
F₁ Generation - F_{2a} litter					
Body weight	GD 0	219.5 \pm 23.63	223.0 \pm 18.12	224.7 \pm 15.15	215.6 \pm 18.65
Body weight	GD 7	243.8 \pm 24.25	247.5 \pm 19.08	251.9 \pm 16.97	240.6 \pm 20.33
Body weight	GD 14	265.4 \pm 28.00	269.5 \pm 21.30	275.7 \pm 20.54	264.7 \pm 22.07
Body weight	GD 20	317.7 \pm 34.27	321.7 \pm 27.91	331.4 \pm 27.14	315.6 \pm 28.68
Body weight gain	GD 0-20	98.3 \pm 15.57	98.7 \pm 15.90	106.7 \pm 15.82	100.0 \pm 13.22
Food consumption ^b	GD 0-20	21.9 \pm 0.71	22.5 \pm 0.55	23.4 \pm 0.71	22.7 \pm 0.64
F₁ Generation - F_{2b} litter					
Body weight	GD 0	249.8 \pm 25.79	255.5 \pm 17.97	258.7 \pm 16.34	250.7 \pm 20.40
Body weight	GD 7	270.6 \pm 26.81	274.3 \pm 20.83	281.4 \pm 17.44	270.3 \pm 23.36
Body weight	GD 14	292.3 \pm 28.98	296.9 \pm 22.38	305.9 \pm 19.47	292.9 \pm 26.73
Body weight	GD 20	350.4 \pm 34.24	352.8 \pm 26.78	364.1 \pm 22.61	349.4 \pm 34.11
Body weight gain	GD 0-20	100.7 \pm 12.16	97.3 \pm 13.84	105.3 \pm 15.75	98.7 \pm 17.75
Food consumption ^b	GD 0-20	22.8 \pm 0.72	22.8 \pm 0.57	24.3 \pm 1.03	24.1 \pm 0.77

a Data were obtained from pages 162, 165, 176-177, 182-183, 261, 264, 275-276, and 281-282 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

b It was stated that overall food consumption was calculated as a mean of means, and the performing laboratory did not statistically analyze these data.

TABLE 3d. Mean (\pm SD) body weights (g), body weight gains (g), and food consumption (g/rat/day) - P and F₁ generation females during lactation^a

Observation/lactation day		Dose Group (mg/kg/day)			
		0	0.2	1.0	6.5
P Generation - F_{1a} litter					
Body weight	LD 1	243.2 \pm 20.53	238.8 \pm 20.57	242.2 \pm 20.02	234.7 \pm 22.29
Body weight	LD 4	252.4 \pm 20.15	247.2 \pm 21.15	249.8 \pm 19.75	243.1 \pm 19.85
Body weight	LD 7	257.7 \pm 19.45	255.7 \pm 21.87	257.4 \pm 19.69	249.6 \pm 19.51
Body weight	LD 14	270.9 \pm 21.62	269.1 \pm 22.45	273.6 \pm 20.31	259.2 \pm 20.72
Body weight	LD 21	266.2 \pm 18.39	267.7 \pm 18.12	269.5 \pm 17.82	255.6 \pm 22.02
Body weight gain	LD 1-21	23.0 \pm 11.98	28.9 \pm 11.91	27.2 \pm 12.33	21.0 \pm 7.83
Food consumption ^b	LD 1-14	40.0 \pm 9.47	40.3 \pm 8.86	41.6 \pm 9.79	41.0 \pm 9.11
P Generation - F_{1b} litter					
Body weight	LD 1	265.9 \pm 23.23	266.2 \pm 26.64	270.9 \pm 22.58	260.1 \pm 23.55
Body weight	LD 4	277.4 \pm 22.44	274.7 \pm 23.44	280.3 \pm 20.43	269.1 \pm 23.84
Body weight	LD 7	284.4 \pm 24.48	285.4 \pm 24.37	288.5 \pm 20.24	275.7 \pm 21.64
Body weight	LD 14	291.4 \pm 23.41	295.2 \pm 21.13	303.7 \pm 19.31	286.5 \pm 21.84
Body weight	LD 21	282.9 \pm 23.16	289.6 \pm 22.15	293.5 \pm 18.40	277.9 \pm 24.39
Body weight gain	LD 1-21	16.9 \pm 8.94	23.4 \pm 14.68	22.6 \pm 13.07	17.8 \pm 6.77
Food consumption ^b	LD 1-14	41.6 \pm 10.69	43.0 \pm 11.05	43.0 \pm 11.92	40.5 \pm 10.20
F₁ Generation - F_{2a} litter					
Body weight	LD 1	247.8 \pm 24.56	248.9 \pm 20.44	255.3 \pm 20.11	245.3 \pm 21.20
Body weight	LD 4	253.3 \pm 27.26	257.6 \pm 22.01	262.1 \pm 18.70	252.9 \pm 20.85
Body weight	LD 7	257.5 \pm 25.03	265.7 \pm 20.88	269.5 \pm 20.63	259.6 \pm 21.70
Body weight	LD 14	273.1 \pm 25.68	272.6 \pm 21.69	281.1 \pm 17.85	266.5 \pm 22.04
Body weight	LD 21	269.9 \pm 23.26	274.4 \pm 22.00	278.7 \pm 19.63	263.6 \pm 21.05
Body weight gain	LD 1-21	22.2 \pm 11.22	25.4 \pm 14.40	23.4 \pm 11.97	18.3 \pm 13.52 (118)
Food consumption ^b	LD 1-14	39.4 \pm 9.86	39.6 \pm 9.14	42.2 \pm 9.92	41.5 \pm 10.13
F₁ Generation - F_{2b} litter					
Body weight	LD 1	268.7 \pm 27.19	271.0 \pm 24.16	283.0 \pm 22.20	273.3 \pm 25.38
Body weight	LD 4	281.5 \pm 27.57	282.6 \pm 25.04	295.0 \pm 18.72	284.6 \pm 23.87
Body weight	LD 7	283.9 \pm 27.38	290.9 \pm 26.65	301.7 \pm 19.27	287.4 \pm 25.58
Body weight	LD 14	298.5 \pm 23.67	298.8 \pm 26.15	308.0 \pm 21.09	294.0 \pm 26.18
Body weight	LD 21	287.0 \pm 22.78	292.4 \pm 20.40	300.6 \pm 15.75	280.6 \pm 25.38
Body weight gain	LD 1-21	18.3 \pm 9.18	21.4 \pm 14.53	17.6 \pm 13.01	7.3 \pm 12.51* (160)
Food consumption ^b	LD 1-14	40.8 \pm 9.50	41.2 \pm 9.46	43.2 \pm 10.00	41.2 \pm 9.33

a Data were obtained from pages 163, 166, 178-179, 184-185, 262, 265, 277-278, and 283-284 of the study report. Percent difference from controls (calculated by reviewers) is included in parentheses.

b It was stated that overall food consumption was calculated as a mean of means, and the performing laboratory did not statistically analyze these data.

