4/29/93

FINAL

DATA EVALUATION RECORD

SUMILARV

Study Type: Developmental Toxicity Study in Rats
(Segments II and III)

Prepared for:

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U.S. Environmental Protection Agency
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DATA EVALUATION REPORT

STUDY TYPE: Developmental toxicity study in rats (Segments II and III)
Segment II: Effect on prenatal development
Segment III: Effect on postnatal development

EPA IDENTIFICATION NUMBERS

EPA ID No.: 010308-RR

PC Code: 129032

MRID No.: 421783-12 (amended MRID 413217-19)

TEST MATERIAL: [1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine

SYNONYMS: S-31183; Sumilarv technical grade

SPONSOR: Sumitomo Chemical Co., Ltd., Osaka, Japan

STUDY NUMBER: 302-2358

TESTING FACILITY: Sumitomo Chemical Co., Ltd., Osaka, Japan

TITLE OF REPORT: Sumilarv -- Study of S-31183 by Oral Administration During the Period of Fetal Organogenesis in Rats

AUTHOR: Tadashi Saegusa

REPORT ISSUED: March 28, 1988

CONCLUSIONS: In a developmental toxicity study, effects on prenatal (Segment II) and postnatal (Segment III) development were assessed in Sprague-Dawley rats by administering S-31183 via gavage at 0, 100, 300, or 1,000 mg/kg/day during gestation days (GDs) 7-17, inclusive. Maternal toxicity was manifested as increased incidences of mortality and clinical signs at 1000 mg/kg/day and decreased body weight, body weight gain, and food consumption, and increased water consumption at 300 and 1,000 mg/kg/day. Based on these results, the maternal NOEL and LOEL were 100 and 300 mg/kg/day, respectively.

In Segment II of the study, developmental toxicity observed at 300 and 1,000 mg/kg/day, was manifested as increased incidences of fetuses with skeletal variations. Consequently, the NOEL and LOEL for prenatal developmental toxicity were 100 and 300 mg/kg/day, respectively.

In Segment III of the study, postnatal developmental toxicity was manifested as increased incidences of visceral and skeletal variations at

1,000 mg/kg/day. Consequently, the NOEL and LOEL for postnatal developmental toxicity were 300 and 1,000 mg/kg/day, respectively.

CLASSIFICATION: Core Minimum Data. This study meets the minimum requirements set forth under Guideline Series 83-3 for a developmental toxicity study in rats.

A. MATERIALS

Test Compound

Purity:	97.2%
Stability:	Not reported (stability confirmed by sponsor)
Description:	White solid
Lot number:	PTG-86011
Receipt date:	Not reported
Contaminants:	Not reported

Vehicle: Corn oil (lot no. V6K5751), Nakarai Chemicals, Ltd., Japan

Test Animals

Species:	Rat
Strain:	Slc:SD rats (SPF)
Source:	Shizuoka Laboratory Animal Center, Shizuoka, Japan
Age:	9 weeks upon arrival, 11 weeks at initiation of mating
Weight:	197.6-296.9 g on GD 0
Males used:	Same strain and supplier

B. STUDY DESIGN

This study was designed to assess the potential developmental effects in fetuses and offspring of pregnant rats dosed with S-31183. Developmental toxicity was evaluated in two separate segments. Segment II was designed to assess the effects on prenatal development. Segment III assessed the effects on postnatal development.

Mating: Following approximately 14 days of acclimation, females were mated 1:1 with males of the same strain and source. Females were checked each morning for the presence of vaginal sperm. The day on which sperm were found was designated GD 0. Cohabitation was discontinued when copulation was confirmed.

Animal husbandry: Food (radiation sterilized pelletized feed; FR-2, Funabashi Farm Co., Ltd.) and chlorine-sterilized well water was available ad libitum throughout the study. A 12/12-hour light/dark cycle was maintained. Temperature and humidity ranges were 24±2°C and 50±10%, respectively. Air changes were approximately 16 per hour.

Group arrangement: Animals were allocated to dose groups using a stratified randomization method based on GD 0 body weight as follows:

Test Group	Dose Level (mg/kg/day)	Number Assigned Per Group
Control	0	36
Low-dose	100	36
Mid-dose	300	36
High-dose	1,000	43[a]

[a]The number excludes five animals that inadvertently received test solutions starting on GD 6.

Dose administration: Doses were administered daily via gavage on GDs 7 through 17 in a volume of 5 mL/kg. The body weights on GD 7 were used to calculate the concentration of the doses. Test material was melted by heating at approximately 60°C, and mixed and diluted with corn oil. Doses were prepared weekly. Stability of the test material over a 7-day period was confirmed by the sponsor prior to the initiation of the study. Analysis for concentration of the test material in the vehicle was conducted on the dosing preparation. Homogeneity of the dosing suspensions was not determined.

Dose rationale: Concentrations of the doses were selected based on the results of a range-finding study conducted in the same strain; seven or eight pregnant rats per group were dosed at 125, 250, 500 or 1,000 mg/kg/day from day 7 to day 17 of gestation. Maternal toxicity was manifested as clinical signs such as soft stools or diarrhea, erythema and swelling of the periproctal region, decreases in body weight/weight gain, (data not given) and food consumption in dams receiving 500 and 1,000 mg/kg/day. Water intake increased in a dose-dependent manner from the initiation of treatment in animals that received 250 mg/kg/day or more. Enlargement of the adrenal glands and involution of the thymus were noted at necropsy in the 1,000 mg/kg/day group. No developmental toxicity was observed.

