6/24/93

FINAL

DATA EVALUATION RECORD

SUMILARV TECHNICAL

Study Type: Reproductive Toxicity

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer Sanju Diwan Date 6/10/93
Sanju Diwan, Ph.D.

Independent Reviewer Sanju Diwan Date 6/10/93
Pia Lindström, DPH

QA/QC Manager for Sharon Segal Date 6/10/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
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Project Officer: Caroline Gordon

Guideline Series 83-4:
Reproductive Toxicity

EPA Reviewer: Ann Clevenger, Ph.D.
Review Section I, Toxicology Branch I/HED

Signature: Ann Clevenger
Date: 6/24/93

EPA Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I/HED

Signature: Marion Copley
Date: 6/24/93

DATA EVALUATION RECORD

STUDY TYPE: Reproductive toxicity

EPA IDENTIFICATION NUMBERS

PC CODE: 129032

TOX CHEM. NO.: NA

MRID NO.: 421783-13

TEST MATERIAL: Sumilarv Technical

SYNONYMS: S-31183; [1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine; Nylar

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan

STUDY NUMBER: 83963

TESTING FACILITY: Bio-Research Laboratories, Ltd., Quebec, Canada

TITLE OF REPORT: A Dietary 2-Generation (1 Litter) Reproduction Study of S-31183 in the Rat

AUTHORS: K. Robinson, G. Washer, and J. Noveroske

REPORT ISSUED: September 23, 1991

CONCLUSIONS

Dose levels: Administred in diet, at dose levels of 0, 200, 1,000, or 5,000 ppm (approximately 0, 18, 87, and 453 mg/kg/day for males and 0, 20, 96, and 498 mg/kg/day for females during the premating period).
Strain: Crl:CD®(SD) BR rats

Systemic NOEL: 1,000 ppm
Systemic LOEL: 5,000 ppm, based on decreased body weight, body weight gain, and food consumption in both sexes and generations, increased liver weights in F_1 males and females and histopathological changes in the liver and kidney of F_1 males.

Reproductive NOEL: 5,000 ppm (HDT)

CLASSIFICATION: Core Minimum Data. This study meets the minimum requirements for a reproduction study (83-4) in rats.

A. MATERIALS

Test Compound	Purity:	95.3%
	Description:	Beige solid
	Lot No.:	PYG-87074
	Received:	March 23 and November 1, 1989
	Contaminants:	Not reported
	Expiration Date:	Not reported
	CAS #:	95737-68-1

Vehicle: None used; the test material was administered in the diet.

Test Animals	Species:	Rat
	Strain:	Crl:CD®(SD) BR
	Source:	Charles River Breeding Laboratories, Kingston, N.Y., U.S.A.
	Age:	F_0 males--44 days on day 1 of treatment
		F_0 females--44 days on day 1 of treatment
	Weight:	F_0 males--205-250 g on day 1 of treatment
		F_0 females--157-195 g on day 1 of treatment

B. STUDY DESIGN

This study was designed to assess the potential of S-31183 to cause reproductive toxicity when administered continuously in the diet for two successive generations.

Mating: After 15 days of acclimatization followed by a minimum of 70 days of dietary treatment, the F_0 females were mated with males from the same group in a ratio of 1:1 until evidence of mating (vaginal plug or presence of sperm in a vaginal smear) was obtained for a maximum of 21 days. The day on which mating was confirmed was designated day 0 of gestation. The F_1 animals were mated in a similar fashion following 77-90 days on the test diet.

Environmental Conditions: Following mating, the animals were housed individually in rooms at a temperature of 21°C ± 3°C and relative humidity of 50% ± 20%. The light/dark cycle was 12 hours. The temperature was within range on all occasions, and occasional fluctuations in relative humidity below the target zone were not considered to be of significance.

