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DATA EVALUATION RECORD

STUDY TYPE: Reproduction and Fertility Effects Study –rat OPPTS 870.3800; OECD 416

PC CODE: 118601 **DP BARCODE:** D313366

TEST MATERIAL (PURITY): chlorsulfuron (97.6% a. i.)

SYNONYMS: DPX-W4189; Glean

CHEMICAL: 2-chloro-N-[[(4-methoxy-6-methyl-1, 3, 5-triazin-2-yl)amino]carbonyl] benzene sulfonamide; 1-(2-chlorophenylsulfonyl)-3-(4-methoxy-6-methyl-1, 3, 5-triazin-2-yl)urea

CITATION: Mylchreest, E. (2005) Chlorsulfuron (DPX-W4189) Technical: Multigeneration Reproduction Study in Rats. DuPont Haskell Laboratory for Health and Environmental; Sciences. Project No. DUPONT.13495, 14601, 904. September 11, 2003 – June 4, 2004. MRID 46493201. Unpublished

SPONSOR: E. I. du Pont de Nemours and CO., Inc.

EXECUTIVE SUMMARY: In a 2-generation reproduction study (MRID 46493201*)*, chlorsulfuron (97.6%; Batch # DPX-W4189-723) was administered to 30 Crl:CD®(SD)IGS BR rats/sex/dose *via* the diet at dose levels of 0, 100, 500, 2500, or 7500 ppm [equivalent to 0, 6, 30,151, 456 mg/kg/day (males)/ 0, 7, 39, 188, 591 mg/kg/day (females)] throughout the 10-week premating period and through gestation/lactation. There was one set of litters per generation.

There were no treatment-related effects on survival, clinical signs, organ weights, or gross/microscopic findings in adult rats of either sex or generation. Slight reductions in body weight (males 94% of control)/body-weight gain (P1 males 88%/F1 males 94% of control), mainly in males, were accompanied by decreases in food efficiency in both generations during the premating periods at 7500 ppm. **The parental systemic LOAEL is 7500 ppm (456 mg/kg bw/day in males, 498 mg/kg bw/day in females), based on decreased body weight, body-weight gain, and food efficiency. The parental systemic NOAEL is 2500 ppm (151 mg/kg bw/day in males, 165 mg/kg bw/day in females)**

Litter size, live birth index, number born dead, viability and lactation indices, clinical observations, and sex ratio were comparable among the groups in both generations. Slightly lower body weight/body-weight gains were observed at 7500 ppm (litter basis and per sex) in both generations, but the magnitude of the reductions was slight (5%-7%) and not considered adverse. Sexual maturation was not affected by treatment in either sex of F1 pups and, consequently, anogenital

distance was not measured in the F2 pups because of the lack of effect on sex ratio and sexual maturation in the F1 pups. There were no treatment-related effects on organ weights (brain, spleen, thymus), gross or microscopic observations in either generation. **The offspring NOAEL is 7500 ppm (456 mg/kg bw/day in males, 498 mg/kg bw/day in females), the highest dose tested.**

There were no treatment-related effects on ovarian follicle counts in F1 females, sperm and estrous cycle parameters in P1 and F1 adults, mating, precoital interval, fertility, gestation length, number of implantation sites, and implantation efficiency in either the P1 or F1 generation. **The reproductive NOAEL is 7500 ppm (456 mg/kg bw/day in males, 498 mg/kg bw/day in females), the highest dose tested.**

This study is acceptable (guideline), and it satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800; OECD 416) in rats.

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

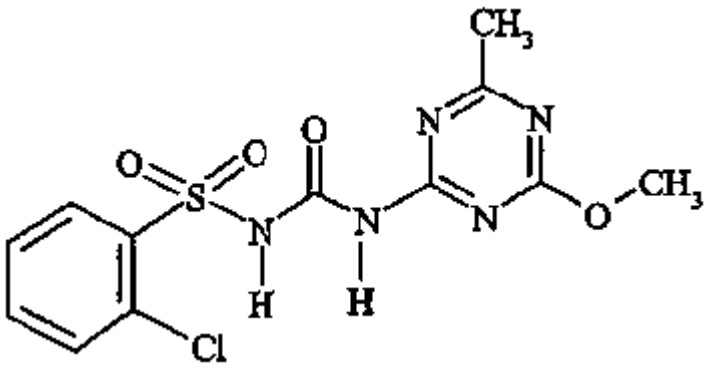
I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Chlorsulfuron (DPX-W4189) technical

Description:	A white solid (supplied by sponsor)
Lot/batch #:	DPX-W4189-723
Purity:	97.6 % a.i.
Compound stability:	stable over study duration (purity analysis at beginning and end of study)
CAS # of TGAI:	64902-72-3
Structure:	

STRUCTURAL FORMULA



EMPIRICAL FORMULA: $C_{12}H_{12}O_4N_5SCL$

2. Vehicle and/or positive control: diet (see below).

3. Test animals:

Species:	Rat
Strain:	**Crl:CD®** Crl:CD®(SD)IGS BR
Age at study initiation (dosing):	(P) 56 days; (F_1) 21 days
Wt. at study initiation (dosing):	(P) Males: 273-308 g; Females: 187-214 g (F_1) Males: 51-67 g; Females: 49-63 g
Source:	Charles River Laboratories, Inc., Raleigh, NC
Housing:	Individually during non-mating periods
Diet:	PMI® Nutrition International, Certified Rodent LabDiet® 5002 meal *ad libitum*
Water:	tap *ad libitum*
Environmental conditions:	**Temperature:** 18-26ºC **Humidity:** 30-70% **Air changes:** #/hr (not provided) **Photoperiod:** 12 hrs dark/12 hrs light
Acclimation period:	14 days (quarantined for 11 days of the 14-day pretest period)

B. PROCEDURES AND STUDY DESIGN:

1. Mating procedure: Each female was continually housed on a 1:1 basis with a randomly selected, non-sibling male of the same dietary concentration level, in the male's cage. During co-housing, each female was examined once daily for the presence of an intravaginal copulation plug or sperm in the vaginal lavage sample (either as evidence of copulation). On the day copulation was confirmed (Day 0 of gestation), the female was transferred back to individual cage housing. Rats were co-housed until evidence of copulation was observed or until 2 weeks

had elapsed. The cohabitation ended in the morning of day 15 of cohabitation.

2. **Study schedule:** The P parental animals were given test diets for at least 70 days before they were mated, and the F_1 parental animals were not mated until at least 70 days after they were selected from the F_1 litters. Selection of parents for the F_1 generation was made when the pups were 21 days of age, and the mated animals in the study were approximately 18 (P1)/13 (F1) weeks of age at mating [P1 animals 8 weeks of age at start of treatment; F1 animals 21 days old at start of dosing].

3. **Animal assignment:** P animals were randomly assigned to test groups (ranked by most recent body weight) as shown in Table 1.