Observations of dams: Dams were observed twice daily for mortality and overt signs of toxicity. Body weight was recorded on GDs 0, 3, 5, and 7, and daily thereafter, and on days 0 (day of delivery), 4, 7, 14, and 21 postpartum. Food and water consumption were measured on GDs 1, 3, 5, and 7 and daily thereafter and on days 1, 4, 7, 14, and 21 postpartum.

For Segment II of the study, 20-23 dams were sacrificed on GD 21 by exsanguination under ether anesthesia and litters were delivered by cesarean section. Examination and/or data collection for these dams and dams sacrificed on day 21 postpartum (for Segment III of the study) included the following:

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- The heart, lungs, liver, spleen, kidneys, adrenal glands, thymus, and ovaries were weighed (ovaries were excluded from weighing at cesarean section) and fixed in 10% formalin.

- The relative weight of each organ (expressed as a ratio per 100 g body weight) was recorded.

- Number of implantation sites was recorded.

- Number of live born pups was recorded.

- Live birth index was calculated.

In addition, for dams sacrificed on GD 21 following cesarean section, the following data collection and/or examination were conducted:

- Ovaries and uterus were removed.

- Number of corpora lutea was counted.

- Numbers and locations of resorptions (early and late), and macerated and dead fetuses were recorded, and live fetuses were examined.

Observation of F_1 fetuses: For live fetuses delivered by cesarean section on GD 21, the following data collection and/or examinations were conducted:

- Individual fetuses were weighed and sexed.

- Approximately one-third of the fetuses in each litter were fixed in Bouin's solution and subjected to visceral examination using the method of Wilson (1965).

- The remaining two-thirds of the fetuses were fixed in 95% alcohol, and skeletal specimens were prepared by the method of Dawson (1926) and then examined.

Observation of delivery and newborns: For Segment III of the study, 10-13 dams in each dose group were permitted to deliver naturally, and the following data collection and/or examinations were conducted:

- The length of the gestation period for each dam allowed to deliver naturally was recorded.

- Numbers of live and stillborn offspring were counted and pups were sexed.

- Pups were examined for external anomalies.

Animals that did not deliver by GD 24 were sacrificed and examined for evidence of pregnancy. On day 4 postpartum, offspring were culled to adjust the size of each litter to eight offspring. The number of male and female offspring was also adjusted to be as nearly equal as possible using computer-generated random numbers. The extra offspring were sacrificed

and examined for skeletal anomalies. Body weight was determined on days 4, 7, 14, and 21 postpartum.

During the lactation period, maternal care of pups and growth development of offspring, including gonadal development after weaning, were observed. Survival rates and the weaning rate (following litter size adjustment) were calculated at day 4. On day 20 postpartum, all offspring were examined for visual placing, Preyer's, righting, and mid-air righting reflexes and response to pain. After weaning on day 21 postpartum, all offspring were necropsied, with the exception of two per sex per litter which were examined further for learning ability. The following endpoints were examined in the necropsied offspring:

- Major organs (heart, lungs, liver, spleen, kidneys, testes including epididymis, and ovaries) were weighed and then fixed in a 10% formalin solution.

- Skeletal anomalies were recorded.

Offspring examined for learning ability were sacrificed at 8 weeks of age and the major organs were examined in the same manner as in the animals sacrificed at 3 weeks of age. The following learning tests were conducted:

- Open field test at 4 weeks of age to determine the frequencies of ambulation, rearing, preening, grooming, as well as to record the number of offspring showing defecation and urination within 3 minutes according to the method of Hall (1934)

- Motor coordination with the rotorod performance test at 5 weeks of age to measure the frequency of falling from a drum according to the method of Lynch et al. (1975)

- Learning ability at 6 weeks of age using the water filled multiple T-maze according to the method of Butcher et al. (1973)

One male and one female offspring from each litter were weighed after weaning every 7-10 days until 11 weeks of age. Thereafter, the two animals from each litter were used for reproductive tests, and they were observed twice daily for clinical signs of toxicity. At 11 weeks, these animals were paired for mating within the same group, avoiding sibling matings. Pairs cohabitated for a maximum of 2 weeks until copulation. If copulation was not confirmed within the initial 2 weeks, offspring were again cohabitated with untreated females or fertile males from the same group for another week, and examinations for reproductive performances were conducted. Copulated females were weighed every 3 days, then necropsied on GD 21. The following were examined:

- Number of corpora lutea

- Number and position of stillborns (at early or late stage) and live fetuses

- Weight and sex of live fetuses

- External, visceral, and skeletal anomalies of live fetuses

Nonfertile male and female rats were necropsied. Their reproductive organs, including testes, seminal vesicles, prostate, ovaries, and uteri were fixed in 10% formalin and/or subjected to histopathological examinations.

Statistical analysis: The following methods were used.