* Significantly different from controls; $p \leq 0.05$

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3. **Water consumption:** No treatment-related effect was observed on water consumption in

either the P or F₁ generations. Water consumption was increased (\uparrow 16%; $p \leq 0.05$) during Weeks 4-5 in the 0.2 mg/kg/day P females during pre-mating; however, this increase was incidental and not dose-dependent. No other alterations were observed.

4. Test substance intake: Based on food consumption, body weight, and dietary analyses, test substance intakes of the P and F₁ generations during pre-mating are presented in Table 4. The mean pre-mating test substance intakes are considered representative of intakes for the study.

TABLE 4. Mean test substance intake during pre-mating (mg/kg body weight/day)^a

Generation	Dose Group (mg/kg/day)		
	0.2	1.0	6.5
Males			
P ^b	0.2	1.1	6.9
F ₁ ^b	0.2	1.1	7.0
Average ^b	0.2	1.1	7.0
Females			
P	0.2	1.0	6.9
F	0.2	1.1	6.9
Average ^b	0.2	1.1	6.9

a Data were obtained from pages 188-194 and 287-293 of the study report.

b Calculated by reviewers

4. Reproductive function

a. **Estrous cycle length:** No effects of treatment were observed on estrous cycle length in the P or F₁ females.

b. **Sperm measures:** No treatment-related effects were noted on sperm enumeration, motility, or morphology in the P or F₁ males.

c. **Ovarian follicle count:** No effects of treatment were observed on the number of growing or primordial follicles in the F₁ females.

5. Reproductive performance: There were no effects of treatment on the precoital or gestation intervals or on mating, fertility, or gestation indices in either generation (Tables 5a and b).

TABLE 5a. Reproductive performance - P generation^a

Observation	Dose Group (mg/kg/day)			
	0	0.2	1.0	6.5
F_{1a} Litter				
Number mated	25	25	25	25
Female mating index (%)	100	100	100	100
Female fertility index (%)	84	96	100	92
Male mating index (%)	100	100	100	100
Male fertility index (%)	84	96	100	92
Precoital interval (mean±SD days)	2.6±1.19	2.6±1.23	2.6±1.22	2.5±1.39
Days 1-4 (%)	100	100	100	96
Days 5-8 (%)	0	0	0	4
Gestation index (%)	100	100	100	100
Duration of gestation (mean±SD days)	21.9±0.30	22.0±0.36	22.0±0.41	22.0±0.47
Females with stillborn pups	2	3	3	3
F_{1b} Litter				
Number mated	25	25	25	25
Female mating index (%)	100	100	100	100
Female fertility index (%)	96	88	84	100
Male mating index (%)	100	100	100	100
Male fertility index (%)	96	88	84	100
Precoital interval (mean±SD days)	2.5±1.12	2.4±1.04	2.5±0.92	2.4±1.19
Days 1-4 (%)	100	100	100	100
Days 5-8 (%)	0	0	0	0
Gestation index (%)	100	100	100	100
Duration of gestation (mean±SD days)	21.8±0.48	21.7±0.48	21.7±0.48	21.8±0.78
Females with stillborn pups	1	1	1	0

^a Data were obtained from pages 196-197 and 199-202 of the study report.

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TABLE 5b. Reproductive performance - F₁ generation^a

Observation	Dose Group (mg/kg/day)			
	0	0.2	1.0	6.5
F_{2a} Litter				
Number males mated	25	25	24	24
Number females mated	24	25	25	25
Female mating index (%)	96	100	100	100
Female fertility index (%)	92	96	96	100
Male mating index (%)	96	100	100	100
Male fertility index (%)	88	96	96	100
Precoital interval (mean±SD days)	2.1±1.03	2.2±1.22	2.8±1.34	2.8±1.38
Days 1-4 (%)	100	100	92	96
Days 5-8 (%)	0	0	8	4
Gestation index (%)	100	100	100	100
Duration of gestation (mean±SD days)	21.9±0.43	22.0±0.29	21.9±0.58	22.0±0.41
Females with stillborn pups	0	2	2	1
F_{2b} Litter				
Number males mated	25	25	24	24
Number females mated	23	25	25	25
Female mating index (%)	92	100	100	100
Female fertility index (%)	96	100	88	100
Male mating index (%)	92	100	100	100
Male fertility index (%)	88	100	88	100
Precoital interval (mean±SD days)	2.3±1.15	3.0±1.17	2.2±1.25	2.3±1.07
Days 1-4 (%)	100	100	96	100
Days 5-8 (%)	0	0	4	0
Gestation index (%)	100	96	100	100
Duration of gestation (mean±SD days)	21.7±0.55	21.9±0.70	21.8±0.50	21.8±0.50
Females with stillborn pups	1	1	3	4

a Data were obtained from pages 295-296 and 298-301 of the study report.

6. Cholinesterase activity: Cholinesterase activity data are presented in Tables 6a and b. In the 6.5 mg/kg/day P and F₁ generations of both sexes, erythrocyte cholinesterase activity was decreased ($p \leq 0.002$) during pre-mating (↓26-46%) and at termination (↓37-60%). Also, at this dose, decreases in brain cholinesterase activity in both sexes (↓52-69%; $p \leq 0.002$) and serum cholinesterase activity in females (↓18-21%, $p \leq 0.05-0.002$) were observed. At 1.0 mg/kg/day, decreases ($p \leq 0.05-0.002$) were observed in brain cholinesterase activity in both sexes (↓13-20%). Also, at 1.0 mg/kg/day, decreases ($p \leq 0.05-0.02$) were observed in erythrocyte cholinesterase

activity in males (16-10%).