TABLE 1. Animal assignment

Test group	Dose in diet [a] (ppm)	Animals/group			
		P Males	P Females	F_1 Males	F_1 Females
Control	0	30	30	30	30
Low	100	30	30	30	30
Mid-Low	500	30	30	30	30
Mid-High	2500	30	30	30	30
High	7500	30	30	30	30

[a] Diets were administered from beginning of the study until sacrifice

4. **Dose selection rationale:** The dose levels were selected based on the results from a previous 3-generation reproduction study [MRID 00031423/00086003], in which 20 rats/sex/group were fed diets containing 0, 100, 500, 2500 ppm chlorsulfuron. Reduced body weight and body-weight gains were observed at 500 ppm and 2500 ppm, and reduced food efficiency was observed at 2500 ppm in males. Equivocal evidence of a reproductive effect consisted of a slight decrease in fertility indices at 2500 ppm. In a 90-day feeding study [MRID], male and female rats fed similar dose levels for 98 days displayed no dietary, biochemical, hematological, clinical, behavioral, or gross or histopathological changes. In a developmental toxicity study in rats [MRID], in which chlorsulfuron was administered *via* gavage at dose levels of 0, 55, 165, 500, or 1500 mg/kg/day, maternal mortality and weight loss, a slight reduction in pregnancy rate, and reduced fetal body weight were observed at 1500 mg/kg/day. Reduced body-weight gain, feed consumption, and an increased incidence of clinical signs occurred at 500 and 1500 mg/kg/day. It was stated that a feeding study with young ratsat dose levels of 500 and 1500 mg/kg/day would correspond to dietary levels of approximately 5000 and 15000 ppm at study start. Dietary levels of 100, 500, and 2500 were selected to replicate the dose levels used in the previous reproduction study and were expected to produce no or minimal toxic effects. The 7500 ppm dose level was expected to produce some systemic toxicity but no mortality and provide additional reproductive data at a higher dose than previously tested.

5. **Dosage preparation and analysis:** Formulations were prepared weekly, or every 2 weeks, when refrigerated stability of the test substance in the diet was confirmed. The test material was added to the rodent diet and thoroughly mixed for 3 minutes in a diet mixer (control diet similarly mixed). Batches of diet were used within the established stability period and then discarded. Samples were analyzed to verify homogeneity and concentration of the test material in the diets. Stability of the test substance in the diet was evaluated (7- and 14-day room temperature; 14- and 21-day refrigerated) from analysis of top, middle, and bottom homogeneity samples

(considered fresh samples) collected from the initial diet preparation. At 3-month intervals during the study, duplicate samples from each dietary level were taken and used to verify concentration. Homogeneity (top, middle, and bottom) was evaluated using the initial diet preparation.

Results:

Homogeneity analysis: From test day 6 on, homogeneity was achieved at all dietary levels [100 ppm (92%-96%); 500 ppm (89%-99%); 2500 ppm (92%-100%); 7500 ppm (95%-104%) of nominal.

Stability analysis: Chlorsulfuron was demonstrated to be stable in the diet under study conditions (refrigerated; 86.2%-105% of nominal).

Concentration analysis: Overall 97.9%±4.9% of nominal [100 ppm (90.7%-101%); 500 ppm (91.2%-96.4%); 2500 ppm (90.4%-101.6%); 7500 ppm (101.3%-105.7%).

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

C. OBSERVATIONS:

1. **Parental animals:** Observations and the schedule for those observations are summarized in Tables 2a and 2b. **Ovarian follicular counts:** A quantitative evaluation of primordial and growing follicles was conducted on all lactating F1 females (surviving to scheduled sacrifice and not suspected of impaired reproductive performance) from control and high-dose groups. Six ovarian cross sections (5 µm thick) were taken from the central area of the ovary using a step section technique. Primordial and growing follicles (up to but not including antral follicles) were enumerated for up to 12 ovarian sections per animal.

TABLE 2a. Key Study Parameters and Schedule

Study Events and Parameters	No. Animals	Timing (P1 and F1 rats)
Viability checks	All	Twice daily
Cage-side examinations (mortality, moribundity, pertinent behavioral changes, signs of difficult or prolonged parturition, all signs of overt toxicity recorded)	All	At least twice daily
Clinical observations (individually handled; examined for abnormal behavior &/or appearance); mortality, moribundity, pertinent behavioral changes, signs of difficult or prolonged parturition, all signs of overt toxicity recorded	All	At least once weekly throughout premating, gestation, lactation periods
Signs of delivery and offspring	P1 & F1 females	At least twice daily from GD 20
Offspring handled individually, examined for abnormal behavior/appearance; dead, missing, abnormal recorded	All	LD 0, 4, 7, 14, 21
Body weights – females	All	Weekly during pre-breeding period; GD 0, 7, 14, and 21; LD 0, 7, 14, 21
Body weights – males	All	Weekly throughout study
Feed consumption – females	All	Weekly during pre-breeding period; GD 0, 7, 14, and 21; LD 0, 7, 14
Feed consumption – males	All	Weekly during pre-breeding period
Estrous cycle evaluation – females	All P1 & F1	3 weeks prior to mating and continuing until copulation; day of necropsy
Reproductive performance	All	N/A
Gross necropsy – adult P1 & F1 females	All	Timing not reported
Gross necropsy – adult P1 & F1 males	All	Timing not reported
Organ weights - adult P1 & F1 females uterus (w/ oviducts & cervix), ovaries, brain, pituitary gland, liver, kidneys, adrenal gland, spleen	All	At necropsy
Organ weights - adult P1 & F1 males testes, epididymides, right cauda epididymis, seminal vesicles w/ coagulating glands & fluids, prostate, brain, pituitary gland, liver, kidneys, adrenal gland, spleen	All	At necropsy
Sperm motility – males	All P1 & F1	At necropsy
Sperm count (testicular and epididymal)	All P1 & F1	At necropsy
Sperm morphology	All P1 & F1	At necropsy
Histopathology pituitary gland, adrenal gland (both sexes) males: testes, epididymides, seminal vesicles, coagulating glands, prostate females: ovaries, uterus w/ oviducts, vagina, cervix	P1 & F1 male & female high-dose & control 10/sex/group	At necropsy

GD = gestation day, LD = lactation day, N/A = Not Applicable.

2. Litter observations: Table 2b provides a summary of observations performed. Offspring were handled individually and examined for abnormal behavior and appearance on the day of delivery and on PND 4, 7, 14, and 21; any dead, missing, or abnormal pups were recorded. Dams with no live pups were sacrificed. Offspring that were moribund, found dead, or that were sacrificed because of the death of the dam during lactation underwent a gross pathological evaluation. Dead pups were examined to the extent possible. Live and dead pups in each litter were counted by sex as soon after delivery as possible. Live pups in each litter were weighed individually. On PND 4, pups in each litter were counted and weighed individually, and the litters were culled randomly to 8 pups (4/sex). Litters with fewer than eight pups were not culled. Excess pups were euthanized and discarded. On days 7, 14, and 21, pups in each litter were counted by sex and weighed individually. Offspring in the F1 litters of each treatment group were selected randomly (one pup/sex/litter) to serve as parents for the F2 generation and placed into individual cages.

