

CONFIDENTIAL

85/SEA043/513

TWO GENERATION REPRODUCTION STUDY OF SC-19129
IN RATS, S.A. NO. 2473

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LSR Report No : 85/SEA043/513

We, the undersigned, hereby declare that the report following constitutes a true and faithful account of the procedures adopted, and the results obtained, in the performance of this study.

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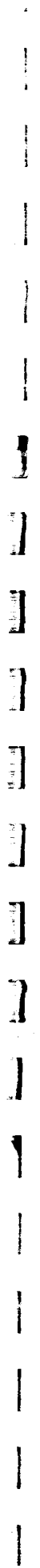




LIFE SCIENCE RESEARCH

TWO GENERATION REPRODUCTION STUDY OF SC-19129
IN RATS, S.A. NO. 2473
LSR Report No : 85/SEA043/513
QUALITY ASSURANCE INSPECTIONS

	DATES	DAY/MONTH/YEAR	
	Inspection	Report to Study Director	Report to Management
<u>PROTOCOL</u>			
Inspection of protocol was made in accordance with LSR Standard Operating Procedure QAU/020.	5/11/84	5/11/84	5/11/84
Dates for inspection of protocol amendments in accordance with this S.O.P. are not quoted			
<u>DATA</u>			
Inspection of data generated on this study was made in accordance with LSR Standard Operating Procedure QAU/050	3/1/85 19/3/85 29/7/85	4/1/85 19/3/85 30/7/85	4/1/85 19/3/85 30/7/85
<u>PROCEDURES</u>			
Inspection of procedures on this study was made in accordance with LSR Standard Operating Procedure QAU/040	9/11/84 12/11/84 12/11/84 12/12/84 14/1/85 21/1/85 22/1/85 28/1/85 15/2/85 18/2/85 25/2/85 5/3/85 5/3/85 12/3/85 2/5/85 16/5/85 20/5/85	9/11/84 13/11/84 13/11/84 17/12/84 14/1/85 21/1/85 22/1/85 29/1/85 15/2/85 20/2/85 25/2/85 6/3/85 8/3/85 12/3/85 2/5/85 21/5/85 21/5/85	9/11/84 13/11/84 13/11/84 17/12/84 14/1/85 21/1/85 22/1/85 29/1/85 15/2/85 20/2/85 25/2/85 6/3/85 8/3/85 12/3/85 2/5/85 21/5/85 21/5/85





LIFE SCIENCE RESEARCH

TWO GENERATION REPRODUCTION STUDY OF SC-19129
IN RATS, S.A. NO. 2473
LSR Report No : 85/SEA043/513 - continued
QUALITY ASSURANCE INSPECTIONS

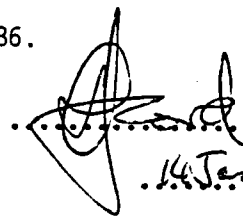
	DATES		DAY/MONTH/YEAR	
	Inspection	Report to Study Director	Report to Management	
Inspection of procedures on this type of study was made in accordance with LSR Standard Operating Procedure QAU/040		4/2/85	12/2/85	
		5/3/85	5/3/85	
		6/3/85	6/3/85	
		21/3/85	21/3/85	
		2/4/85	2/4/85	
		6/6/85	7/6/85	
		21/6/85	21/6/85	
		21/6/85	21/6/85	
		24/6/85	26/6/85	
		26/7/85	26/7/85	

Other routine procedures used in this type of study, and facilities were inspected regularly and reports made in accordance with LSR Standard Operating Procedures QAU/040.

This report has been reviewed by the LSR Quality Assurance Unit employing methods laid down in LSR Standard Operating Procedure QAU/060. The reported methods and procedures were found to describe those used and the results to constitute an accurate representation of the data recorded.

This review was completed on: 14 January 1986.

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(Head of Quality Assurance Unit).


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14 January 1986

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1. SUMMARY

1.1 Procedures

- 1.1.1 The influence of continuous administration of SC-19129 upon reproductive capacity was assessed in two successive generations of rats of the Charles River CD strain.
- 1.1.2 For the purpose of this assessment, SC-19129 was administered in the diet at treatment levels of 0, 250, 500 or 750 mg/kg/day to male rats of the F_0 generation for 71 days prior to pairing, continued throughout the mating period and until successful littering had been achieved. Female rats of the F_0 generation received the treated diets for 15 days prior to pairing, throughout the mating period and during gestation and lactation. F_1 animals received the treated diets from weaning until termination.

Concentration of SC-19129 in the diets was adjusted weekly to achieve the intended dosages.

- 1.1.3 Approximately twelve of the females were killed on Day 20 of gestation to permit examination of their uterine contents; the remainder were allowed to give birth and rear their young to weaning at Day 21 post partum. The development and behavioural performance of offspring were examined using a battery of standard tests.
- 1.1.4 Representative numbers of offspring were randomly selected, reared to maturity, and used to investigate the growth, reproductive performance and fertility of the F_1 generation.