TABLE 6a. Cholinesterase activities ($\mu\text{kat/L}$) - P and F₁ generation males^a

Measurement	Dose Group (mg/kg/day)			
	0	0.2	1.0	6.5
P Generation				
Serum (before dosing)	13.47±2.15	13.72±2.30	13.59±1.57	13.90±2.19
Serum (pre-mating)	10.45±1.29	10.99±1.78	11.68±1.71** (112)	10.43±1.72
Serum (termination)	11.18±1.19	12.09±1.89	12.37±2.06** (111)	10.87±20.4
Erythrocyte (before dosing)	30.44±3.55	28.77±4.24	29.24±3.81	30.06±3.00
Erythrocyte (pre-mating)	31.62±4.28	32.55±4.38	29.64±4.34	23.45±3.97*** (126)
Erythrocyte (termination)	34.72±4.26	33.03±4.70	31.75±4.11** (19)	22.02±4.96*** (137)
Brain (termination)	2.26±0.92	2.26±0.93	1.80±0.74* (120)	1.09±0.57*** (152)
F₁ Generation				
Serum (pre-mating)	10.56±1.87	11.45±2.10	11.16±1.36	10.10±1.72
Serum (termination)	11.78±2.48	12.63±2.25	12.47±1.79	10.95±2.25
Erythrocyte (pre-mating)	32.36±3.45	31.80±3.12	30.41±4.34* (16)	20.77±4.32*** (136)
Erythrocyte (termination)	36.83±5.23	34.34±4.88	33.09±4.23** (110)	20.63±5.72*** (144)
Brain (termination)	1.68±0.45	1.66±0.63	1.47±0.48** (113)	0.70±0.21*** (158)

^a Data were obtained from pages 336-343 and 346-351 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

* Significantly different from controls; $p \leq 0.05$ ** Significantly different from controls; $p \leq 0.02$

*** Significantly different from controls; $p \leq 0.002$

TABLE 6b. Cholinesterase activities ($\mu\text{kat/L}$) - P and F₁ generation females^a

Measurement	Dose Group (mg/kg/day)			
	0	0.2	1.0	6.5
P Generation				
Serum (before dosing)	16.97±3.03	16.88±3.20	16.72±2.90	17.74±3.67
Serum (pre-mating)	58.24±15.19	54.69±16.24	53.40±14.73	51.35±13.42
Serum (termination)	46.41±10.40	43.34±9.49	42.69±15.83	36.56±8.64*** (121)
Erythrocyte (before dosing)	32.44±4.78	31.18±4.19	32.32±5.05	33.02±3.70
Erythrocyte (pre-mating)	32.17±4.61	32.41±3.46	30.06±3.70	17.38±2.78*** (146)
Erythrocyte (termination)	32.00±5.45	33.10±4.49	29.83±5.00	12.88±3.15*** (160)
Brain (termination)	2.46±0.79	2.66±1.16	2.03±0.82* (117)	0.76±0.25*** (169)
F₁ Generation				
Serum (pre-mating)	43.46±15.11	44.30±12.79	46.23±13.92	41.45±10.11
Serum (termination)	41.94±13.20	41.74±8.64	41.73±15.76	34.31±11.15* (118)
Erythrocyte (pre-mating)	31.46±4.84	32.92±3.63	31.38±4.52	20.08±4.09*** (136)
Erythrocyte (termination)	31.82±5.05	32.00±4.67	30.38±3.83	13.36±3.13*** (158)
Brain (termination)	1.62±0.33	1.46±0.26	1.30±0.23*** (120)	0.52±0.11*** (168)

^a Data were obtained from pages 336-343 and 346-351 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

* Significantly different from controls; $p \leq 0.05$ ** Significantly different from controls; $p \leq 0.02$

*** Significantly different from controls; $p \leq 0.002$

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7. Postmortem results

a) **Organ weights:** Organ weight data are presented in Table 7. There were no differences from controls in absolute or relative (to body) organ weights in the P generation. In the F₁ generation 6.5 mg/kg/day males, absolute prostate weights ($\downarrow 16\%$, $p \leq 0.01$) and relative prostate weights ($\downarrow 12\%$, $p \leq 0.05$) were decreased. No other treatment-related effects were observed on organ weights. The following alterations ($p \leq 0.05$) in organ weight were observed in the F₁ generation but were minor, not dose-dependent, and/or not corroborated by pathological findings: i) absolute pituitary gland weights were decreased in the 6.5 mg/kg/day F₁ males; ii) absolute and relative pituitary gland weights were increased in the ≥ 0.2 mg/kg/day females ($\uparrow 12-20\%$); iii) absolute and relative thyroid gland weights were increased in the 0.2 and 1.0 mg/kg/day females ($\uparrow 27-33\%$); and iv) absolute adrenal gland weights were increased in the 0.2 mg/kg/day females ($\uparrow 9\%$).

TABLE 7. Selected absolute and relative (to body) organ weights - F₁ generation^a

Organ weight	Dose (mg/kg/day)			
	0	0.2	1.0	6.5
Males				
Terminal body weight	442.056±35.880	443.644±33.969	451.096±32.147	429.229±48.868
Prostate				
absolute (g)	1.151±0.212	1.134±0.130	1.080±0.205	0.965±0.163** ($\downarrow 16$)
relative (to body, %)	0.260±0.044	0.257±0.031	0.240±0.046	0.228±0.051* ($\downarrow 12$)
Pituitary				
absolute (mg)	9.880±1.453	9.240±1.268	9.783±1.506	8.875±1.393* ($\downarrow 10$)
relative (to body, %)	0.002±0.0	0.002±0.0	0.002±0.0	0.002±0.0
Females				
Terminal body weight	244.508±23.231	250.828±17.661	256.45±15.200	248.325±26.142
Pituitary gland				
absolute (mg)	12.360±2.119	14.440±1.710** ($\uparrow 17$)	14.625±1.861** ($\uparrow 18$)	13.792±1.769* ($\uparrow 12$)
relative (to body, %)	0.005±0.001	0.006±0.001** ($\uparrow 20$)	0.006±0.001** ($\uparrow 20$)	0.006±0.001** ($\uparrow 20$)
Thyroid gland				
absolute (mg)	16.880±3.528	21.440±3.343** ($\uparrow 27$)	22.500±3.683** ($\uparrow 33$)	18.958±3.043
relative (to body, %)	0.007±0.001	0.009±0.001** ($\uparrow 29$)	0.009±0.001** ($\uparrow 29$)	0.008±0.001
Adrenal gland				
absolute (mg)	72.720±9.396	79.080±9.708* ($\uparrow 9$)	76.583±8.949	72.292±9.778
relative (to body, %)	0.030±0.004	0.032±0.004	0.030±0.004	0.029±0.004

a Data were obtained from pages 362-365 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