TABLE 2b. Key Study Parameters and Schedule

Study Events and Parameters	No. Animals	Timing (both generations unless indicated otherwise)
Dam/Litter clinical observations	All	PND 0, 4, 7, 14, 21
Dam/Litter cageside observations	All	Daily from PND 0 – 21
No. of live & dead pups	All	PND 0, 4, 7, 14, and 21
Pup sex & body weight	All	PND 0, 4 (BC), 7, 14, and 21
Culling	All	PND 4
Weaning	All	PND 21
Gross necropsy – weanlings	All	PND 22
Organ weights (brain, spleen, thymus)/histopathology – weanlings	1/sex/litter	PND 22
Vaginal Opening (VO)	All F1 females selected for mating	PND 21 until achieved or PND 43
Preputial Separation (PPS)	All F1 males selected for mating	PND 35 until achieved or PND 53
Anogenital Distance (***no indication of treatment-related effects on sex ratio or sexual maturation of F1 pups)***	F2 pups (not performed)	N/A
Body Weight at Pubertal Onset	All F1 animals selected for mating	Day of VO or PPS acquisition

PND = postnatal day, BC = Before Culling, AC = After Culling; N/A = Not Applicable

3. Postmortem observations:

a. Parental animals: All surviving P1 and F1 adult rats were sacrificed by carbon dioxide anesthesia and exsanguination. Details as to when sacrifice occurred (timeframe; *e.g.,* age of rat; when in the study) were not provided. These animals were subjected to a gross

pathological examination. The uteri of all cohabited females were examined for the presence and number of implantation sites. The reproductive organs of rats with suspected impaired reproductive performance (*e.g.,* failure to mate, conceive, sire, or deliver healthy offspring) were evaluated microscopically from all groups. These included 20 P1 pairs and 29 F1 pairs across all groups.

The following tissues (Y) were prepared for microscopic examination and/or weighed (XX):

YXX	Ovaries	YXX	Testes
YXX	Uterus w/ oviducts and cervix	YXX	Epididymides
Y	Vagina	YXX	Prostate
XX	Brain	XX	Right cauda epididymis
XX	Liver	YXX	Seminal vesicles w/ coagulating glands and fluids
XX	Kidneys	XX	Spleen
YXX	Adrenal glands	Y	Lesions
YXX	Pituitary gland		

b. Offspring: All F1 and F2 weanlings were sacrificed by carbon dioxide anesthesia and exsanguination. These animals were subjected to postmortem examinations. One weanling/sex/litter was designated for organ weight (brain, spleen, and thymus) and histopathological (all gross lesions) evaluation.

D. DATA ANALYSIS:

1. Statistical analyses: (1) Incidence of clinical observations, mating index, fertility index, gestation index, and litter survival: Cochran-Armitage test for trend. (2) Sex ratio (covariate: litter size), mean pup weights (covariate: litter size): preliminary test (Levene's test for homogeneity; Shapiro-Wilk test of normality); if preliminary test not significant: analysis for covariance and Dunnett-Hsu; if preliminary test is significant: non-parametric analysis of covariance. (3) body weight, body-weight gain, food consumption, food efficiency, gestation length, implantation site numbers, implantation efficiency, mean number of pups per litter, percent born alive, 0-4 day viability, viability index, lactation index, precoital interval, vaginal patency, preputial separation, estrous cycle parameters, sperm parameters, ovarian follicle counts, organ weights: preliminary test (Levene's test for homogeneity & Shapiro_wilk test for normality; if preliminary test no significant, one-way analysis of variance & Dunnett's test; if preliminary test significant, Kruskal-Wallis test & Dunn's test. Male and female parental data were evaluated separately. For litter parameters, the proportion of affected pups per litter or the litter mean was used as the experimental unit for statistical evaluation. For each parameter analyzed with a trend test, the test was applied sequentially. If a significant dose-response was detected, data from the top dose group was excluded and the test repeated until no significant trend was detected. The level of significance selected was $p<0.05$.

2. Indices:

Reproductive indices: The following reproductive indices were calculated from breeding and parturition records of P1 and F1 animals in the study:

$$\text{Mating index (\%)} = \frac{\text{\# copulated}}{} \times 100$$

$$\text{Fertility index (\%)} = \frac{\text{\# pregnant}}{\text{\# cohabited}} \times 100$$

$$\text{Gestation index (\%)} = \frac{\text{\# litters w/ at least 1 live pup}}{\text{\# copulated}} \times 100$$

$$\text{Implantation efficiency (\%)} = \frac{\text{\# pups born}}{\text{\# litters}} \times 100$$

$$\text{Pups born alive (\%)} = \frac{\text{\# pups born alive}}{\text{\# implantations sites}} \times 100$$

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

$$\text{0-4 Day viability index (\%)} = \frac{\text{\# pups alive day 4 preculling}}{\text{\# pups born}} \times 100$$

$$\text{Lactation index (\%)} = \frac{\text{\# pups alive at weaning (LD 21)}}{\text{\# pups born alive}} \times 100$$

$$\text{Litter survival (\%)} = \frac{\text{\# pups alive day 4 postculling}}{\text{\# litters weaned}} \times 100$$

$$\frac{\text{\# litters weaned}}{\text{\# of viable litters delivered}} \times 100$$

3. **Historical control data:** not provided.

II. RESULTS:

A. PARENTAL ANIMALS:

1. **Mortality and clinical signs:** There was no treatment-related mortality in P1 or F1 males during the premating phases or in P1 or F1 females during premating, gestation or lactation at any dose level. No clinical signs attributable to chlorsulfuron were reported in either sex of P1 and F1 adult animals.

2. **Body weight and food consumption: P1 Males**: A statistically-significant (slight) decrease in body weight (94% of control) was observed from week 2 of the premating period at 7500 ppm, but the magnitude of the decrease remained the same throughout [Table 3a]. Body-weight gains (77% of control during week 2) were reduced at 7500 ppm throughout the premating period starting at week 1, which suggested a possible palatability problem, but food consumption was not affected. However, food efficiency was significantly reduced (80%*-89%* of control) in males at 7500 ppm throughout the premating period. Similar findings (body-weight gain 83%*of control during week 2; food efficiency 82%*-91%* of control) were observed in males at 2500 ppm, but the magnitude of the effects was less. **P1 Females**: During the first week of premating, females at 7500 ppm displayed a significant reduction in body-weight gain (74%* of control) and a significant reduction in food efficiency (72% of control) compared to the control [Table

3a].

F1 Males: A statistically-significant (slight) decrease in body weight (94% of control) was observed at the end of the premating period (day 70) at 7500 ppm, and body-weight gains were reduced from the second week of premating (93%-94% of control). Food consumption and food efficiency were comparable among the groups. **F1 Females:** At 7500 ppm, females displayed a significant reduction in body weight (92% of control) at the end of the premating period. Decreased body-weight gain was observed during the third week (79% of control) and overall (91% of control) at 7500 ppm. Food efficiency was reduced overall (93% of control) at 7500 ppm.

Reported body weight/body-weight gain and selected food consumption/efficiency results are summarized in Tables 3a and 3b.