Group Arrangement: F_0 animals were assigned to one of four groups (using a computer-based randomization procedure based on body weight) as follows:

Test Group	Dietary Level (ppm)	Number Assigned per Group F_0 Males	F_0 Females	F_1 Males	F_1 Females
Control	0	26	26	26	26
Low dose	200	26	26	26	26
Mid dose	1,000	26	26	26	26
High dose	5,000	26	26	26	26

Dosage Administered: The test material was administered continuously in the diet (Purina® Certified Rodent Chow #5002) for two consecutive generations. The test diets were prepared weekly and stored at room temperature. A premix was prepared by adding S-31183 to a basal diet. Serial dilutions from the premix with basal diet were performed to prepare diets of appropriate concentration. Mixing of the premix was performed in a Hobart blender and subsequent dilutions in a V-blender. The purity of the test material was analyzed upon receipt. Homogeneity of mixing was determined using the week 1 diet mixes. Stability analyses of 100-20,000 ppm feed samples were conducted during an earlier range-finding study. Concentration analyses of the test diet samples were conducted during study weeks 1, 4, 5, 8, 16, 24, and 32.

Dosage Rationale: The dosage levels were selected based on results from a preliminary reproduction study ("A Dietary Range-Finding Reproduction Study of S-31183 in the Rat") performed in rats by the same laboratory. S-31183 was administered in doses of 0, 1,000, 3,000, 6,000, and 10,000 ppm for 4 weeks prior to mating and during the mating, gestation, and lactation periods. Body weight and/or body weight gain and food consumption were lower than controls at ≥3,000 ppm in females and ≥6,000 ppm in males. Lower pup weights were evident at ≥6,000 ppm by day 4 postpartum.

Observations: Observations for moribundity and overt signs of toxicity were conducted once a day, and mortality checks were conducted twice a day. A more detailed clinical examination was performed weekly. Body weight and food consumption were recorded weekly for both sexes. In addition, for females, they were determined on gestation days 0, 6, 12, 18, and 21 and on lactation days 0, 4, 7, 10 (food), 14, 17 (food), 19 (food consumption only), and 21. Terminal body weight was recorded for all animals. The estrous cycle for all females was recorded for 10 days prior to mating.

The following data were recorded for each litter:

- Number of live and dead pups, pup weight (collectively by sex and separately), sex, and external malformations at birth and on lactation days 0, 4, 7, and 14

- Number of live and dead pups, individual pup body weight, external abnormalities, and sex at weaning on lactation day 21

- Daily clinical signs

On lactation day 4, pups were randomly culled to 4/sex/litter whenever possible; culled pups were weighed, sacrificed, and discarded. Pups found dead or moribund were necropsied. F_1 pups were weaned on day 21; 26 male and 26 female pups were randomly selected as F_1 parental animals. F_2 pups were sacrificed and necropsied on day 21. F_1 offspring not selected for mating were sacrificed and necropsied at weaning (10/sex/group from 10 litters).

Parental animals found dead or sacrificed and moribund females that did not deliver were necropsied. Parental F_0 and F_1 animals were sacrificed and subjected to a gross pathological examination including a thorough evaluation of the reproductive system. The following tissues were preserved in 10% neutral buffered formalin:

- Pituitary[a]
- Seminal vesicles[a,b]
- Prostate[a,b]
- Uterus[b]
- Ovaries[b]
- Liver[a,b,c]
- Mammary gland (thoracic and inguinal)
- Brain[a,c]
- Testes[a,b,d]
- Epididymides[a,b,d]
- Vagina[b]
- Kidneys[a,c,e]
- Gross abnormalities[e]

[a] Organ weight for F_1 adults only (paired organs were weighed separately).
[b] Histological examination for control and high dose rats.
[c] Retained for F_1 adults only.
[d] Fixed with Zenker's fluid (sacrificed animals only).
[e] Histological examination for all groups.

Statistical Analysis: The following analyses were conducted:

- Parental and pup body weights, maternal body weight gain, organ weights, food consumption, and mean live litter sizes -- ANOVA and Dunnett's test

- Conception rate, mating, fertility, and gestation indices, and incidence of dead pups -- Fisher's exact probability test

- Postimplantation losses, pup numbers, viability, survival and lactation indices, length of gestation, and pup sex ratio (% male) -- Kruskal-Wallis and Mann-Whitney 'U' tests

Compliance

- A signed Statement of No Data Confidentiality Claim, dated December 13, 1991, was provided.

- A signed Statement of Compliance with EPA GLPs, dated September 23, 30, and December 13, 1991, was provided.