* Significantly different from controls; $p \leq 0.05$

** Significantly different from controls; $p \leq 0.01$

b) **Pathology**

- 1) **Macroscopic examination:** No treatment-related findings were observed.
- 2) **Microscopic examination:** Microscopic findings are presented in Table 8. At 6.5 mg/kg/day, focal vacuolization of the epididymides was observed in the P (7/25; minimal to moderate) and F₁ (13/25; slight to severe) males, both compared to controls. Also, the following were increased in incidence and/or severity in the 6.5 mg/kg/day F₁ males: i) slight to severe vacuolization of the cauda epididymides (6/25) compared to controls (4/25; minimal to slight); ii) slight to severe reduced secretion of the dorso-lateral prostate gland (19/25) compared to controls (12/25; minimal to moderate); and iii) moderate to severe diffuse epithelial atrophy of the dorso-lateral prostate gland (15/25) compared to controls (7/25). All other microscopic findings were incidental or similar in number and severity to controls.

B. OFFSPRING

1. **Viability and clinical signs:** Litter data for the F₁ and F₂ pups are presented in Tables 9a and b, respectively. There were no effects of treatment on the survival, live birth, viability, or lactation indices or on the sex ratio in any generation. The decreased ($p \leq 0.05$) viability index of the F_{1b} litter was attributed to a single litter in which 6 of 8 pups died/were cannibalized on PND 1, and was not considered treatment-related. The decreased ($p \leq 0.01$) lactation index of the F_{2b} litter was attributed to a single litter in which 10 of 10 pups were not properly nursed on PND 4-5, and were cannibalized by the dam on PND 4-6. This finding was also not considered treatment-related. No clinical signs of toxicity were observed in either generation.

TABLE 8. Selected microscopic pathology findings (# animals affected) - P and F₁ generation males^a

Finding	Dose (mg/kg/day)			
	0	0.2	1.0	6.5
P Generation				
Epididymides				
focal vacuolization (total)	0	0	0	7
minimal	0	0	0	1
slight	0	0	0	1
moderate	0	0	0	5
F₁ Generation				
Epididymides				
focal vacuolization (total)	0	0	0	13
slight	0	0	0	8
moderate	0	0	0	4
severe	0	0	0	1
Cauda epididymides				
vacuolization (total)	4	6	3	6
minimal	2	5	2	0
slight	2	1	1	5
severe	0	0	0	1
Prostate gland (dorso-lateral)				
reduced secretion (total)	12	14	15	19
minimal	1	3	0	0
slight	7	5	8	6
moderate	4	4	7	6
severe	0	2	0	7
diffuse epithelial atrophy (total)	7	4	2	15
moderate	6	2	1	9
severe	1	2	1	6

^a Data were obtained from pages 359 and 368-369 of the study report. n=25

TABLE 9a. Litter parameters - F₁ litters^a

Observation	Dose Group (mg/kg/day)				
	0	0.2	1.0	6.5	
F_{1a} Generation					
Mean (±SD) implantation sites	NA	NA	NA	NA	
Number born live	206	244	259	235	
Number born dead	2	3	5	3	
Mean sex ratio (% live ♂) on Day 0	53.9	48.8	49.8	52.3	
# Deaths Days 1-4	0	1	0	3	
# Deaths Days 5-21	1	0	0	0	
Mean (±SD) litter size	Day 0	9.8±1.89	10.2±2.82	10.4±1.60	10.2±1.76
	Day 4 ^b	9.8±1.89	10.1±2.77	10.3±1.59	10.1±1.78
	Day 4 ^c	7.9±0.48	7.5±1.35	8.0±0.00	8.0±0.21
	Day 7	7.9±0.48	7.5±1.35	8.0±0.00	8.0±0.21
	Day 14	7.8±0.51	7.5±1.35	8.0±0.00	8.0±0.21
	Day 21	7.8±0.51	7.5±1.35	8.0±0.00	7.9±0.46
Post-implantation survival (%)	NA	NA	NA	NA	
Live birth index (%)	99	99	98	99	
Viability (Days 0-4) index (%)	100	100	99	99	
Lactation (Days 4-21) index (%)	99	100	100	99	
F_{1b} Generation					
Mean (±SD) implantation sites	NA	NA	NA	NA	
Number born live	262	232	244	251	
Number born dead	1	1	1	0	
Mean sex ratio (% live ♂) on Day 0	54.6	50.4	49.6	47.4	
# Deaths Days 1-4	1	1	1	10	
# Deaths Days 5-21	1	0	0	0	
Mean (±SD) litter size	Day 0	10.9±2.55	10.5±2.06	11.6±2.25	10.0±3.06
	Day 4 ^b	10.8±2.57	10.5±2.11	11.6±2.20	9.6±3.43
	Day 4 ^c	7.7±0.91	7.9±0.29	8.0±0.22	7.2±2.11
	Day 7	7.7±0.91	7.9±0.29	8.0±0.22	7.2±2.11
	Day 14	7.7±0.91	7.9±0.29	8.0±0.22	7.2±2.11
	Day 21	7.7±0.92	7.9±0.29	8.0±0.22	7.2±2.11
Post-implantation survival (%)	NA	NA	NA	NA	
Live birth index (%)	100	100	100	100	
Viability (Days 1-4) index (%)	99	100	100	96*	
Lactation (Days 4-21) index (%)	99	100	100	100	

^a Data were obtained from pages 200 and 202-208 of the study report.