- Means ± standard deviation were analyzed by Student's T-test or Welch's test.
- Values expressed as frequency (i.e., copulation rate and fertility rate) were analyzed by Chi-Square test and Wilcoxon's rank sum test.
- Numbers of litters with resorptions, dead fetuses, nonlive or affected implants, and anomalies were analyzed by Chi Square test and Fisher's Exact test
- Body weight gain and food consumption were analyzed by ANOVA

Compliance

- A signed Statement of No Data Confidentiality Claim, dated December 13, 1991, was provided.
- A signed Statement of Compliance with EPA and Japanese MAFF GLPs, dated September 28, 1989, October 6, 1989, and November 30, 1989, was provided.
- A signed Quality Assurance Statement, dated March 28, 1988, was provided.

C. RESULTS

Test Material Analysis

Purity of the test compound was approximately 97.2%. Analyses conducted on dosing solutions for concentration revealed a range of 90.0%-96.6% of nominal values. No homogeneity analysis was conducted. Stability of the dosing solutions for 7 days was confirmed by the sponsor.

Maternal Toxicity

Mortality: Compound-related mortality (29%) was noted at 1,000 mg/kg/day. A total of 12 dams died (Table 1); 3 on GD 10, 2 on GD 11, 2 on GD 12, 4 on GD 13, and 1 on GD 15. Necropsy findings revealed thymus and spleen atrophy, liver and kidney congestion, hemorrhagic mucous membranes, and enlargement of spleen, adrenal, kidney, and cecum.

Clinical observations: Compound-related clinical signs were observed at 1,000 mg/kg/day (Table 1) and included diarrhea, erythema, and swelling of the periproctal area, hypoactivity, wasting, hypothermia, lacrimation,

blanching of the auricle and extremities, and bloody dirtiness around the nose. Only one animal at 300 mg/kg/day exhibited clinical signs of hypoactivity, wasting, hypothermia, and blanching on GD 22.

Body weight: Compound-related decreases in body weight and weight gain were observed at 300 and 1,000 mg/kg/day. A summary of maternal body weight gain (calculated by the reviewers for selected intervals) is presented in Table 2. Detailed results are stated in the text.

Maternal body weight (data not shown) decreased from GD 9 through GD 21 at 1,000 mg/kg/day ($p<0.01$; ≥5%); from GD 13 to GD 20 at 300 mg/kg/day ($p<0.05$; ≥5%); and from GD 11 to GD 21 at 100 mg/kg/day (≥7%, nonsignificantly). Body weight gain decreased significantly from GD 8 through GD 21 ($p<0.01$; up to 54%) at 1,000 mg/kg/day; from GD 10 through GD 20 ($p<0.01$ or <0.05; up to 15%) at 300 mg/kg/day; and from GD 11 through GD 17 ($p<0.01$ or <0.05; up to 8%) at 100 mg/kg/day (data not shown). The effects on body weight/weight gain at 100 mg/kg/day were not considered to be biologically important. For the entire dosing period (Table 2), body weight gain decreased nonsignificantly to 46% and 86% of controls at 300 and 1,000 mg/kg/day, respectively. During the post-dosing period (Table 2) at these same dose levels, body weight gain increased by 18% and 14%, respectively. The corrected body weight gain over the entire gestation period (Table 2) significantly decreased (21.5%) at 1,000 mg/kg/day.

Food consumption: Compound-related decreases in food consumption were observed at 300 and 1,000 mg/kg/day. A summary of food consumption (g/animal; calculated by the reviewers for selected intervals) is presented in Table 3. Detailed results are stated in the text.

Food consumption significantly ($p \leq 0.05$) decreased for the following periods: GD 5 (7%), GDs 8-17 (≥10%), and GDs 19-21 (≥11%) at 1,000 mg/kg/day; GDs 9-16 (≥9%), and GD 17 (12%) at 300 mg/kg/day; and GD 10-12 (≥7%) and GD 14 (8%) at 100 mg/kg/day (data not shown). Decreased food consumption at 300 mg/kg/day and 1,000 mg/kg/day during the dosing period was considered to be treatment related although the values did not reach significant levels (Table 3).

Water consumption: Compound-related increases in water consumption were observed at 300 and 1,000 mg/kg/day. A summary of water consumption (mL/day; calculated by the reviewers for selected intervals) is presented in Table 4. Detailed results are stated in the text.

Significant ($p<0.01$ or <0.05) increases in water consumption were noted for the following periods: GDs 8-17 (≥26%; data not shown) and GDs 17-21 (≥46%; Table 4) at 1000 mg/kg/day; GDs 8-17 (≥13%; data not shown) and GDs 17-21 (≥17%; Table 4) at 300 mg/kg/day; and GDs 8 and 9 (≥13%) at 100 mg/kg/day. The overall water consumption during the entire gestation period at 300 and 1,000 mg/kg/day increased by 17% and 44%, respectively. These increases were considered to be compound-related.

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Results of Segment II

Gross pathology observations: Compound related significant increases in kidney and adrenal weights (absolute and relative) and decreases in thymus weights (absolute and relative) were observed in dams at 1,000 mg/kg/day (Table 5). Incidental changes in absolute heart weight at 1,000 mg/kg/day and in relative liver and kidney weights at 300 mg/kg/day were not considered to be compound related. Changes in thymus and adrenal glands were accompanied by histopathological findings.

Detailed histopathological findings are discussed below (also see Table 6). Animals receiving 1000 mg/kg/day sacrificed on day 21 of gestation had thymus atrophy (13 animals) and adrenal enlargement (15 animals).