- A signed Quality Assurance Statement, dated September 20 and 23, 1991, was provided.

C. RESULTS

Test Material Analysis

The purity of the test material was 95.3% as determined before initiation of the study. Homogeneity analyses of week 1 diets demonstrated adequacy of mixing (coefficient of variation ≤8%). Concentrations of the test material in the diets ranged from 92.2% to 119.3% of nominal values. Analyses for stability of the test material in the diet over 14 days of storage (at room temperature) were conducted during an earlier range-finding study and were not reported.

Parental Toxicity

Mortality: No compound-related mortality was observed for any sex and generation.

In the F_0 generation, one male from the 200-ppm group, was sacrificed due to poor health condition on day 98 of treatment; pathological examination showed multiple renal findings including a cyst. One female from the same dose group was sacrificed on day 11 postpartum after the death of her litter due to technical error. At 5,000 ppm, a moribund female and her entire litter were sacrificed on day 1 postpartum (day 96 of treatment); necropsy revealed clear fluid in the thoracic and abdominal cavities and 3 dead fetuses.

In the F_1 generation, one male from the control group died on day 98 of treatment; the cause of death was determined to be a urinary tract problem related to prostatitis. Two males from the 200-ppm group were sacrificed because of poor health conditions on days 63 and 114 of treatment; one had fractured nasal bones and the cause of the death of the other could not be determined.

Clinical Observations: No compound-related clinical signs were observed for any sex and generation. Cranial/periorbital staining, scabs in the cervical region, and alopecia in cervical/thoracic regions and on limbs and/or paws were noted at similar incidences in all dosage groups for both sexes and generations.

Body Weight: Compound-related effects were observed at 5,000 ppm for both sexes and generations. Summaries of body weight changes from selected time intervals are presented in Tables 1 and 2. Detailed results are presented in the text.

In the F_0 generation, body weight (data not shown) for males was decreased (≥5%) significantly ($p<0.05$) at 5,000 ppm on weeks 10 (premating period) and 11 (week of mating). Body weight gain (Table 1) for these males was significantly ($p<0.05$) decreased at 5,000 ppm 1 week

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prior to initiation of treatment (7%; data not shown) and on weeks 6-7 (16%) and 9-10 (49%). Body weight gain at 5,000 ppm for the entire premating period (weeks 0-10) significantly ($p<0.05$) decreased below controls (8%).

Among F_0 females, body weight (data not shown) was decreased significantly ($p<0.05$) below controls at 5,000 ppm throughout the premating period (weeks 1-10; 4-11%). Body weight gain (Table 1) was decreased significantly ($p<0.05$) at 5,000 ppm during premating on weeks 0-1 (19%), 1-2 (20%), and 8-9 (41%), and at 1,000 ppm on weeks 8-9 (50%). Body weight gain at 5,000 ppm for the entire premating period (weeks 0-10) was decreased significantly ($p<0.01$) below controls (21%). Body weights were decreased significantly ($p<0.05$; data not shown) below controls at 5,000 ppm during days 0-21 of the gestation (8-10%) and during 0-14 of lactation (8-11%) periods. However, body weight gain during gestation (Table 2) did not differ significantly between groups but did increase ($\geq$100%) significantly during lactation (data not shown).

In the F_1 generation, body weight (data not shown) for males was consistently significantly ($p<0.01$) decreased by 10-23% at 5,000 ppm throughout the premating period (weeks 1-12). Body weight gain (Table 1), however, was decreased significantly ($p<0.01$) at this dose level only for weeks 0-2 ($\geq$15%), 3-4 (9%), and for the entire premating period (9%). During the postmating period (weeks 13-18), the body weight gain at 5,000 ppm was significantly ($p<0.05$) lower for weeks 14-15 (37%) and over the entire postmating period (10%).

Among F_1 females, body weight during the premating period (data not shown) was consistently significantly ($p<0.05$ or <0.01) decreased by 7-20% at 5,000 ppm. Body weight gain (Table 1) was decreased significantly ($p<0.05$) at this dose level only for weeks 7-9 ($\geq$25%). Body weights (data not shown) for females decreased significanlty at 5,000 ppm during the entire gestation period ($\geq$7%) and during lactation on days 0-14 ($\geq$8%). Body weight gain for females at 5,000 ppm never differed significantly above controls during gestation (Table 2). Body weight gain was significantly increased at 5,000 ppm during lactation (data not shown).