TABLE 3a. Mean (±SD) Body weight and food consumption - pre-mating [a]

Observations/study week	Dose groups				
	0 ppm	**100 ppm**	**500 ppm**	**2500 ppm**	**7500 ppm**
***P1* Generation males - Pre-mating**					
Mean body weight (g)					
Week 0	293.1±13.9	294.2±13.7	290.6±13.9	289.9±17.2	291.0±14.8
Week 1	339.218.2	339.3±19.0	334.4±18.3	332.4±23.3	328.0±19.7
Week 2	381.1±23.3	377.9±25.7	370.5±20.7	367.3±27.7 (96)	360.0±24.9* (94)
Week 3	418.0±28.1	412.8±30.6	406.3±23.0	401.4±31.2 (96)	392.5±31.1* (94)
Week 10	557.7±47.0	554.8±52.1	544.1±32.2	535.4±46.5 (96)	523.2±53.0* (94)
Mean body weight gain (g)					
Day 0-7	46.0±6.6	45.1±7.6	43.8±6.9 (95)	42.4±8.7 (92)	36.9±8.4* (80)
Day 7-14	41.9±7.8	38.6±8.5	36.1±4.5* (86)	34.9±6.1* (83)	32.1±7.5* (77)
Day 14-21	36.9±6.4	34.9±7.6	35.8±4.6	34.1±7.0 (92)	32.5±7.3* (88)
Day 0-70	264.6±37.6	260.7±42.6	253.5±25.1	245.7±39.1 (93)#	232.2±42.2* (88)
Day 0-105	311.2±50.1	306.5±44.0	290.8±28.4 (93)	284.8±43.6 (92)	275.5±45.2 (89)
Mean food consumption (g/rat/day)					
Week 1	25.5±1.8	26.6±2.8	26.1±2.6	26.0±2.4	25.2±2.5
Week 2	26.4±2.1	26.7±2.3	26.0±2.1	26.7±2.6	25.2±2.3
Week 3	26.5±2.2	26.5±2.1	26.2±1.8	26.9±3.0	26.1±2.5
Week 10	27.0±2.0	27.6±2.2	27.1±2.0	26.7±2.4	26.4±2.3
Mean food efficiency (g wt gain/g food consumed)					
Week 1	0.257±0.026	0.244±0.037	0.241±0.037	0.232±0.038*(90)	0.209±0.041*(81)
Week 2	0.227±0.035	0.205±0.033*	0.199±0.024*	0.187±0.026*(82)	0.181±0.037*(80)
Week 3	0.198±0.025	0.187±0.033	0.196±0.022	0.181±0.024*(91)	0.176±0.027*(89)
Week 10	0.140±0.014	0.134±0.014	0.134±0.012	0.131±0.012 (94)	0.125±0.015*(89)
***P1* Generation females - Pre-mating**					
Mean body weight (g)					
Week 0	200.9±9.9	201.7±12.5	202.0±11.8	203.0±11.0	200.0±12.8
Week 1	220.9±12.0	220.1±16.5	220.8±17.3	220.7±14.7	214.8±16.7
Week 2	229.9±12.9	233.0±18.8	230.9±20.5	231.4±20.1	223.3±20.3
Week 3	238.7±15.2	242. ±1±20.4	243.0±23.9	244.1±21.7	233.8±22.5
Week 10	286.2±22.4	294.6±28.9	296.0±30.6	289.4±28.0	277.5±27.5
Mean body weight gain (g)					
Day 0-7	20.0±5.0	18.4±7.4	18.7±8.2	17.7±5.7	14.7±6.3* (74)
Day 7-14	9.0±5.6	12.9±5.6	10.1±7.3	10.7±8.5	8.6±7.2 (96)
Day 14-21	8.8±7.3	9.2±7.8	12.1±8.2	12.7±6.7	10.4±8.6
Day 0-70	85.3±15.9	92.8±21.2	94.0±22.3	86.5±21.2	77.2±18.8 (91)
Mean food consumption (g/rat/day)					
Week 1	18.9±1.5	20.1±2.8	21.5±3.2*	18.8±2.1	19.1±2.3
Week 2	19.7±2.1	19.0±2.1	19.8±2.5	19.6±2.5	18.2±2.3*(92)

TABLE 3a. Mean (±SD) Body weight and food consumption - pre-mating [a]					
Observations/study week	**Dose groups**				
	0 ppm	**100 ppm**	**500 ppm**	**2500 ppm**	**7500 ppm**
Week 3	18.1±1.8	18.7±2.4	19.1±2.3	18.7±2.1	18.7±1.9
Week 10	19.6±1.4	19.5±1.7	20.5±1.8	19.6±2.2	19.4±1.9
Mean food efficiency (g wt gain/g food consumed)					
Week 1	0.151±0.033	0.130±0.048	0.123±0.049*(81)	0.133±0.036(88)	0.109±0.046*(72)
Week 2	0.064±0.040	0.096±0.041	0.073±0.052	0.075±0.056	0.064±0.049
Week 3	0.067±0.055	0.067±0.058	0.087±0.056	0.096±0.048	0.078±0.062
Week 10	0.062±0.010	0.068±0.012	0.066±0.014	0.063±0.012	0.057±0.014 (92)

Data from Tables 17-20, pages 64-71 and Tables 33-36, pages 88-95 of the study report; * p<0.05; ** p<0.01; n=30 (except #; weighing error on day 70 {n=10})