Necropsy of dead animals from the 1,000 mg/kg/day group revealed thymus atrophy (12 animals), liver congestion (11 animals), spleen and adrenal atrophy (12 animals), kidney congestion (6 animals), stomach ulcer (3 animals), and hemorrhagic gastric mucous membranes (6 animals). These effects were considered to be compound related.

Cesarean section observations: A summary of cesarean section data is presented in Table 7. No compound-related effects were noted for any parameters at any dose level. The increased incidence of early resorptions at 1,000 mg/kg/day (and consequently % postimplantation loss) was not significant and therefore, not considered to be compound related. Two animals receiving 1000 mg/kg/day had totally resorbed litters.

Developmental Toxicity (Effects on Prenatal Development)

Incidences of external, visceral, and skeletal anomalies are presented in Table 8. Compound-related increases in the incidence of skeletal variations were noted at 300 and 1,000 mg/kg/day.

External examinations: Cyclopia with proboscis (one fetus) and polydactyly (one fetus) were observed at 300 mg/kg/day (Table 8).

Visceral examinations: The following incidental visceral malformations were observed (Table 8): arhinocephaly (one mid-dose fetus), ventricular septal defect (five control fetuses, three low-dose fetuses, and one high-dose fetus), left umbilical artery (two control fetuses, two low-dose fetuses, and one mid-dose fetus), unilateral absence of optic nerve (one control fetus), unilateral hypoplasia of thymus gland (one mid-dose fetus), and dislocation of esophagus (one control fetus).

Skeletal examinations: Skeletal malformations included multiple anomalies of ribs and vertebral arches (one control fetus), and multiple anomalies of the ribs and fusion of exoccipital and atlas and sternbrae (one mid-dose fetus). Variations were noted in all dose groups in the ribs, sternebrae, phalanges of fore and hind paws, metacarpus, and metatarsus. The number of fetuses with poorly ossified sternebrae increased in a dose-related manner (two control fetuses in 2 litters, three low-dose fetuses in 3 litters, four mid-dose fetuses in 4 litters, and six high-dose fetuses in 4 litters). Significant increases in the number of fetuses with opening of foramen transversarium of the 7th cervical vertebrae (3

low-dose fetuses in 3 litters; 10 mid-dose fetuses in 5 litters; and 22 high-dose fetuses in 11 litters) and in the total number of fetuses with skeletal variations (37 high-dose fetuses in 17 litters versus 14 control fetuses in 10 litters; 24% versus 7% in control fetuses) were considered to be compound-related findings (Table 8).

Results of Segment III

Gross pathology observations: No compound-related effects were noted in dams sacrificed on day 21 postpartum. Incidental findings included thymus atrophy (one low-dose and one high-dose dam), yellow-grayish liver (one mid-dose dam), and enlargement of the spleen (one mid-dose dam), adrenal (one mid-dose and one high-dose dam), and cecum (one high-dose dam). An incidental significant decrease in absolute spleen weight was observed at 1,000 mg/kg/day.

Effects on maternal and fetal offspring parameters: Maternal body weight and food consumption at 1000 and 300 mg/kg/day remained lower than control throughout lactation period; however, body weight gain significantly increased at 1000 mg/kg/day and decreased at 300 mg/kg/day compared to control during the same period (data not shown). Water consumption increased at 1000 and 300 mg/kg/day during lactation period (data not shown). No compound-related effects were noted on the reproductive parameters examined; a summary of effects on these parameters is presented in Table 9.

Significant increases in the mean body weight of male offspring on day 21 (Table 9) and female offspring on day 14 at 300 mg/kg/day (data not shown) were not considered to be compound related. One animal receiving 300 mg/kg/day had not delivered by GD 22 and began to show a decline in health. The animal was sacrificed on GD 25. At necropsy, two late fetal deaths and one early resorption were detected.

Effects on Postnatal Development

Compound-related increases in the number of offspring with visceral variations were noted at 1,000 mg/kg/day. No malformations were observed.

a. External, visceral, and skeletal variations

A summary of incidences of variations is presented in Table 10. Compound-related increases in the number of offspring with visceral and (possibly) skeletal variations were observed at 1,000 mg/kg/day.

External examination: No external variations were found in offspring from any dose group.

Visceral examination: Compound-related increases in the total number of offspring with visceral variations were noted at 1,000 mg/kg/day at days 21 and 56 of age (Table 10) and were evident as dilatations of renal pelvis (at 21 days: three high-dose pups; at 56 days: one low-dose, one mid-dose, and five high-dose pups). Incidental findings included protrusion of liver parenchyma on diaphragmatic side (two high-dose offspring) (data not shown).

Skeletal examination: Skeletal variations (only reported for pups of 21 days of age) were observed in offspring at all dose levels (Table 10). These included variations of ribs, vertebrae, and 1st lumbar transverse process. Offspring at 1,000 mg/kg/day had hypoplasia of the 2nd cervical vertebral body (two high-dose offspring), variation of the 7th lumbar vertebrae (two high-dose offspring), and opening of foramen transversarium of the 7th cervical vertebrae (two high-dose offspring). These findings were possibly compound related.

b. Effects on postnatal growth and development

No compound-related effects were noted. The differentiation of the male sex organ was significantly slower at 300 mg/kg/day as evident by delay in testicular descent. This effect was not dose-dependent. No adverse effects were observed in the sensory reflexes examined (data not shown).

c. Effects on locomotor activity and emotionality

No compound-related effects were observed in locomotor activity and emotionality of offspring as measured by the open field test (data not shown). The responses in the parameters measured (including ambulation, rearing, preening, grooming, defecation, and urination) were comparable in all dose groups.