^b Before standardization (culling)

^c After standardization (culling)

* Significantly different from controls; $p \leq 0.05$

NA Not applicable. The performing laboratory stated that while the uteri were stained and examined for implantations, summary data of the number of implantations were not provided as it would be impossible to determine with certainty if rudiments of implantations belonged to the first or second litter.

TABLE 9b. Litter parameters - F₂ litters^a

Observation	Dose Group (mg/kg/day)			
	0	0.2	1.0	6.5
F_{2a} Generation				
Mean (±SD) implantation sites	NA	NA	NA	NA
Number born live	247	251	281	261
Number born dead	0	2	2	3
Mean sex ratio (% live ♂) on Day 0	46.2	48.6	49.1	48.3
# Deaths Days 1-4	8	7	5	1
# Deaths Days 5-21	1	0	1	0
Mean (±SD) litter size				
Day 0	11.2±1.90	10.5±3.11	11.7±1.76	10.4±2.43
Day 4 ^b	10.9±2.14	10.1±3.33	11.5±1.98	10.4±2.38
Day 4 ^c	8.0±0.21	7.3±1.95	7.8±0.82	7.9±0.33
Day 7	7.9±0.29	7.3±1.95	7.8±0.82	7.9±0.33
Day 14	7.9±0.29	7.3±1.95	7.8±0.83	7.9±0.33
Day 21	7.9±0.29	7.3±1.95	7.8±0.83	7.9±0.33
Post-implantation survival (%)	NA	NA	NA	NA
Live birth index (%)	100	99	99	99
Viability (Days 0-4) index (%)	97	97	98	100
Lactation (Days 4-21) index (%)	99	100	99	100
F_{2b} Generation				
Mean (±SD) implantation sites	NA	NA	NA	NA
Number born live	256	285	248	265
Number born dead	1	5	3	5
Mean sex ratio (% live ♂) on Day 0	49.6	48.4	48.8	49.1
# Deaths Days 1-4	7	4	3	6
# Deaths Days 5-21	0	3	1	12
Mean (±SD) litter size				
Day 0	11.6±1.53	11.4±3.23	11.3±2.00	10.6±2.12
Day 4 ^b	11.2±1.41	11.2±3.22	11.1±2.03	10.4±2.10
Day 4 ^c	8.0±0.00	7.6±1.63	7.9±0.43	7.8±0.47
Day 7	8.0±0.00	7.6±1.69	7.9±0.47	7.4±1.76
Day 14	8.0±0.00	7.5±1.69	7.9±0.47	7.4±1.75
Day 21	8.0±0.00	7.5±1.69	7.9±0.47	7.4±1.75
Post-implantation survival (%)	NA	NA	NA	NA
Live birth index (%)	100	98	99	98
Viability (Days 1-4) index (%)	96	99	99	98
Lactation (Days 4-21) index (%)	100	98	99	94**

a Data were obtained from pages 299 and 301-307 of the study report.

b Before standardization (culling)

c After standardization (culling)

** Significantly different from controls; $p \leq 0.01$

NA Not applicable. The performing laboratory stated that while the uteri were stained and examined for implantations, summary data of the number of implantations were not provided as it would be impossible to determine with certainty if rudiments of implantations belonged to the first or second litter.

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2. **Body weight:** Mean pup body weight data are presented in Tables 10a and b. Body weight gains (Days 4-21) were decreased ($p \leq 0.05$) in the 6.5 mg/kg/day F_{1b} pups of both sexes ($\downarrow 7\%$). No other effects of treatment were observed on body weight gains. Body weights were generally increased ($p \leq 0.05$) in the 1.0 mg/kg/day F_{2b} pups of both sexes, but this finding was not dose-dependent. Other differences ($p \leq 0.05$) were sporadic and not related to treatment. Litter weights were not provided.

TABLE 10a. Mean (\pm SD) male pup weights (g)^a

PND	Dose Group (mg/kg/day)			
	0	0.2	1.0	6.5
F_{1a} Pups				
1	6.6 \pm 0.50	6.6 \pm 0.63	6.7 \pm 0.70	6.5 \pm 0.61
4 ^b	9.9 \pm 0.81	9.6 \pm 1.47	10.0 \pm 1.22	9.7 \pm 1.12
4 ^c	9.9 \pm 0.84	9.5 \pm 1.48	9.9 \pm 1.19	9.7 \pm 1.13
7	15.3 \pm 1.03	15.1 \pm 1.67	15.2 \pm 1.51	14.9 \pm 1.51
14	29.9 \pm 1.52	29.8 \pm 2.78	29.9 \pm 2.35	28.7 \pm 2.45
21	48.0 \pm 2.56	48.2 \pm 4.17	48.6 \pm 3.63	46.3 \pm 4.36
Gain (Days 4-21)	38.1 \pm 2.24	38.6 \pm 3.49	38.7 \pm 2.89	36.6 \pm 3.66
F_{1b} Pups				
1	6.5 \pm 0.65	6.6 \pm 0.63	6.5 \pm 0.64	6.3 \pm 0.78
4 ^b	9.6 \pm 1.21	9.7 \pm 1.06	9.5 \pm 1.10	9.3 \pm 1.29
4 ^c	9.7 \pm 1.19	9.7 \pm 1.01	9.5 \pm 1.09	9.3 \pm 1.24
7	15.2 \pm 1.59	15.2 \pm 1.58	15.0 \pm 1.66	14.3 \pm 2.12
14	31.2 \pm 3.20	31.3 \pm 3.01	31.3 \pm 2.43	29.5 \pm 3.37
21	50.6 \pm 4.91	51.1 \pm 4.62	50.7 \pm 3.47	47.4 \pm 5.41
Gain (Days 4-21)	40.9 \pm 4.11	41.4 \pm 3.92	41.2 \pm 2.79	38.1 \pm 4.47* (17)
F_{2a} Pups				
1	6.2 \pm 0.54	6.4 \pm 0.53	6.4 \pm 0.55	6.6 \pm 0.82
4 ^b	9.1 \pm 1.10	9.5 \pm 1.04	9.5 \pm 1.04	9.8 \pm 1.53
4 ^c	9.2 \pm 1.09	9.5 \pm 1.06	9.5 \pm 1.03	9.8 \pm 1.54
7	14.3 \pm 1.74	14.9 \pm 1.64	15.1 \pm 1.66	14.9 \pm 2.18
14	28.9 \pm 3.14	30.4 \pm 2.58	31.2 \pm 2.32* (18)	30.2 \pm 3.13
21	47.0 \pm 4.98	49.2 \pm 3.95	49.6 \pm 3.30	48.2 \pm 5.01
Gain (Days 4-21)	37.9 \pm 4.16	39.7 \pm 3.50	40.2 \pm 2.96	38.4 \pm 3.89
F_{2b} Pups				
1	6.1 \pm 0.57	6.2 \pm 0.51	6.6 \pm 0.63* (18)	6.4 \pm 0.57
4 ^b	9.0 \pm 1.05	9.3 \pm 0.88	9.8 \pm 0.81	9.5 \pm 1.46
4 ^c	9.1 \pm 1.02	9.3 \pm 0.85	9.9 \pm 0.80* (19)	9.6 \pm 1.47
7	14.4 \pm 1.70	14.8 \pm 1.23	15.7 \pm 1.04* (19)	15.3 \pm 2.00
14	29.9 \pm 2.62	31.5 \pm 2.14	32.8 \pm 2.26** (110)	31.5 \pm 3.99
21	48.8 \pm 4.02	51.3 \pm 3.90	52.5 \pm 3.47* (18)	50.4 \pm 6.37
Gain (Days 4-21)	39.8 \pm 3.23	42.0 \pm 3.53	42.7 \pm 3.36	40.7 \pm 5.64