TABLE 3b. Mean (±SD) Body weight and food consumption - pre-mating [a]					
Observations/study week	**Dose groups**				
	0 ppm	**100 ppm**	**500 ppm**	**2500 ppm**	**7500 ppm**
***F1* Generation males - Pre-mating**					
Mean body weight (g)					
Day 0	58.9±7.2	59.0±7.6	58.0±6.0	58.8±5.6	57.1±6.1
Day 7	103.3±12.6	104.3±14.3	102.5±7.9	103.1±9.3	99.3±9.5 (96)
Day 14	164.4±18.5	166.8±22.1	163.1±13.0	163.4±13.0	156.9±13.7 (95)
Day 21	228.1±21.7	230.1±27.7	225.4±18.1	222.6±15.7	216.3±18.1 (95)
Day 70	514.1±46.2	516.2±51.1	507.8±39.4	503.6±26.4	483.3±45.8*(94)
Mean body weight gain (g)					
Day 0-7	44.4±7.0	45.3±7.5	44.7±3.9	44.3±5.2	42.2±5.3 (95)
Day 7-14	61.2±6.8	62.5±8.4	59.8±6.4	60.4±4.9	57.6±5.8 (94)
Day 14-21	63.6±5.7	63.3±7.8	62.3±7.7	59.2±4.6*(93)	59.4±6.3*(93)
Day 0-70	455.2±43.4	457.2±48.5	449.7±36.4	444.9±25.0	426.1±43.8*(94)
Mean food consumption (g/rat/day)					
Week 1	16.1±3.2	16.2±2.9	15.4±2.1	15.7±1.9	14.3±2.0
Week 2	21.4±3.3	21.3±2.6	21.3±2.4	20.62.1	21.1±2.8
Week 3	25.3±2.7	25.2±2.8	24.6±2.9	24.32.4	24.7±2.7
Week 0-10	27.5±2.6	27.5±2.3	27.3±2.5	26.7±2.0	26.8±2.3
Mean food efficiency (g wt gain/g food consumed)					
Week 1	0.399±0.054	0.403±0.049	0.419±0.045	0.407±0.045	0.430±0.087
Week 2	0.412±0.050	0.419±0.038	0.405±0.049	0.421±0.042	0.396±0.059
Week 3	0.362±0.033	0.360±0.041	0.362±0.032	0.349±0.027	0.346±0.036
Week 0-10	0.237±0.013	0.238±0.017	0.215±0.017	0.239±0.013	0.227±0.015
***F1* Generation females - Pre-mating**					
Mean body weight (g)					
Day 0	56.9±6.4	57.0±6.4	54.8±5.8	57.2±3.9	55.5±4.5
Day 7	95.0±9.8	96.2±11.9	92.1±8.1	94.8±5.3	92.4±6.5
Day 14	140.6±14.1	139.4±15.8	136.8±12.0	139.4±8.7	135.6±9.3
Day 21	173.8±16.3	171.7±17.7	170.2±15.4	172.8±10.2	167.5±11.3 (96)
Day 70	291.5±30.7	283.3±27.7	284.9±20.1	284.1±21.7	268.7±23.2*(92)
Mean body weight gain (g)					
Day 0-7	38.2±5.2	39.2±6.6	37.7±4.6	37.7±3.2	36.9±4.2
Day 7-14	45.6±5.7	43.2±5.8	43.8±5.4	44.5±5.7	43.3±4.5
Day 14-21	33.2±6.1	32.3±7.4	33.4±7.1	33.5±4.2	31.9±4.4
Day 21-28	26.8±8.1	25.9±8.6	23.3±6.6	24.0±6.9	21.2±6.6*(79)
Day 0-70	234.6±27.4	226.5±25.3	230.1±18.4	227.0±21.5	213.3±22.3*(91)
Mean food consumption (g/rat/day)					
Week 1	15.4±2.7	15.9±3.4	14.9±4.8	15.3±1.3	14.3±2.7 (93)
Week 2	19.9±2.7	19.3±3.0	18.9±2.4	19.2±1.9	19.4±2.2
Week 3	20.7±2.2	21.4±3.2	21.2±3.8	21.5±3.7	22.4±3.8
Week 10	21.2±2.1	21.7±2.9	20.8±1.6	20.8±2.0	20.7±2.0
Mean food efficiency (g wt					

TABLE 3b. Mean (±SD) Body weight and food consumption - pre-mating [a]					
Observations/study week	**Dose groups**				
	0 ppm	**100 ppm**	**500 ppm**	**2500 ppm**	**7500 ppm**
gain/g food consumed)					
Week 1	0.361±0.061	0.359±0.052	0.379±0.071	0.353±0.035	0.381±0.091
Week 2	0.332±0.054	0.323±0.041	0.335±0.047	0.333±0.044	0.320±0.031
Week 3	0.229±0.034	0.218±0.055	0.229±0.052	0.227±0.040	0.207±0.036 (90)
Week 0-10	0.159±0.016	0.151±0.016	0.158±0.012	0.157±0.015	0.148±0.015*(93)

Data from Tables 17-20, pages 64-71 and Tables 33-36, pages 88-95 of the study report; * p<0.05; ** p<0.01; n=30 (except #; weighing error on day 70 {n=10})

Body weight and body-weight gains were comparable among the groups during gestation and lactation of both generations [Table 3c]. P1 females at 7500 ppm displayed a slight (non-significant) decrease (93% of control) in body-weight gain during the first week of gestation. F1 females at 7500 ppm displayed a slight decrease in body weight (93% of control) on Day 0 of gestation only.

TABLE 3c. Mean (±SD) Body Weight/Body-Weight Gain – gestation and lactation[a]					
Observations/study week	**Dose groups**				
	0 ppm	**100 ppm**	**500 ppm**	**2500 ppm**	**7500 ppm**
***P1* Generation females – gestation**					
Mean body weight (g)					
Day 0	288.1±28.7	290.6±29.1	297.0±30.1	287.3±29.4	275.1±26.2 (95)
Day 7	325.2±28.7	328.3±31.7	344.9±31.6	325.2±30.9	309.5±26.9 (95)
Day 14	349.9±28.7	353.4±33.5	362.5±32.5	350.6±33.2	336.0±26.4
Day 21	423.5±37.8	425.4±43.8	430.6±38.7	421.1±37.5	404.1±35.6 (95)
Mean body weight gain (g)					
Day 0-7	37.1±8.3	37.6±10.5	37.9±6.1	37.9±9.7	34.5±8.0 (93)
Day 7-14	24.7±6.8	25.1±8.4	27.6±7.9	25.5±7.0	26.4±9.2
Day 14-21	73.6±27.7	72.1±18.9	67.4±22.6	72.6±16.3	68.1±19.5 (93)
Day 0-21	135.4±27.2	134.8±26.2	132.3±25.4	135.9±22.4	129.0±25.2 (95)
***P1* Generation females – lactation**					
Mean body weight (g)					
Day 0	316.4±40.6	326.8±34.4	322.8±33.2	314.8±35.2	303.7±31.6
Day 7	334.6±33.8	341.1±28.5	344.8±25.2	339.1±32.1	326.4±32.4
Day 14	345.8±25.1	350.5±24.9	348.5±26.3	349.0±24.0	333.6±21.9
Day 21	335.3±24.6	333.9±23.7	329.7±22.4	330.0±23.8	323.4±22.4
Mean body weight gain (g)					
Day 0-7	18.2±37.3	15.6±16.2	22.3±22.1	24.3±23.6	22.7±34.0
Day 7-14	11.2±19.0	9.4±17.0	5.0±13.3	9.9±18.0	7.2±18.2
Day 14-21	-10.5±10.7	-16.7±11.9	-18.8±15.3	-19.1±15.1	-10.2±16.1
Day 0-21	18.9±28.0	8.3±22.1	6.4±24.1	15.2±26.8	19.7±25.1
***F1* Generation females – gestation**					
Mean body weight (g)					
Day 0	298.5±38.0	295.6±30.1	290.5±17.6	296.0±26.6	277.3±23.0* (93)
Day 7	335.0±41.5	336.6±37.3	327.2±21.0	335.6±29.2	317.0±24.4 (95)
Day 14	368.1±44.8	367.0±40.5	357.7±22.8	367.0±31.4	351.1±25.1
Day 21	451.4±61.5	432.5±45.9	436.0±31.6	435.5±32.4	429.4±31.6 (95)
Mean body weight gain (g)					
Day 0-7	36.5±9.1	41.0±13.8	36.7±10.3	39.5±7.8	39.7±9.1
Day 7-14	33.1±6.5	30.4±7.6	30.6±5.3	31.4±8.0	34.2±8.5
Day 14-21	82.8±22.8	65.5±30.1	76.8±20.5	68.5±21.3	78.3±18.0
Day 0-21	151.9±31.5	136.9±34.2	145.5±21.8	139.5±21.4	152.1±25.5
***F1* Generation females – lactation**					
Mean body weight (g)					
Day 0	347.0±45.8	348.4±45.1	333.6±33.4	341.4±31.4	324.6±31.9 (94)
Day 7	359.4±41.8	361.6±36.0	348.4±22.3	359.1±25.0	335.6±24.6*(93)
Day 14	359.2±36.2	362.9±33.4	351.6±23.1	359.2±21.5	343.3±21.0
Day 21	340.9±30.2	340.1±46.0	336.4±21.9	337.3±23.6	326.0±19.3
Mean body weight gain (g)					