Effect on motor coordination: No compound-related effects on motor coordination as measured by the rotorod test were observed in offspring at any dose level.

Effect on learning ability: The learning ability of female offspring as measured by the water-filled multiple T-maze test was significantly greater at 1,000 mg/kg/day on day 2 of the test (data not shown). This was considered to be incidental.

d. Effects on reproductive performance: No compound-related effects were noted in the incidences of mating and fertility of male and female F_1 rats (Table 11).

D. REVIEWERS' DISCUSSION/CONCLUSIONS

Acceptance Criteria

The reviewers have completed an Acceptance Criteria check list (Attachment I) to be included with the evaluation of the study. Criteria 2 and 6 were partially fulfilled. All other criteria were satisfied.

Test Material Analyses

No data were provided to substantiate the study author's claim that the test material was "stable over a 7-day period." Dose solution analyses (single replicates by unknown method) dated November 8 and December 1, 1986 showed that the test material concentrations were within 5% of target.

Maternal Toxicity

Compound-related maternal toxicity was observed at 300 and 1,000 mg/kg/day. It was manifested as an increased incidence of mortality and clinical signs at 1,000 mg/kg/day; decreased body weight, body weight gain, and food consumption and increased water consumption at 300 and 1,000 mg/kg/day; changes in selected organ weights at 1,000 mg/kg/day; and an increased incidence of histopathological findings at 1,000 mg/kg/day.

Based on these results, the maternal NOEL and LOEL were 100 and 300 mg/kg/day, respectively.

Developmental Toxicity

Segment II (effect on prenatal development)

a. Deaths/resorptions: No compound-related effects were noted at any dose level in the number of dead or resorbed fetuses overall or per litter.

b. Altered growth: No compound-related effects were noted.

c. Developmental anomalies: Compound-related effects were noted at 300 and 1,000 mg/kg/day as evident by "increases in the incidence of fetuses with opening of foramen transversarium of 7th cervical vertebra." In addition, an increase in the total number of fetuses with skeletal variations was noted at 1,000 mg/kg/day.

Based on these results, the developmental NOEL and LOEL for prenatal toxicity were 100 and 300 mg/kg/day, respectively.

Segment III (effect on postnatal development)

a. Developmental anomalies: A compound-related increase in the incidence of visceral anomalies (dilatation of renal pelvis) was noted in offspring on days 21 and/or 56 of age. In addition, skeletal variations (of 7th lumbar and cervical vertebrae), and hypoplasia of the 2nd cervical body observed at 1,000 mg/kg/day were possibly compound related.

b. Physical and emotional development: No compound-related effects were noted.

c. Motor coordination and learning ability: No compound-related effects were noted.

d. Reproductive performance (fertility) test: No compound-related effects were noted.

Based on these results, the developmental NOEL and LOEL for postnatal toxicity were 300 and 1,000 mg/kg/day, respectively.

E. STUDY/REPORTING DEFICIENCIES

- Although the analytical data on compound stability were not provided, the concentration analyses of the dosing suspensions indicated that the compound was stable.
- The incidence of mortality at the highest dose level was >10%. However, there was a sufficient number of animals available for the evaluation of the test results.
- The historical control data for resorptions were not submitted; they would have confirmed that the slightly increased rate at 1,000 mg/kg/day was not compound related.
- No protocol was submitted.
- No stability analysis was conducted.

F. CORE CLASSIFICATION: Core Minimum Data

Maternal NOEL = 100 mg/kg/day
Maternal LOEL = 300 mg/kg/day (decreased body weight, body weight gain, and food consumption; increased water consumption)

Prenatal toxicity

Developmental toxicity NOEL = 100 mg/kg/day
Developmental toxicity LOEL = 300 mg/kg/day (increased incidence of skeletal variations)

Postnatal toxicity

Developmental toxicity NOEL = 300 mg/kg/day
Developmental toxicity LOEL = 1,000 mg/kg/day (increased incidences of visceral and skeletal variations)

E. RISK ASSESSMENT: Not applicable

ATTACHMENT I

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.	YES	Technical form of the active ingredient tested.
2.	Y/N	At least 20 pregnant animals/dose group for mice, rats, or hamsters are available. At least 12 pregnant animals/dose group for rabbits are available (three test groups and control group).
3.	YES	At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).
4.*	YES	At the low dose, no developmental toxicity is reported.
5.	YES	Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6.*	Y/N	Analysis for test material stability, homogeneity, and concentration in dosing medium.
7.	YES	Individual daily observations.
8.	YES	Individual body weights.
9.	YES	Individual food consumption.
10.	YES	Necropsy on all animals.
11.	YES	Individual uterine examination, including numbers of fetal deaths, early and late resorptions, and viable fetuses per sex.
12.	Y/N	All ovaries examined to determine number of corpora lutea.
13.	YES	Individual litter weights and/or individual fetal weights/sex/litter.
14.	YES	Individual fetal external examination.
15.	YES	Individual fetal skeletal examination for 1/3 to 1/2 of each litter for rodents and all for rabbits.
16.	YES	Individual fetal soft tissue examination.