a Data were obtained from pages 209-216 and 308-315 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

b Before standardization (culling)

c After standardization (culling)

* Significantly different from controls; $p \leq 0.05$

** Significantly different from controls; $p \leq 0.01$

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TABLE 10b. Mean (\pm SD) female pup weights (g)^a

PND	Dose Group (mg/kg/day)			
	0	0.2	1.0	6.5
F_{1a} Pups				
1	6.3 \pm 0.57	6.3 \pm 0.60	6.5 \pm 0.62	6.3 \pm 0.61
4 ^b	9.7 \pm 0.92	9.3 \pm 1.17	9.6 \pm 1.16	9.5 \pm 1.12
4 ^c	9.7 \pm 0.93	9.4 \pm 1.19	9.7 \pm 1.15	9.5 \pm 1.16
7	14.9 \pm 1.17	14.6 \pm 1.65	14.9 \pm 1.44	14.4 \pm 1.47
14	29.4 \pm 1.75	29.0 \pm 2.84	29.3 \pm 2.24	28.1 \pm 2.41
21	46.6 \pm 2.78	46.4 \pm 4.03	47.1 \pm 3.58	44.9 \pm 3.97
Gain (Days 4-21)	36.9 \pm 2.34	37.0 \pm 3.14	37.5 \pm 2.88	35.4 \pm 3.28
F_{1b} Pups				
1	6.2 \pm 0.55	6.2 \pm 0.58	6.1 \pm 0.65	6.0 \pm 0.69
4 ^b	9.2 \pm 1.04	9.3 \pm 1.08	9.1 \pm 1.23	8.9 \pm 1.25
4 ^c	9.3 \pm 1.05	9.3 \pm 1.04	9.2 \pm 1.25	8.9 \pm 1.27
7	14.5 \pm 1.36	14.5 \pm 1.53	14.4 \pm 1.87	13.6 \pm 2.07
14	30.4 \pm 2.81	30.5 \pm 2.82	30.3 \pm 2.76	28.7 \pm 3.31
21	48.7 \pm 4.15	49.2 \pm 4.30	48.8 \pm 3.76	45.8 \pm 5.17
Gain (Days 4-21)	39.5 \pm 3.45	39.9 \pm 3.50	39.7 \pm 2.82	36.8 \pm 4.17* (17)
F_{2a} Pups				
1	5.9 \pm 0.62	6.1 \pm 0.45	6.1 \pm 0.53	6.3 \pm 0.71* (17)
4 ^b	8.8 \pm 1.25	9.2 \pm 1.01	9.1 \pm 1.04	9.5 \pm 1.36
4 ^c	8.8 \pm 1.26	9.3 \pm 0.99	9.0 \pm 1.01	9.5 \pm 1.36
7	13.6 \pm 1.81	14.6 \pm 1.46	14.2 \pm 1.50	14.6 \pm 1.94
14	27.9 \pm 3.07	29.8 \pm 2.22* (17)	29.8 \pm 2.15* (17)	29.6 \pm 2.79
21	45.1 \pm 4.95	47.5 \pm 2.50	47.3 \pm 3.20	46.8 \pm 4.38
Gain (Days 4-21)	36.2 \pm 3.98	38.2 \pm 2.10	38.2 \pm 2.61	37.3 \pm 3.51
F_{2b} Pups				
1	5.7 \pm 0.53	5.9 \pm 0.53	6.2 \pm 0.57** (19)	6.0 \pm 0.51
4 ^b	8.6 \pm 0.95	8.7 \pm 0.87	9.4 \pm 0.69* (19)	9.0 \pm 1.37
4 ^c	8.6 \pm 0.94	8.7 \pm 0.90	9.4 \pm 0.72* (19)	9.0 \pm 1.31
7	13.7 \pm 1.57	13.8 \pm 1.25	15.0 \pm 0.93* (19)	14.4 \pm 1.80
14	28.8 \pm 2.58	29.9 \pm 2.21	31.4 \pm 1.94** (19)	30.0 \pm 3.84
21	46.5 \pm 3.74	47.5 \pm 3.23	49.8 \pm 3.32* (17)	47.6 \pm 5.97
Gain (Days 4-21)	38.0 \pm 3.17	38.8 \pm 2.79	40.4 \pm 3.18	38.4 \pm 5.61

a Data were obtained from pages 209-216 and 308-315 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

b Before standardization (culling)

c After standardization (culling)

* Significantly different from controls; $p \leq 0.05$

** Significantly different from controls; $p \leq 0.01$

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3. **Sexual maturation (F₁):** No effects of treatment were observed on age or body weight at preputial separation or vaginal patency.