TABLE 3c. Mean (±SD) Body Weight/Body-Weight Gain – gestation and lactation[a]					
Observations/study week	**Dose groups**				
	0 ppm	**100 ppm**	**500 ppm**	**2500 ppm**	**7500 ppm**
Day 0-7	12.4±14.9	12.1±19.7	14.8±23.3	15.4±16.1	11.0±23.0
Day 7-14	-0.2±12.7	1.2±10.6	3.2±10.2	0.0±11.9	6.4±11.9
Day 14-21	-18.3±10.9	-22.8±23.8	-15.2±12.9	-21.9±26.5	-17.3±11.8
Day 0-21	-6.2±21.6	-9.5±34.9	2.9±25.1	-6.5±27.9	3.0±23.6

[a]Data from Tables 21-24, pages 72-75 and Tables 29-32, pages 84-87 of the study report; * p<0.05; ** p<0.01; n= varies

3. **Test substance intake:** The overall mean daily intake of chlorsulfuron during the pre-mating period (both sexes) and during gestation (females) and lactation (females) is shown in Table 4. The values for the P1 generation are considered to be representative of the test substance intake for the entire study. It is to be noted, however, that the dams in both generations consumed approximately twice as much test material during the first two weeks of lactation as they did during the premating and gestation periods.

TABLE 4. Mean intake during premating (both sexes)/gestation and lactation (females) - mg/kg body weight/day [a]								
	Male				**Female**			
	100 ppm	**500 ppm**	**2500 ppm**	**7500 ppm**	**100 ppm**	**500 ppm**	**2500 ppm**	**7500 ppm**
P1								
Premating	6.01	30.1	151	456	7.47	39.3	188	591
Gestation					6.53	32.6	165	498
Lactation*					**12.62**	**61.2**	**326**	**1040**
F1								
Premating	9.11	45.9	226	701	10.8	53.0	261	810
Gestation					7.15	35.5	180	556
Lactation*					**11.23**	**62.9**	**312**	**972**

[a] Data obtained from page 35 in the study report. * during first 2 weeks of lactation

4. **Reproductive function:**

   a. **Estrous cycle length and periodicity:** There were no treatment-related effects on the mean percent days in estrus, diestrus, or proestrus, or mean cycle length in either the P1 or F1 females at any dose level [Table 5]. The distribution of estrous cycle stages at sacrifice was similar across groups in both P1 and F1 females.

Table 5. Estrus Cycle Parameters and Precoital Interval					
Parameter	**Dose group (ppm)**				
	0	**100**	**500**	**2500**	**7500**
P1 Females					
Mean % days in					
estrus	23	22	21	21	26
diestrus	69	71	72	71	67
Proestrus	8	7	7	8	7
Mean cycle length (days)	4.7±1.0	4.8±1.5	4.5±0.7	4.4±0.7	4.2±0.4
Mean precoital interval (days)	3.4±2.9	2.3±1.9	3.0±1.4	2.5±1.4	2.2±2.0
n= (mean/length/interval)	23/22/19	29/29/27	28/28/28	29/29/30	27/27/27
F1 Females					
Mean % days in					
estrus	26	22	25	32	36
diestrus	68	70	68	62	58
Proestrus	6	8	7	6	5
Mean cycle length (days)	4.3±0.5	4.6±1.0	4.3±0.4	4.5±0.9	5.2±3.3
Mean precoital interval (days)	3.6±2.6	2.8±2.4	3.3±1.8	3.1±2.4	2.6±1.7
n= (mean/length/interval)	30/30/27	28/28/26	30/30/27	30/29/29	30/28/28

Data from Tables 51 and 52, pages 114-115 of the study report

b. <u>Sperm measures</u>: There were no treatment-related effects on sperm motility, morphology, epididymal sperm, or testicular spermatid numbers in either the P1 or F1 males at any dose level [Table 6]. The statistically significant increase in the mean number of epididymal sperm per cauda at 7500 ppm (261 *vs* 225) was considered by the study author to be due to a slightly higher cauda epididymis weight (mean number of epididymal sperm expressed relative to cauda weight was 874 *vs* 785). The finding is not considered adverse.

Table 6. Summary of Sperm Parameters					
Parameter	**Dose group (ppm)**				
	0	**100**	**500**	**2500**	**7500**
P1 Males					
Motility (% motile)	83.0±8.4	80.8±7.7	83.0±8.2	84.6±6.0	83.3±7.0
Morphology (% normal)	99.2±0.7	99.1±0.8	99.2±0.8	99.0±1.4	99.3±0.8
Epididymal sperm (millions)					
per cauda	225.1±58.1	242.5±41.3	236.3±49.2	243.6±55.2	260.6±43.9*
per g cauda	784.6±173.3	851.5±132.4	808.5±163.5	871.7±148.1	874.0±149.1
Testicular spermatids (millions)					
per testis	128.3±27.6	125.3±23.8	130.0±23.6	120.0±30.6	120.2±29.9
per g testis	84.2±14.9	82.1±12.7	84.0±12.9	79.9±15.0	79.1±17.7
F1 Males					
Motility (% motile)	77.7±6.6	78.9±7.0	75.6±9.4	78.2±6.2	77.7±8.8
Morphology					
% normal	99.5±0.4	99.2±1.3	99.5±0.6	99.2±0.8	98.9±1.9
Epididymal sperm (millions)					
per cauda	208.9±43.3	197.1±40.9	208.2±47.9	212.2±40.1	216.1±46.8
per g cauda	738.4±125.0	749.8±170.8	770.2±162.9	811.5±122.4	786.4±125.3
Testicular spermatids (millions)					
per testis	120.6±41.6	120.0±44.7	105.2±31.4	118.8±41.5	120.3±37.8
per g testis	73.3±22.5	73.3±23.7	65.0±15.8	73.6±20.7	73.3±19.4

Data from Tables 49 and 50, pages 112 -113 of the study report

c. <u>Ovarian follicle counts</u>: No significant difference was noted between the control and high-dose group [Table 7].

Table 7. Ovarian Follicle Counts – Lactating F1 Female Rats		
Dose group (ppm)	**0**	**7500**
count♪	146±44 (22)	124±50 (20)

Data from Table 62, page 125 of the study report; ♪primordial & growing follicles enumerated for each of 12 sections/rat; (n)

5. **Reproductive performance:** Results for the parental animals are summarized from the report in Table 8. There were no adverse effects on mating or fertility in either generation, and the number of implantations sites per dam and implantation efficiency were comparable among the groups in each generation. Gestation length was comparable among the groups in both generations.