Criteria marked with a * are supplemental, may not be required for every study.

TABLE 1. Incidence of Mortality/Pregnancy Status and Frequently Observed Clinical Signs[a,b]

Observation	Dose Level (mg/kg/day)			
	0	100	300	1,000
Mortality/Pregnancy Status				
No. mated	36	36	36	43
No. pregnant	36	36	36	42
No. found dead	0	0	0	12
No. aborted	0	0	0	0
No. premature deliveries	0	0	0	0
Physical signs				
Diarrhea	0	0	0	42
Erythema/swelling of periproctal	0	0	0	19
Hypoactivity	0	0	1	10
Wasting	0	0	1	9
Lacrimation	0	0	0	2
Hypothermia	0	0	1	9
Blanching of auricle/extremity	0	0	1	3
Bloody dirtiness around nose	0	0	0	6

[a]Data were extracted from Study no. 302-2358, Tables 1, 13 and 17.

[b]Data represent the number of animals exhibiting the clinical sign at least once.

TABLE 2. Mean Body Weight Gain (g ± S.D.)[a,b]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-7)	Dosing Period (GD 7-17)	Post Dosing Period (GD 17-21)	Corrected Gestation Period (GD 0-21)
0	27.29 ± 7.32	54.77 ± 7.05	44.78 ± 32.96	126.84 ± 34.12
100	27.57 ± 6.40	50.76 ± 6.59	52.48 ± 6.78	130.82 ± 16.54
300	25.04 ± 6.36	47.24 ± 9.61	52.78 ± 17.52	125.07 ± 22.91
1,000[c]	23.20 ± 6.86	25.43 ± 25.43	51.19 ± 13.08**	99.51 ± 35.78**

[a]Data were extracted from Study no. 302-2358, Appendix 23.

[b]Calculated by the reviewer; statistically analyzed using ANOVA

[c]N = 30 due to excessive mortality between GD 11-18

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

TABLE 3. Mean Food Consumption (g/animal ± S.D.)[a,b]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-7)	Dosing Period (GD 7-17)	Post Dosing Period (GD 17-21)	Gestation Period (GD 0-21)
0	18.22 ± 1.48	16.59 ± 1.22	19.56 ± 1.25	17.48 ± 1.05
100	19.11 ± 4.40	16.67 ± 1.64	19.84 ± 1.86	17.84 ± 1.81
300	18.02 ± 1.93	15.77 ± 1.57	19.15 ± 2.20	16.97 ± 1.56
1,000[c]	16.94 ± 4.35	12.60 ± 3.69	19.26 ± 5.24	14.94 ± 3.94

[a]Data were extracted from study no. 302-2358, Appendix 24.

[b]Calculated by the reviewers; statistically analyzed using ANOVA

[c]N = 42, GD 7-10; N = 39, GD 11; N = 37, GD 12; N = 35, GD 13; N = 31, GD 14-16; N = 30, GD 16 due to excessive mortality in the high dose group

TABLE 4. Mean Water Consumption (mL/day)[a,b]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-7)	Dosing Period (GD 7-17)	Post Dosing Period (GD 17-21)	Gestation Period (GD 0-21)
0	25.75	27.32	32.42	28.13
100	26.80	29.05	34.32	29.84
300	26.37	32.07	38.58**	33.04
1,000[c]	24.67	40.20	50.92**	40.37

[a]Data were extracted from Study no. 302-2358, Appendix 32.

[b]Calculated by the reviewers; statistically analyzed using ANOVA

[c]N = 42, GD 7-10; N = 39, GD 11; N = 37, GD 12; N = 35, GD 13; N = 31, GD 14-16; N = 30, GD 16 due to excessive mortality in the high dose group

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

TABLE 5. Absolute and Relative Weights of Selected Organs from Dams Fed Sumilarv During Gestation (Segment II)[a]

Organ	Dose Level (mg/kg/day) 0	100	300	1,000
Thymus				
Absolute (g)	0.26 ± 0.05[b]	0.25 ± 0.05	0.24 ± 0.04	0.15 ± 0.05**
Relative[c]	71.5 ± 13.8	69.1 ± 11.9	68.4 ± 12.5	43.1 ± 13.7 **
Kidney				
Absolute (g)	1.45 ± 0.11	1.45 ± 0.09	1.51 ± 0.11	1.55 ± 0.19*
Relative	399.0 ± 33.4	398.8 ± 20.4	424.2 ± 40.7*	468.3 ± 105.0**
Adrenal				
Absolute (g)	0.06 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.08 ± 0.02**
Relative	17.26 ± 2.06	17.53 ± 1.99	17.66 ± 2.13	25.03 ± 7.84**

[a]Data were extracted from Study no. 302-2358, Table 11.

[b]Mean ± S.D.