Food Consumption: Compound-related effects were observed in food consumption at 5,000 ppm in both sexes and generations. Summaries of food consumption from selected time intervals are presented in Tables 3 and 4. Detailed results are presented in the text.

In the F_0 generation, daily food consumption (g/animal) for males significantly decreased below controls prior to treatment (week -1-0; 8%) and for weeks 0-1 (6%) and 5-6 (6%) and for females for weeks 7-9 (9%) during the premating period (Table 3) at 5,000 ppm. It was significantly decreased for females on gestation days 0-12 ($\geq$9%; Table 4).

In the F_1 generation males, daily food consumption significantly ($p<0.05$) decreased ($\geq$7%) for weeks 0-2, 3-4, 6-7, 9-10 during premating (Table 3), for weeks 11-12 (8%) during mating (data not shown), and for weeks 15-18 ($\geq$7%) during post mating (data not shown) at 5,000 ppm. For females, food consumption significantly decreased for premating weeks 0-1 (11%;

Table 3) and gestation days 6-12 (13%; Table 4) at 5,000 ppm and for days 18-21 of gestation (≥11%) at all three dosage levels (Table 4).

Compound Intake: In the F_0 generation, mean daily compound intake during the premating period was 0, 16, 76, and 386 mg/kg/day for males and 0, 18, 87, and 442 mg/kg/day for females at 200, 1,000, and 5,000 ppm, respectively. For females during the gestation period, the mean daily compound intake was 0, 15, 75, and 381 mg/kg/day for these same dosage levels. In the F_1 generation, mean daily compound intake during premating was 0, 19, 97, and 519 mg/kg/day for males and 0, 21, 105, and 554 mg/kg/day for females at 200, 1,000, and 5,000 ppm, respectively. For females during gestation, the mean daily compound intake was 0, 14, 70, and 365 mg/kg/day for these same dosage levels.

Gross and Microscopic Pathology: Compound-related increases in the kidney weights of F_1 males and liver weights of F_1 males and females were observed at 5,000 ppm. The increases in these organ weights in males were accompanied by increased incidence of focal clear cells of the liver and of chronic interstitial nephritis of the kidney.

Organ Weights: Selected organ weights are presented in Table 5. A compound-related increase in kidney weight was observed in F_1 males.

In the F_0 generation, no organ weight data were reported.

In the F_1 generation, absolute and relative (to body and brain weights) liver weights increased significantly in both sexes at 5,000 ppm. Kidney weight was increased significantly at 1,000 ppm and 5,000 ppm in males when expressed as relative to body weight, but not on an absolute or brain weight basis.

Histopathology: In the F_0 generation, no histopathological changes were observed in either sex in the organs examined.

In the F_1 generation, the increase in the liver weight in males at 5,000 ppm was accompanied by a slightly higher incidence of focal clear cells (2/26, 2/9, 4/8, and 9/26 animals at 0, 200, 1,000, 2,000 ppm, respectively). This change was generally associated with a pale area at the fissure of the medium lobe (3/26, 3/26 ,5/26, and 10/26 animals at 0, 200, 1,000, 2,000 ppm, respectively), something which is frequently observed in male rats (according to the study pathologist). The significance of this finding was unclear. An increased incidence of chronic interstitial nephritis was observed in males receiving 5,000 ppm (7/26, 3/26, 7/26, and 15/26 animals at 0, 200, 1,000, 2,000 ppm, respectively). Consequently, kidney effects in males at 5,000 ppm were considered to be treatment-related.

Both liver (clear cell focus) and kidney (chronic interstitial nephritis) changes were statistically significantly increased at 5,000 ppm by Fisher's exact test.

Reproductive Performance

No compound-related effects on reproductive performance were observed in either generation. Summaries of results are presented in Tables 7 and 8.

Offspring: In both generations at 5,000 ppm, pup body weight for sexes combined (Tables 7 and 8) or separated (data not shown) was decreased ($\geq$10%) significantly ($p<0.05$) for lactation days 14-21. The decreased body weights remained in the adult animals as well. This decrease was considered to be a compound related but systemic effect.