TABLE 8. Reproductive performance [a]					
Observation	**Dose group (ppm)**				
	0	**100**	**500**	**2500**	**7500**
P1 Generation					
Mating index (%)	86.7	93.3	100	100	100
Fertility index (%)	88.5	89.3	93.3	96.7	93.3
Gestation length (days)	22.3	22.3	22.4	22.3	22.3
# of implantation sites/dam	14.1±4.5	15.3±3.3	14.9±2.6	15.5±2.1	14.9±1.9
Implantation efficiency (%)	95.1±9.8	96.2±5.4	94.8±7.5	94.3±7.9	92.3±7.9
F1 Generation					
Mating index (%)	90.0	92.9	90.0	96.7	93.3
Fertility index (%)	81.5	88.5	92.6	96.6	78.6
Gestation length (days)	22.2	22.3	22.3	22.5	22.1
# of implantation sites/dam	15.5±3.1	13.5±4.9	15.3±2.7	13.5±3.8*	15.1±3.5
Implantation efficiency (%)	92.5±9.4	88.9±19.4	95.4±6.8	86.2±22.3	94.2±6.1

[a] Data obtained from Tables 53-54, pages 116-117 in the study report.
* Statistically different from control, $p<0.05$.

6. **Parental postmortem results:**

   a. **Organ weights: P1 adults**: The report noted slight increases in kidney (9%), testes (9%), epididymis (10%), and right cauda epididymis (8%) weights relative to body weight in the high-dose P1 males. These increases were considered to be the result of the slightly decreased body weights (6%) of this group. In the P1 female rats, a statistically significant increase (6%) in kidney weight relative to body weight was observed at 7500 ppm. This difference was not considered adverse since it was small and not associated with significant changes in any other kidney weight parameters. **F1 adults**: Similar increases in kidney (8%) and testes (12%) relative weights were observed in F1 males at 7500 ppm (body weight 7.3% less than control at necropsy). A slight decrease in absolute brain weight (3%) was noted in F1 males at 7500 ppm, but it was not considered to be related to treatment.

   b. **Pathology:**

      1. **Macroscopic examination:** There were no treatment-related gross observations in either generation or sex following the administration of the test substance.

      2. **Microscopic examination:** There were no treatment-related findings.

B. **OFFSPRING:**

1. **Viability and clinical signs:** There were no treatment-related differences in clinical signs reported in either generation. Litter size, live birth index, number born dead, viability and lactation indices, and sex ratio were comparable among the groups in both generations [Table 9]. Although the sex ratio was significantly higher (55% males *vs* 45% in the F1 control) at 7500 ppm in the F1 litters compared to the control, it is not considered treatment-related based on the fact that it is within the historical control range (45%-59%; mean 50% in 17 studies from 2000-2004), a similar effects was not observed in the F2 litters, and the F2 control sex ratio was 55% males.

TABLE 9. Litter parameters for F_1 and F_2 generations [a]

Observation	Dose groups (ppm)				
	0	100	500	2500	7500
F_1 Generation					
Mean implantation sites♪	14.1±4.5	15.3±3.3	14.9±2.6	15.5±2.1	14.9±1.9
Number implantations♪	325	383	418	450	418
Number born live♪	276	344	366	400	375
Number born dead (litters)♪	13 (6)	8 (5)	21 (5)	9 (5)	10 (7)
Sex ratio day 0 (% %)	45	48	52	48	55*
# Deaths days 0-4 (%)	4 (4.7)	7 (2.3)	22 (5.7)	22 (2.3)	7 (2.7)
# Deaths days 4-21 (%)	3 (1.4)	10 (3.0)	0	1 (0.3)	8 (1.9)
Mean litter size Day 0	12.5±4.9	14.3±3.2	13.6±3.0	14.3±2.2	13.4±2.1
Day 4 [b]	12.1±4.6	14.0±3.1	12.6±3.5	13.5±2.8	13.1±2.2
Day 4 [c]	7.3±1.9	7.9±0.6	7.9±0.4	7.8±0.9	8.0±0.0
Day 7	7.2±1.9	7.8±0.7	7.9±0.4	7.8±0.9	8.0±0.2
Day 14	7.2±1.9	7.8±0.7	7.9±0.4	7.8±0.9	7.8±1.1
Day 21	7.1±1.9	7.8±0.7	7.9±0.4	7.8±1.0	7.7±1.2
Birth index (% born live)	95.1	96.2	94.8	94.3	92.3
Live birth index	93.4	97.5	95.2	97.9	97.4
Viability index	97.6	98.0	92.5	94.3	98.0
Lactation index	98.3	98.9	100	99.6	96.4
F_2 Generation					
Mean implantation sites♪	15.4±3.1	13.5±4.9	15.4±2.7	13.5±3.8*	15.1±3.5
Number implantations♪	340	311	385	379	332
Number born live♪	314	275	362	330	299
Number born dead♪	2	5	8	12	12
Sex ratio day 0 (% %)	55	44	50	47	53
# Deaths days 0-4 (%)	7 (2.2)	4 (1.5)	11 (3.0)	19 (5.8)	14 (4.7)
# Deaths days 4-21 (%)	0	0	0	6 (1.9)	8 (2.8)
Mean litter size Day 0	14.3±3.4	12.0±5.3	14.5±2.7	12.2±4.1	13.6±3.4
Day 4 [b]	14.0±3.3	11.8±5.4	14.0±2.7	12.0±4.1	13.0±3.4
Day 4 [c]	7.8±0.6	6.5±2.6	7.8±0.8	7.3±1.7	7.7±0.9
Day 7	7.7±0.6	7.1±2.2	7.8±0.8	7.2±1.7	7.7±0.9
Day 14	7.8±0.6	7.1±2.2	7.8±0.8	7.1±1.7	7.7±0.9
Day 21	7.8±0.6	7.1±2.2	7.8±0.8	7.1±1.7	7.7±0.9
Birth index (% born live)	92.5	88.9	91.6	86.2	94.2
Live birth index	99.1	96.7	98.2	96.5	96.1
Viability index	98.0	92.9	96.7	98.7	95.5
Lactation index	100	100	100	97.1	100

[a] Data obtained from pages 699, 702, 705, 708, 711, 714, 717, 720, 723, 726 (F1 litters)/731, 734, 737, 740, 743, 746, 749, 752 (F2 litters) in the study report; ♪implantations (sites/#)/# dead and # live calculated by reviewer [pages 685-689; 699, 705, 711, 717, 723 (P1)/692-696; 731, 737, 743, 749 (F1)]

[b] Before standardization (culling); [c] After standardization (culling); * $p<0.05$

2. **Body weight:** Offspring body weights were comparable among the groups in both generations [Table 10]. Although the 7500 ppm litters displayed slightly lower body weight in both generations, the magnitude of the reduction was small (5%-7%), and in the F1 generation, the number of pups/litter was greater at 7500 ppm than in the control, which could account for the slightly lower pup weight. In the F2 generation, the 7500 ppm group showed a slightly lower body-weight gain (Days 0-4: 90% of control; Days 4-21: 91% of control) compared to the control, but the magnitude of the reduction is not considered adverse.