[c]Organ weight relative to body weight (mg %)

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

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

TABLE 6. Incidence of Selected Gross Pathological Findings[a]

Organ/Finding	Dose Level (mg/kg/day) 0	100	300	1,000
Dead				
No of dams found dead	0	0	0	12
Thymus				
Atrophy	0	0	0	12
Liver				
Congestion	0	0	0	11
Spleen				
Atrophy	0	0	0	12
Adrenal				
Enlargement	0	0	0	12
Kidney				
Congestion	0	0	0	6
Stomach				
Hemorrhage of mucous membrane	0	0	0	6
Ulcer	0	0	0	3
Sacrificed on day 21 of pregnancy				
No of dams sacrificed	23	23	23	20
Thymus				
Atrophy	0	0	0	14
Adrenal				
Enlargement	0	0	0	15

[a]Data were extracted from Study no. 302-2358, Tables 10 and Appendices 37–40.

TABLE 7. Cesarean Section Observations[a]

Parameter	Dose Level (mg/kg/day) 0	100	300	1,000
No. pregnant dams sacrificed	23	23	23	20
Total no. corpora lutea[b]	348	353	356	304
Mean no. corpora lutea/litter	15.1 ± 2.6[c]	15.3 ± 2.4	15.5 ± 1.7	15.2 ± 2.7
Total no. implantations[b]	318	322	324	276
Mean no. implantations/litter	13.8 ± 2.0	14.0 ± 1.7	14.1 ± 2.8	13.8 ± 1.9
Total live fetuses[b]	303	299	299	232
Mean no. live fetuses/litter	13.2 ± 2.2	13.0 ± 1.7	13.0 ± 2.8	11.6 ± 4.5
Resorptions/dead fetuses (%)				
Total	4.7	7.0	7.7	14.6
Early	4.4	6.7	7.7	14.6
Late	0.3	0.3	0.0	0.0
No. totally resorbed litters	0	0	0	2
Preimplantation loss (%)[b]	7	8	13	8
Postimplantation loss (%)[b]	5	7	8	15
Mean fetal body weight (g)				
Male	5.0 ± 0.2	5.0 ± 0.2	5.0 ± 0.2	5.0 ± 0.3
Female	4.7 ± 0.2	4.8 ± 0.2	4.8 ± 0.2	4.7 ± 0.2
Sex ratio (% male)	49	52	54	50

[a]Data were extracted from study no. 302-2358, Table 13 and Appendices 45-48.

[b]Calculated by the reviewers

[c]Mean ± S.D.

TABLE 8. Incidence of Fetal Malformations and Skeletal Variations (Segment II)[a]

Findings[b]	Dose Level (mg/kg/day) 0	100	300	1,000
External malformations				
No. fetuses (litters) examined	303 (23)	299 (23)	299 (23)	232 (18)
Cyclopia with proboscis	0	0	1	0
Polydactyly	0	0	1	0
No. litters with malformed fetuses	0	0	2	0
No. fetuses with external malformations (%)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Visceral malformations				
No. fetuses (litters) examined	101 (23)	99 (23)	99 (23)	78 (18)
Arhinencephaly	0	0	1	0
Ventricular septal defect	5 (5)	3 (2)	0	1
Left umbilical artery	2 (2)	2 (2)	1	0
Unilateral absence of optic nerve	1	0	0	0
Unilateral nerve hypoplasia of thyroid	0	0	1	0
Dislocation of esophagus	1	0	0	0
No. litters with malformed fetuses	9	4	3	1*
No. fetuses with visceral malformations (%)	9 (8.9)	5 (5.1)	3 (3.0)	1 (1.3)*
Skeletal malformations				
No. fetuses (litters) examined	202 (23)	200 (23)	200 (23)	154 (18)
Fusion of exoccipital and atlas, vertebral arches, ribs, sternebrae, defect of cervical vertebral arch,	0	0	1	0
Fusion of ribs, thoracic vertebral arches, defect of the rib and hypoplasia of the cervical vertebral arches	1	0	0	0
No. litters with malformed fetuses	1	0	1	0
No. fetuses with skeletal malformations (%)	1 (0.5)	0 (0.0)	2 (1.0)	0 (0.0)
Skeletal variations				
No. fetuses (litters) examined	202 (23)	200 (23)	200 (23)	154 (18)
Lumbar rib	7 (7)	6 (5)	4 (4)	11 (6)
Lumbarization of 1st sacral vertebra	0	0	1	3 (2)
Opening of foramen transversarium of 7th cervical vertebra	0	3 (3)	10*(5)	22**(11)
Cervical rib	6 (4)	3 (2)	2 (2)	1
Shortening of 13th rib	1	1	1	1
Poorly ossified sternebrae	2 (2)	3 (3)	4 (4)	6 (4)
No. litters with fetal skeletal variations	10	11	10	17
No. fetuses with skeletal variations (%)	14 (6.9)	14 (7.0)	15 (7.5)	37 (24.0)**

[a]Data were extracted from Study no. 302-2358, Tables 14-16 and Appendices 49-60.
[b]More than one type of anomaly may be found in one fetus.
*Signficantly different from control, $p<0.05$; **Significantly different from control, $p<0.01$

TABLE 9. Summary of Reproductive Effects on Maternal (F_0) and Fetal (F_1) Parameters (Segment III)[a]