No compound-related effects were reported in clinical or pathological findings in pups (including external malformations) from any litter or generation.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

Test Material Analyses

Purity, homogeneity, and stability of the test compound in the diet were confirmed. Data to support the stability over 14 days were not provided. Concentrations of the test compound in the diet were within $\pm$ 10% of target concentrations with the exception of week 1 (all dose levels, 78-85% of target), week 4 (1000 ppm, 113%), week 5 (200 ppm, 114%), and week 32 (200 ppm, 119%).

Systemic and Reproductive Toxicity

Compound-related parental toxicity was observed at 5,000 ppm in both sexes and generations. It was manifested as significantly decreased body weight, body weight gain, and food consumption. No treatment-related clinical signs or mortality were observed.

The pups of both generations experienced significant reduction in body weight from lactation days 14 to 21. This body weight gain deficit was maintained after weaning.

The NOEL and LOEL for systemic toxicity were 1,000 and 5,000 ppm, respectively, based on decreased parental body weight and pup body weight during lactation. Histopathological changes in the liver and kidney were seen in F_1 males and liver weights of F_1 males and females were also increased at 5,000 ppm.

The NOEL for reproductive toxicity was 5,000 ppm, based on a lack of effect on reproductive performance at any dose in either generation.

Study and/or Reporting Deficiencies

The results of stability analysis should be submitted.

E. CLASSIFICATION Core Minimum Data

Systemic Toxicity NOEL = 1,000 ppm (≈ 92 mg/kg/day)
Systemic Toxicity LOEL = 5,000 ppm (≈ 476 mg/kg/day; based on decreased parental and pup body weight during lactation and histopathological changes in the liver and kidney of F_1 males and increase in liver weights of F_1 males and females)

Reproductive Toxicity NOEL = 5,000 ppm (≈ 476 mg/kg/day)

F. RISK ASSESSMENT Not applicable

Table 1. Mean Body Weight Gain (g ± S.D.) During the Premating Period for Rats Fed S-31183 for Two Successive Generations[a]

Study Week	Dietary Level (ppm) 0	200	1,000	5,000
F_0 Males				
1- 2	52.0 ± 7.4	51.5 ± 7.6	53.1 ± 6.8	50.0 ± 8.8
3- 4	35.7 ± 4.9	38.1 ± 6.5	39.1 ± 6.1	34.5 ± 6.1
6- 7	26.6 ± 4.7	23.4 ± 6.5	23.7 ± 5.8	22.3 ± 5.0*
9-10	18.9 ± 8.6	16.8 ± 5.9	14.8 ± 6.3	9.6 ± 6.1**
0-10	316.6 ± 31.6	314.6 ± 41.6	314.7 ± 33.3	289.7 ± 32.8*
F_0 Females				
1- 2	22.8 ± 7.2	22.2 ± 7.8	23.1 ± 4.3	18.3 ± 5.1*
3- 4	15.4 ± 6.5	16.7 ± 7.0	15.9 ± 7.5	13.7 ± 3.9
6- 7	6.4 ± 6.1	4.8 ± 5.8	4.6 ± 6.6	4.8 ± 3.7
9-10	10.9 ± 9.8	12.2 ± 11.9	14.4 ± 6.6	9.6 ± 8.9
0-10	144.9 ± 23.3	141.9 ± 27.9	140.8 ± 16.5	113.9 ± 15.4**
F1 Males				
1- 2	66.2 ± 8.1	67.4 ± 7.4	66.9 ± 6.5	56.6 ± 7.7**
3- 4	67.4 ± 8.9	67.7 ± 6.2	68.0 ± 5.0	61.1 ± 7.8**
6- 7	41.6 ± 9.1	32.7 ± 21.1	39.1 ± 8.2	36.8 ± 6.3
9-10	25.0 ± 9.0	26.4 ± 7.0	24.6 ± 7.9	22.4 ± 5.7
0-12	498.0 ± 58.2	500.6 ± 44.2	501.8 ± 48.6	453.9 ± 54.9*
F_1 Females				
1- 2	46.4 ± 5.4	46.2 ± 6.9	44.7 ± 4.0	43.8 ± 6.1
3- 4	28.8 ± 7.6	29.3 ± 6.7	30.6 ± 6.3	26.4 ± 6.6
6- 7	16.5 ± 5.6	16.1 ± 5.7	16.0 ± 6.1	15.1 ± 4.8
9-10	10.9 ± 6.1	10.3 ± 5.6	10.9 ± 5.4	8.3 ± 3.7
11-12	10.8 ± 13.4	12.1 ± 14.8	9.8 ± 11.3	3.8 ± 6.6
0-12	258.5 ± 31.0	266.2 ± 34.6	257.5 ± 16.2	239.6 ± 30.2