4. **Offspring postmortem results**

a) **Organ weights:** No treatment-related effects were observed on organ weights. In the F_{2b} pups, absolute thymus weights were increased ($p \leq 0.05$) in the 1.0 mg/kg/day males ($\uparrow 13\%$) and males and females when combined ($\uparrow 11\%$), but this effect was not dose-dependent. Additionally, in pups culled on PND 4, relative (to body) brain weights were decreased ($p \leq 0.05$) in the 6.5 mg/kg/day females ($\downarrow 10\%$) and males and females when combined ($\downarrow 8\%$). This decrease was not observed in pups on PND 21; therefore, this finding was considered incidental.

b) **Pathology**

1) **Cholinesterase activity:** Brain cholinesterase activity was measured in the controls and 6.5 mg/kg/day groups only. The results (Table 11) indicated that brain cholinesterase activity in 6.5 mg/kg/day F_{1b} female pups culled on PND 4 was slightly decreased ($\downarrow 10\%$; $p \leq 0.02$). However, no effect was seen in F_{1b} generation PND 4 pups of both sexes and F_{2b} generation PND 4 pups of males.

TABLE 11. Brain cholinesterase activities ($\mu\text{kat/L}$) - F_{1b} and F_{2b} pups^a

Pup generation	Dose Group (mg/kg/day)			
	Males		Females	
	0	6.5	0	6.5
F _{1b}	1.07±0.08	1.03±0.09	1.12±0.08	1.02±0.10** ($\downarrow 10$)
F _{2b}	1.23±0.12	1.16±0.21	1.24±0.16	1.15±0.22

a Data were obtained from pages 344-345 and 352-353 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

** Significantly different from controls; $p \leq 0.02$

2) **Macroscopic examination:** There were no treatment-related gross pathological findings in the F₁ or F₂ pups (Table 12). In the F_{1a} litters, hemorrhagic thymus was observed in the 0.2 (1.0% fetuses; 8.7% litters), 1.0 (0.9% fetuses; 4.0% litters), and 6.5 (1.6% fetuses; 8.7% litters) mg/kg/day groups compared to 0 concurrent controls. However, this finding fell within the range of historical controls (0.0-8.9% fetuses; 0.0-28.0% litters). Hydroureter was noted in the 1.0 (0.4% fetuses; 4.2% litters) and 6.5 (0.4% fetuses; 4.0% litters) mg/kg/day groups compared to 0 concurrent controls. However, these findings fell within the range of historical controls (0.0-0.4% fetuses; 0.0-4.5% litters). The following findings were increased at 6.5 mg/kg/day over concurrent controls, but did not achieve statistical significance and were considered minor and incidental: i) misshapen spleen (0.5% fetuses; 4.3% litters); ii) enlarged eye bulge (0.4% fetuses; 4.0% litters); iii) kinked tail (0.8% fetuses; 8.0% litters); and iv) diaphragmatic hernia in the 0.2

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(0.4% fetuses; 4.3% litters) and 6.5 (0.8% fetuses; 8.0% litters) mg/kg/day groups. The following findings were increased at 6.5 mg/kg/day over concurrent controls, but fell within the range of historical controls: i) empty stomach (1.6% fetuses; 8.0% litters); ii) malpositioned testes (0.4% fetuses; 4.0% litters); and iii) small testes in the 0.2 (0.3% fetuses; 4.0% litters) and 6.5 (0.4% fetuses; 4.0% litters) mg/kg/day groups. In the F_{2a} litters, macroglossia was noted in the 6.5 mg/kg/day group (1.1% fetuses; 4.0% litters), and cleft palate was observed in the 0.2 (0.4% fetuses; 4.3% litters) and 6.5 (1.1% fetuses; 4.0% litters) mg/kg/day groups, both compared to 0 concurrent and historical controls. These findings occurred in the same 3 pups from a single litter at the high dose, and did not achieve statistical significance; therefore, they were considered incidental. Pale-yellowish liver was observed in the 6.5 mg/kg/day group compared to 0 concurrent and historical controls; however, it was unclear if this finding was adverse.

TABLE 12. Selected macroscopic findings (% fetuses affected [% litters affected])^a

Finding	Dose Group (mg/kg/day)				Historical controls
	0	0.2	1.0	6.5	
F_{1a} Litters					
Pups (litters) evaluated	157 (21)	193 (23)	212 (25)	186 (23)	5757 (593)
Hemorrhagic thymus	0 (0)	1.0 (8.7)	0.9 (4.0)	1.6 (8.7)	0.0-8.9 (0.0-28.0)
Misshapen spleen	0 (0)	0 (0)	0 (0)	0.5 (4.3)	0.0-0.4 (0.0-4.2)
F_{1b} Litters					
Pups (litters) evaluated	263 (24)	232 (22)	245 (21)	247 (25)	5757 (593)
Enlarged eye bulge	0 (0)	0 (0)	0 (0)	0.4 (4.0)	Not observed
Empty stomach	0 (0)	0 (0)	0 (0)	1.6 (8.0)	0.0-1.6 (0.0-4.3)
Kinked tail	0 (0)	0 (0)	0 (0)	0.8 (8.0)	0.0-0.4 (0.0-4.5)
F_{2a} Litters					
Pups (litters) evaluated	240 (22)	248 (23)	276 (24)	263 (25)	5757 (593)
Macroglossia	0 (0)	0 (0)	0 (0)	1.1 (4.0)	Not observed
Cleft palate	0 (0)	0.4 (4.3)	0 (0)	1.1 (4.0)	Not observed
Diaphragmatic hernia	0 (0)	0.4 (4.3)	0 (0)	0.8 (8.0)	0.0-0.5 (0.0-4.2)
Pale-yellowish liver	0 (0)	0 (0)	0 (0)	1.5 (8.0)	Not observed
Hydroureter	0 (0)	0 (0)	0.4 (4.2)	0.4 (4.0)	0.0-0.4 (0.0-4.5)
F_{2b} Litters					
Pups (litters) evaluated	249 (22)	287 (25)	248 (22)	258 (25)	5757 (593)
Empty stomach	0 (0)	0 (0)	0 (0)	1.2 (4.0)	0.0-1.6 (0.0-4.3)
Malpositioned testes	0 (0)	0 (0)	0 (0)	0.4 (4.0)	0.0-0.4 (0.0-4.2)
Small testes	0 (0)	0.3 (4.0)	0 (0)	0.4 (4.0)	0.0-0.5 (0.0-4.5)

^a Data were obtained from pages 225-232, 324-335, and 1558-1560 of the study report.