TABLE 10. Mean (±SD) Litter and pup weights (g) [a]

	Dose group (ppm)									
	0	100	500	2500	7500	0	100	500	2500	7500
PND	**F_1 Litters**					**F_2 Litters**				
0	6.6±0.8	6.4±0.7	6.5±0.7	6.3±0.8	6.2±0.7	6.5±0.6	6.4±0.5	6.4±0.6	6.6±0.8	6.3±0.7
4 b	10.6±1.8	10.4±2.2	10.7±1.4	10.4±1.8	10.1±1.5	10.6±1.9	10.4±1.4	9.9±1.5	11.1±1.9	10.1±1.8
4 c	10.6±1.9	10.4±2.3	10.8±1.4	10.4±1.8	10.1±1.5	10.7±1.9	10.3±1.5	10.0±1.6	11.1±1.9	10.1±1.8
7	16.7±3.3	16.8±3.7	17.3±2.1	16.9±2.9	16.3±2.7	17.2±2.4	17.0±2.4	16.4±2.4	18.1±2.8	16.5±2.5
14	25.5±4.8	35.8±4.9	35.3±3.4	35.5±4.5	34.2±4.8	36.0±3.4	34.9±4.2	35.2±3.2	37.6±4.2	34.3±3.6
21	58.2±6.3	58.7±6.9	57.7±4.8	58.1±6.3	55.5±7.2	59.4±6.0	56.3±8.5	57.0±4.7	60.4±6.8	55.1±5.4
	F_1 Pups – male					**F_2 Pups – male**				
0	6.6±0.7	6.5±0.7	6.6±0.7	6.4±0.8	6.3±0.7	6.6±0.6	6.5±0.5	6.6±0.7	6.7±0.7	6.5±0.7
4 b	10.4±1.9	10.7±2.2	10.9±1.5	10.6±1.8	10.4±1.5	10.8±1.8	10.8±1.4	10.1±1.5	11.1±1.7	10.3±1.8
4 c	10.5±1.9	10.6±2.3	11.0±1.4	10.7±1.8	10.4±1.5	10.8±1.9	10.7±1.5	10.1±1.5	11.1±1.7	10.4±1.8
7	16.8±3.4	17.2±3.8	17.5±2.2	17.2±3.1	16.5±2.7	17.4±2.4	17.7±2.2	16.6±2.5	18.2±2.5	17.0±2.5
14	35.7±4.5	36.5±5.0	35.6±3.6	35.8±4.5	34.7±5.0	36.1±3.4	36.6±2.5	35.5±3.2	37.7±3.8	35.0±3.7
21	59.0±6.2	60.2±7.3	58.6±4.8	59.4±6.8	56.6±7.6	60.2±5.8	59.4±6.7	57.8±4.8	60.5±6.2	56.3±5.6
	F_1 Pups – female					**F_2 Pups – female**				
0	6.4±0.9	6.2±0.6	6.3±0.7	6.3±0.8	6.0±0.6	6.3±0.6	6.3±0.5	6.2±0.5	6.4±0.8	6.1±0.7
4 b	10.5±1.9	10.2±2.3	10.5±1.3	10.3±1.7	9.7±1.5	10.4±2.0	10.1±1.3	9.6±1.4	10.8±2.1	9.8±1.7
4 c	10.5±1.9	10.1±2.3	10.6±1.3	10.3±1.7	9.9±1.5	10.6±1.9	10.1±1.4	9.8±1.6	10.8±2.1	9.8±1.8
7	16.5±3.2	16.4±3.6	17.0±2.1	16.7±2.8	16.0±2.8	17.1±2.5	16.8±2.6	16.2±2.4	17.5±3.1	16.0±2.4
14	35.1±5.2	35.0±4.8	34.9±3.2	35.1±4.5	33.7±4.7	35.8±3.6	34.6±5.2	34.9±3.3	36.6±4.6	33.6±3.5
21	57.1±6.3	57.2±6.4	56.7±4.6	56.8±5.6	54.2±6.7	58.7±6.2	55.3±9.6	56.2±4.5	58.8±7.3	53.8±5.0

[a] Data obtained from Tables 59 & 60, page 122-123 in the study report; PND postnatal day
[b] Before standardization (culling); [c] After standardization (culling)

3. **Sexual maturation (F_1):** Sexual maturation was not affected by treatment in either sex [Table 11]. Anogenital distance was not recorded in F2 pups on Day 0 postpartum because there was no indication of treatment-related effects on sex ratio or sexual maturation of F1 pups.

Table 11. Developmental Landmarks in F1 Rats (mean # days ± s.d.)

Dose (ppm)	0	100	500	2500	7500
Preputial separation (males)	43.4±2.3	43.3±2.9	44.0±2.6	43.9±3.3	43.8±2.7
Vaginal patency (females)	32.3±1.7	32.0±1.9	32.9±2.2	33.4±2.1	32.7±1.6

Data from Table 61, page 124 of the report

4. **Offspring postmortem results:**

   a. **Organ weights:** There were no treatment-related effects on organ weights in either sex or generation.

b. **Pathology**: There were no treatment-related gross observations/microscopic findings in either sex or generation.

1. Macroscopic examination: none.

2) Microscopic examination: none.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: Under the conditions of the study, the no-observed-effect level (NOEL) for all effects in P1 and F1 rats was 2500 ppm (equivalent to mean daily intakes of 151-226 mg/kg body weight/daay for male rats during premating and 165-261 mg/kg body weight/day for female rats during premating and gestation) based on reduced body weights, weight gain, and food efficiency at 7500 ppm. The NOEL for reproductive toxicity and effects on F1 and F2 offspring was 7500 ppm, the highest concentration tested (equivalent to mean daily intakes of 456-701 mg/kg body weight/day for male rats during premating and 498-810 mg/kg body weight/day for female rats during premating and gestation).

B. REVIEWER COMMENTS: There were no adverse effects on clinical signs or survival of the adult rats following a 10-week premating dietary exposure period. Slight reductions in body weight/body-weight gain and food efficiency were observed mainly in males at 7500 ppm during both generations. P1 females at 7500 ppm displayed a transient reduction in body-weight gain and food efficiency, and F1 females at 7500 ppm displayed a decrease in body weight, body-weight gain, and food efficiency following the 10-week premating exposure period. Reproductive function and performance were not affected in either generation, as evidenced by a lack of effect on estrous cycle length/periodicity, sperm measures, ovarian follicle counts, mating/fertility indices, gestation length, and implantation efficiency. Litter size, live birth index, number born dead, viability and lactation indices, and sex ratios were comparable among the groups in both generations. Offspring body weights were not adversely affected in either generation, and sexual maturation was not adversely affected by treatment of either sex.

C. STUDY DEFICIENCIES: None that would adversely affect study interpretation.