[a]Data were extracted from Study No. 83963, Tables 5, 6, 11, 33, 34, and 39 and Appendices 5, 6, 11, 33, and 34.

*Significantly different from controls ($p<0.05$)

**Significantly different from controls ($p<0.01$)

Table 2. Mean Body Weight Gain (g ± S.D.) During Gestation for Rats Fed S-31183 for Two Successive Generations[a]

Gestational Days	Dietary Level (ppm) 0	200	1,000	5,000
F_0 Generation				
0- 6	33.8 ± 8.7	32.7 ± 10.6	34.3 ± 8.0	28.4 ± 7.5
6-12	25.4 ± 6.9	26.7 ± 6.7	24.5 ± 6.4	23.7 ± 4.6
12-18	60.9 ± 12.7	54.6 ± 10.5	61.1 ± 10.0	59.8 ± 11.7
18-21	45.6 ± 21.4	45.0 ± 14.5	53.4 ± 8.9	45.1 ± 14.5
0-21	165.6 ± 33.9	159.0 ± 24.7	173.4 ± 19.9	155.8 ± 24.2
F_1 Generation				
0- 6	28.3 ± 6.0	28.7 ± 6.9	30.2 ± 9.4	24.1 ± 6.1
6-12	29.5 ± 5.8	26.7 ± 7.2	23.1 ± 10.0	26.3 ± 5.0
12-18	57.1 ± 11.3	54.5 ± 11.4	55.6 ± 13.1	61.3 ± 10.0
18-21	57.1 ± 11.3	45.8 ± 13.8*	45.2 ± 15.6*	49.6 ± 10.3
0-21	171.9 ± 22.8	155.7 ± 26.7	154.1 ± 25.1	162.1 ± 21.5

[a]Data were extracted from Study No. 83963 Tables 7 and 35 and Appendices 7 and 35.

*Significantly different from controls ($p<0.05$)

Table 3. Mean Food Consumption (g/animal/day ± S.D.) During the Premating Period for Rats Fed S-31183 for Two Successive Generations[a]

	Dietary Level (ppm)			
Study Week	0	200	1,000	5,000
F_0 Males				
1- 2	215.8	218.6	216.6	218.5
3- 4	223.9	224.2	224.8	221.0
6- 7	222.9	222.6	218.8	212.1
9-10	219.2	218.1	218.9	206.5
F_0 Females				
1- 2	149.8	158.4	155.7	146.8
3- 4	157.7	165.8	167.2	152.6
6- 7	162.5	161.6	158.7	152.3
9-10	157.2	156.2	157.1	147.1
F_1 Males				
1- 2	162.6	164.2	164.3	142.9**
3- 4	216.8	216.4	214.3	196.9**
6- 7	238.3	220.5*	234.7	220.1*
9-10	233.1	231.2	236.8	217.7
11-12	234.3	228.3	228.4	215.3**
F_1 Females				
1- 2	145.3	145.5	146.4	136.7
3- 4	156.2	154.5	157.7	153.7
6- 7	158.9	161.3	159.7	151.9
9-10	156.7	156.6	159.8	152.6
11-12	154.0	160.2	157.8	144.4

[a]Data were extracted from Study No. 83963, Tables 9, 10, 37, and 38 and Appendices 9, 10, 37, and 38.