Parameter	Dose Level (mg/kg/day) 0	100	300	1,000
No. pregnant females	13	13	13	10
No. females with live newborns	13	13	12	10
Delivering rate (%)[b]	100	100	92	100
Gestational length (days)	21.7	21.5	21.6	21.5
Mean no. implantations	14.2	14.9	12.7	14.4
Birth rate (%)[c]	93	90	86	86
Total of stillbirths	3	0	0	0
Total no. live pups				
Day 0	173	175	151	124
Day 4 (precull)	167	157	149	121
Day 21	98	95	85	79
No. live pups/litter				
Day 0	13.3	13.5	11.6	12.4
Day 4 (precull)	12.8	13.1[d]	11.5	12.1
Day 21	7.5	7.9	7.1	7.9
Survival rate (%) (M/F)				
Day 0 to Day 4	96/97	89/90	97/100	97/100
Day 21 to Day 56	100/100	100/100	100/100	100/100
Day 56 to Day 77	100/100	100/100	100/100	100/100
Pup body weight (g ± S.D.)				
Day 0 - Male	5.8 ± 0.4	5.7 ± 0.4	5.9 ± 0.3	5.7 ± 0.4
- Female	5.5 ± 0.4	5.3 ± 0.3	5.5 ± 0.3	5.3 ± 0.4
Day 7 - Male	10.3 ± 1.9	11.2 ± 1.7	11.3 ± 1.9	11.5 ± 2.1
- Female	10.1 ± 1.5	10.7 ± 1.7	10.9 ± 2.2	11.1 ± 1.9
Day 21 - Male	34.9 ± 4.8	37.5 ± 4.0	38.3 ± 3.9*	38.3 ± 5.6
- Female	34.8 ± 4.2	37.1 ± 4.2	37.9 ± 2.1	37.1 ± 5.0

[a]Data were extracted from Study no. 302-2358, Tables 17, 18, 19, and 20, and Appendices 62-76.

[b](No. of females with live newborns/No. of pregnant females) x 100

[c](No. of live newborns/No. of implantations) x 100

[d]N=12

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

TABLE 10. Incidences of Variations In Offspring at Different Ages (Segment III)[a]

Findings[b]	Dose Level (mg/kg/day) 0	100	300	1,000
No. dams delivering live litters	13	13	12	10
External Variations				
No. offspring (litters) examined at birth	173 (13)	175 (13)	151 (12)	124 (10)
No. offspring (litters) with variation(s) on day 21	0	0	0	0
% offspring with variation(s)	0	0	0	0
Visceral Variations				
No. offspring (litters) examined on day 21	46 (13)	47 (12)	41 (12)	39 (10)
No. offspring (litters) with variation(s)	1	0	0	4 (2)
% offspring with variation(s)	2.2	0	0	10.3
No. offspring (litters) examined on day 56	26 (13)	24 (12)	22 (12)	20 (10)
No. offspring with variation(s)	0	1	1	7* (6)
% offspring with variation(s)	0	4.2	4.5	35.0
No. offspring (litters) examined at the end of the fertility test	26 (13)	24 (12)	22 (12)	20 (10)
No. offspring (litters) with variation(s)	5 (5)	4 (4)	4 (3)	6 (5)
% offspring with variation(s)	19.2	16.7	18.2	30.0
Skeletal Variations				
No. offspring (litters) examined on day 21	46 (13)	47 (12)	41 (11)	39 (10)
No. offspring (litters) with variation(s)	4 (4)	5 (3)	7 (5)	7 (6)
% offspring with variation(s)	8.7	10.6	17.1	17.9

[a]Data were extracted from Study no. 302-2358, Table 24 and Appendices 89-92 and 99-102.

[b]One fetus may have more than one finding; for type of anomaly see text.

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

TABLE 11. Reproductive Performance of F_1 Rats[a]

Parameter	Dose Level (mg/kg/day) 0	100	300	1000
1st Mating[b]				
No. of matings	13	12	11	10
Copulated/Mated (%)	77	92	100	100
Pregnant/Copulated (%)	80	82	90	100
2nd Mating[c]				
No. of matings (Male/Female)	3/3	1/1	--	--
Copulated/Mated (%)	100/0	100/0	--	--
Pregnant/Copulated (%)	100	100	--	--
Effects on F_2 Fetuses (From 1st Mating)				
No. dams sacrificed	8	9	10	10
Total no. corpora lutea	107	132	133	129
No. corpora lutea/litter	13.4 ± 1.8[d]	14.7 ± 1.9	13.3 ± 1.4	12.9 ± 1.2
Total no. implantations	90	116	123	113
No. implantations/litter	11.3 ± 4.6	12.9 ± 1.5	12.3 ± 2.5	11.3 ± 3.1
Implantation rate	84	89	92	88
Resorbed/dead fetuses (%)	2	7	6	2
Total no. live fetuses	88	108	116	110
No. live fetuses/litter	11.0 ± 4.6	12.0 ± 1.5	11.6 ± 2.6	11.0 ± 3.0
Sex ratio (% male)	52	46	44	54
Fetal body weight				
Male	5.0 ± 0.4	4.8 ± 0.2	5.0 ± 0.2	5.1 ± 0.2
Female	4.7 ± 0.2	4.5 ± 0.3	4.7 ± 0.3	4.7 ± 0.2

[a]Data were extracted from Study no. 302-2358, Tables 33 and 34, and Appendices 116-119.

[b]1st Mating: Animals were mated in the same dose groups for 2 weeks.

[c]2nd Mating: Males were mated with non-treated females for 1 week. Females were mated with males confirmed fertile in the same dose group for 1 week.

[d]Mean ±S.D.