3) **Microscopic examination:** Microscopic examinations were not performed.

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III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: Under the conditions of this study, Dimethoate did not influence reproductive performance or fertility of the P or F₁ parents. Signs of systemic parental toxicity occurred exclusively at 6.5 mg/kg/day. No substance-induced signs of developmental toxicity at any dose level in any of the progeny.

B. REVIEWER COMMENTS

1. PARENTAL ANIMALS: There were no unscheduled deaths in the P generation parents. In the F₁ parents, two males and one female in the 1.0 mg/kg/day group and one 6.5 mg/kg/day male were found dead. Additionally, one 6.5 mg/kg/day female was found in moribund condition and was killed. None of these deaths were considered to be related to treatment.

In the parental animals, no treatment-related effects were observed on survival, clinical signs, or food or water consumption.

At 6.5 mg/kg/day, overall (LD 1-21) body weight gains were decreased in the F₁ females during lactation of both the F_{2a} (↓18%; not significant [NS]) and F_{2b} (↓60%; p≤0.05) litters. In P and F₁ parents, erythrocyte cholinesterase activity was decreased (p≤0.002) during pre-mating (↓26-46%) and at termination (↓37-60%). Also, at this dose, decreases in brain cholinesterase activity in both sexes (↓52-69%; p≤0.002) and serum cholinesterase activity in females (↓18-21%, p≤0.05-0.002) were observed. In the F₁ males, absolute and relative (to body) prostate weights were decreased (↓12-16%; p≤0.05-0.01). Focal vacuolization of the epididymides was observed in the P (7/25; minimal to moderate) and F₁ (13/25; slight to severe) males, both compared to controls. Also, the following were observed in the F₁ males compared to controls: i) slight to severe vacuolization of the cauda epididymides (6/25); ii) slight to severe reduced secretion of the dorso-lateral prostate gland (19/25); and iii) moderate to severe diffuse epithelial atrophy of the dorso-lateral prostate gland (15/25). However, reproductive performance was unaffected.

At 1.0 mg/kg/day, decreases (↓13-20%; p≤0.05-0.002) were observed in brain cholinesterase activity in both sexes of P and F₁ generations. Decreases (↓6-10%; p≤0.05-0.02) in erythrocyte cholinesterase activity were also seen in males of P and F₁ generations during pre-mating and at termination.

At 0.2 mg/kg/day, no compound related effects were seen in the parental animals.

The LOAEL for parental toxicity was 1.0 mg/kg/day, based on decreased erythrocyte (in males) and brain cholinesterase activity (in both sexes). The NOAEL was 0.2 mg/kg/day.

2. OFFSPRING: In the offspring, no treatment-related effects were observed on survival, live birth, viability, or lactation indices, on the sex ratio, clinical signs, body weight, sexual

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maturation, organ weights, or gross pathology.

Body weight gains were decreased ($p \leq 0.05$) in the 6.5 mg/kg/day F_{1a} pups (17%). Brain cholinesterase activity was measured in the controls and 6.5 mg/kg/day groups only. Brain cholinesterase activity in 6.5 mg/kg/day F_{1b} female pups culled on PND 4 was slightly decreased (110%; $p \leq 0.02$). However, no effect was seen in F_{1b} generation PND 4 pups of both sexes and F_{2b} generation PND 4 male pups.

The LOAEL for offspring toxicity was 6.5 mg/kg/day, based on decreased brain cholinesterase activity in female pups culled on PND 4. The NOAEL was not determined.

The reproductive parameters measured were not affected by dimethoate in both P and F_1 generations. **The NOAEL for reproductive effects was 6.5 mg/kg/day (HDT).**

This study is classified as **acceptable/guideline** and satisfies the Guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

C. STUDY DEFICIENCIES: No deficiencies were noted.

DATA FOR ENTRY INTO ISIS

Reproductive Study - rats (870.3800)

PC code	MRID	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg	Doses tested mg/kg	NOAEL mg/kg	LOAEL mg/kg	Endpoints(s)	Comments
035001	46181001	reproductive	rats	2 generation	oral	diet	0.2-6.5	0, 0.2, 1.0, 6.5	1.0	6.5	BWG, ChEI; RBC, brain	Parental
035001	46181001	reproductive	rats	2 generation	oral	diet	0.2-6.5	0, 0.2, 1.0, 6.5	1.0	6.5	BWG	Offspring
035001	46181001	reproductive	rats	2 generation	oral	diet	0.2-6.5	0, 0.2, 1.0, 6.5	6.5	Not observed		Reproductive

APPENDIX

Pup Death Data from Dimethoate dietary reproductive toxicity study.

	live pups/ litters born	deaths* PND 0-4	deaths PND 4-11	deaths PND 4-21	total deaths PND 0-21	total pup deaths as % livebirth
F0/first mating						
control	206/21	0/0	1/1	1/1	1/1	0.5
0.2 mg/kg	244/24	1/1	0/0	0/0	1/1	0.4
1.0 mg/kg	259/25	2/2	0/0	0/0	2/2	0.7
6.5 mg/kg	235/23	3/3	0/0	0/0	3/3	1.3
F0/second mating						
control	262/24	2/2	0/0	1/1	3/3	1.1
0.2 mg/kg	232/22	1/1	0/0	0/0	1/1	0.4
1.0 mg/kg	244/21	1/1	0/0	0/0	1/1	0.4
6.5 mg/kg	251/25	10/4	0/0	0/0	10/4	4.0
F1/first mating						
control	247/22	8/3	1/1	1/1	9/4	3.6
0.2 mg/kg	251/24	8/6	0/0	0/0	8/6	3.2
1.0 mg/kg	281/24	5/4	1/1	1/1	6/5	2.1
6.5 mg/kg	261/25	1/1	0/0	0/0	1/1	0.4
F1/second mating						
control	256/22	9/7	0/0	0/0	9/7	3.5
0.2 mg/kg	285/25	4/4	2/2	3/3	7/6	2.5
1.0 mg/kg	248/22	3/2	1/1	1/1	4/2	1.6
6.5 mg/kg	265/25	6/5	11/3	12/4	18/6	6.8

*values represent total pup deaths/total litters with pup deaths

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