*Significantly different from controls ($p<0.05$)

**Significantly different from controls ($p<0.01$)

Table 4. Mean Food Consumption (g/animal/day) During Gestation for Rats Fed S-31183 for Two Successive Generations[a]

Gestational Days	Dietary Level (ppm) 0	200	1,000	5,000
F_0 Generation				
0- 6	159.1	154.5	157.2	142.7*
6-12	180.2	184.0	176.9	163.1**
12-18	189.1	181.1	181.0	176.7
18-21	81.3	76.4	81.8	77.2
F_1 Generation				
0- 6	150.3	149.6	155.0	142.5
6-12	171.5	163.5	162.0	150.0**
12-18	174.8	167.8	174.7	166.7
18-21	80.8	71.4**	71.3**	70.9**

[a]Data were extracted from Study No. 83963, Tables 11 and 39 and Appendix 11.

*Significantly different from controls ($p<0.05$)

**Significantly different from controls ($p<0.01$)

Table 5. Absolute (g) and Relative (mg %) Organ Weights for Parental Rats Fed S-31183 for Two Successive Generations[a]

Organ		Dietary Level (ppm) 0	200	1,000	5,000
F_1 Generation - Males					
Terminal body weight		626.50	616.50	616.50	548.20**
Left, kidney	Absolute	2.20	2.14	2.34*	2.12**
	Relative to body wt.	0.35	0.35	0.38*	0.39**
	Relative to brain wt.	98.50	96.03	104.15	98.57
Right, kidney	Absolute	2.24	2.19	2.40**	2.17**
	Relative to body wt.	0.36	0.36	0.39**	0.40**
	Relative to brain wt.	100.11	98.31	106.68	100.87
Liver,	Absolute	19.20	18.82	20.75**	21.41**
	Relative to body wt.	3.06	3.05	3.35**	3.90**
	Relative to brain wt.	863.57	844.09	921.37	992.46**
F_1 Generation - Females					
Terminal body weight		354.90	361.70	357.60	338.50*
Left, kidney	Absolute	1.34	1.39	1.40	1.33
	Relative to body wt.	0.37	0.38	0.39	0.39
	Relative to body wt.	64.80	67.40	68.55	67.60
Right, kidney	Absolute	1.39	1.45	1.44	1.38
	Relative to body wt.	0.39	0.40	0.40	0.41
	Relative to brain wt.	67.66	70.13	70.20	70.32
Liver,	Absolute	16.81	16.57	18.31	20.37**
	Relative to body wt.	4.74	4.60	5.13	6.03**
	Relative to brain wt.	814.39	802.27	892.21	1037.00**

[a]Data were extracted from Study No. 83963, Tables 46, 47, 48, and 49 and Appendices 46, 47, 48, and 49.

*Significantly different from control ($p<0.05$)

**Significantly different from control ($p<0.01$)

TABLE 6. Summary of Effects of Dietary Administration of S-31183 on F_0 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	200	1,000	5,000
No. female matings (F_0 parents)	26	24	23	25
Mating index (%)	100.0	92.3	88.5	96.2
No. pregnancies	22	22	20	21[b]
Fertility index (%)[c]	84.6	84.6	76.9	84.6
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	21.9[e]	21.7	21.7	21.7
Total No. stillborn pups	13	6	4*	6
Total No. live pups[f]				
Day 0	327	317	315	309[g]
Day 4 precull	312	314	305	289[g,h]
Day 21	159	158[i]	154	157[g,h]
Mean no. live pups/litter				
Day 0	14.9	14.4	15.8	14.7
Day 4 precull	14.2	14.3	15.3	14.5
Day 21	7.2	7.5	7.7	7.9
Live birth index (%)[j]	96.2	98.1	98.8	98.1
Viability index (%)[k]	95.4	99.0	97.2	98.1
Lactation index (%)[l]	94.9	94.0	96.3	98.1
Pup body weight (g)				
Day 0	6.4 ± 0.5	6.5 ± 0.7	6.4 ± 0.6	6.3 ± 0.5[g]
Day 4 precull	9.7 ± 1.7	10.4 ± 1.5	10.3 ± 1.1	9.3 ± 1.3[g,h]
Day 14	30.4 ± 5.1	30.9 ± 2.9	32.1 ± 3.4	27.3 ± 2.9*[g,h]
Day 21	51.0 ± 6.2	53.4 ± 4.6	53.1 ± 6.5	43.8 ± 3.4**[g,h]
Sex ratio (% male)	51.0	53.2	49.9	52.5

[a]Data were extracted from Study No. 83963, Tables 14, 15, 22, 23, 26, and Appendix EE.

[b]One litter excluded because days of mating and littering unknown.

[c]Fertility index was calculated as: $\frac{\text{No. of pregnant females}}{\text{No. of females placed for mating}} \times 100$

[d]Gestation index was calculated as: $\frac{\text{No. of dams with live pups at birth}}{\text{No. of pregnant rats}} \times 100$

[e]Sample size (N) of 21; mating not detected for one litter.

[f]Calculated by the reviewers using individual animal data.

[g]Exact day of littering unknown in one litter, excluded from statistical analysis.

[h]One litter was sacrificed day 1 postpartum because of poor condition of dam, excluded from viability statistics.

[i]All pups in one litter died because of technical error, excluded from statistical analysis.

[j]Live birth index was calculated as: $\frac{\text{No. of pups born alive}}{\text{No. of pups born}} \times 100$

[k]Viability index was calculated as: $\frac{\text{No. of pups alive on day 4 precull}}{\text{No. of pups born alive}} \times 100$

[l]Lactation index was calculated as: $\frac{\text{No. of pups alive on day 21}}{\text{No. of pups alive on day 4 postcull}} \times 100$

*Significantly different from controls ($p<0.05$)
**Significantly different from controls ($p<0.01$)

TABLE 7. Summary of Effects of Dietary Administration of S-31183 on F_1 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	200	1,000	5,000
No. female matings (F_1 parents)	23	23	26	24
Mating index (%)	88.5	88.5	100.0	92.3
No. pregnancies	20	19	21	21
Fertility index (%)[b]	76.9	73.1	80.8	80.8
Gestation index (%)[c]	100.0	100.0	95.2	100.0
Gestation length (days)	21.8	21.8	21.9	21.6
Total no. stillborn pups	5	4	7	11
Total no. live pups[d]				
Day 0	308	280	303[e]	321
Day 4 precull	300	276	300[e]	308
Day 21	160	146	158[e]	164
Mean no. live pups/litter				
Day 0	15.4	14.7	15.1[e]	15.3
Day 4 precull	15.0	14.5	15.0[e]	14.7
Day 21	8.0	7.7	7.9[e]	7.8
Live birth index (%)[d,f]	98.4	98.6	97.7	96.7
Viability index (%)[g]	97.1	98.2	99.1	95.3
Lactation index (%)[h]	100.0	96.8	98.8	99.4
Pup body weight (g)				
Day 0	6.3 ± 0.4	6.3 ± 0.3	6.4 ± 0.5	6.2 ± 0.5
Day 4 precull	9.8 ± 1.2	9.6 ± 1.8	10.3 ± 1.8	9.5 ± 0.9
Day 14	33.6 ± 3.0	31.4 ± 5.1	33.4 ± 3.8	30.6 ± 2.0*
Day 21	55.5 ± 4.3	51.4 ± 8.2	54.1 ± 6.0	49.0 ± 3.3**
Sex ratio (% male)	51.7	49.9	49.7	54.2

[a]Data were extracted from Study No. 83963, Tables 42, 43, 56, 57, and 60 and Appendices 43, 55, and 58.

[b]Fertility index was calculated as: $\frac{\text{No. of pregnant females}}{\text{No. of females placed for mating}} \times 100$

[c]Gestation index was calculated as: $\frac{\text{No. of dams with live pups at birth}}{\text{No. of pregnant rats}} \times 100$

[d]Calculated by the reviewers using individual animal data.

[e]Based on sample size (N) of 20; one litter was born dead.

[f]Live birth index was calculated as: $\frac{\text{No. of pups born alive}}{\text{No. of pups born}} \times 100$

[g]Viability index was calculated as: $\frac{\text{No. of pups alive on Day 4 precull}}{\text{No. of pups born alive}} \times 100$

[h]Lactation index was calculated as: $\frac{\text{No. of pups alive on Day 21}}{\text{No. of pups alive on Day 4 postcull}} \times 100$

*Significantly different from controls ($p<0.05$)
**Significantly different from controls ($p<0.01$)

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