1.2 Results

1.2.1 F_0 generation

- 1.2.1.1 Intake levels of SC-19129 were within 10% of intended dosages throughout the F_0 generation.
- 1.2.1.2 General condition, bodyweight gain, food intake and food conversion efficiency were essentially unaffected by the presence of SC-19129 in the diet.
- 1.2.1.3 Oestrous cycles, mating performance and fertility were unaffected by treatment.
- 1.2.1.4 Litter examination at Day 20 post coitum and foetal evaluations at necropsy and after foetal processing revealed no adverse treatment-related findings.

- 1.2.1.5 Gestation length and litter size, viability and growth of offspring to weaning were similar in all groups. Offspring development and performance in behavioural tests showed no adverse reaction to treatment.
- 1.2.1.6 Terminal necropsy of culled and surplus offspring and of adults revealed no treatment-related abnormalities. Analysis of reproductive organ weights of parental animals showed no inter-group differences.

1.2.2 F₁ generation

- 1.2.2.1 With a small number of exceptions, achieved dosage levels were within 10% of the intended dosage for the F₁ generation.
- 1.2.2.2 General condition of F₁ animals was similar in all groups. Bodyweight gain was slightly reduced at all levels for males, but was significantly reduced only at 750 mg/kg/day, and was accompanied by slight reductions in food intake. Bodyweight gain and food consumption were unaffected in females.
- 1.2.2.3 Oestrous cycles, mating performance and fertility were similar in all groups.
- 1.2.2.4 Litter examination at Day 20 post coitum and foetal evaluations at necropsy and after processing revealed no adverse responses to treatment.
- 1.2.2.5 Gestation length, litter size, offspring viability and growth were similar in all groups.
- 1.2.2.6 Necropsy of F₁ adults and F₂ offspring revealed no abnormalities that could be related to treatment.

2. INTRODUCTION

The aim of this investigation was to assess the influence of continuous administration of SC-19129 upon the reproductive capacity of two successive generations of rats.

The rat was selected because it satisfies the requirements of regulatory authorities. The Charles River CD strain of rat was chosen in particular because of the background data available for this strain in these laboratories.

SC-19129 was administered by the dietary route to simulate the route of human exposure. Dosages were provided by the Sponsor.

The study commenced at Life Science Research, Eye, Suffolk, England, on 12 November 1984. Live animal work was completed on 8 July 1985 and laboratory studies on 30 July 1985.

Original data pertaining to this study and the final report are stored in archives by Life Science Research.

3. MATERIAL

Two batches of SC-19129 were received as follows:

Date of receipt	Lot number	Net weight
29 October 1984	84K 047 101	12.0 kg
2 May 1985	84K 052 101	2.5 kg

The material was a fine white powder and was stored at room temperature protected from the light.

Unused material was returned to the Sponsor on 17 July 1985.

4. METHODS

4.1 Design conditions

4.1.1 Animals

Virgin male and female rats of the CD strain (of Sprague Dawley origin) were obtained from Charles River U.K. Limited, Margate, Kent, England, to form the F₀ generation.

At commencement of treatment the males were in the weight range 140 g to 181 g and the females were in the range 185 g to 220 g.

The males were allowed 5 days and females were allowed 3 days acclimatisation, during which time they were maintained on a basal laboratory diet and tap water, and inspected daily to check their physical condition.

4.1.2 Environmental control

The animals were housed inside a barriered limited-access rodent facility with approximately 15 room air changes per hour. The temperature and relative humidity in the animal room were recorded daily; the achieved values have been included in Addendum 1.

The animals were subjected to a 12-hour light : 12-hour dark cycle.

4.1.3 Basal diet and water supply

The rats were allowed free access to pelleted rodent diet (Labsure Laboratory Animal Diet No. 2 ground, from K. and K. Greeff Chemicals Limited, Croydon, Surrey, England) and to tap water. Analyses of the diet and water, conducted by Labsure and the East Anglian Water Company, respectively, have been included with the raw data.

4.1.4 Contaminants

No contaminants were reasonably expected to be present in either the diet, water or bedding at levels known to be capable of interfering with the purpose or conduct of the study.

4.1.5 Caging

Rats were housed in RC1, modified RM2 and RB3 cages from North Kent Plastics Limited, Dartford, Kent, England. The cages consisted of high density polypropylene bodies with stainless steel lids and mesh floors (if present). Cages with mesh floors were suspended in batteries over trays covered with absorbent crepe paper which was changed on alternate weekdays. Autoclaved wood shavings were provided for bedding during the littering phase. The cages were distributed on the racking to equalise, as far as possible, environmental influences amongst the groups. Cages were changed and cleaned approximately fortnightly, except for females in RB3 cages with litters where the same cage was used for approximately three weeks.

At various stages of the study, the maximum number of rats per cage was as follows:

<u>Stage</u>	<u>Number of rats</u>		<u>Cage type</u>
	<u>M</u>	<u>F</u>	
Pre-mating	5	5	RC1
Mating	1 :	1	modified RM2
Males to termination	5	-	RC1
Females <u>post coitum</u> and to Day 14-18 <u>post partum</u>	-	1 + litter	RB3
Lactation (Day 14-18 <u>post partum</u> until weaning)	-	1 + litter	RC1
Post-weaning	1 litter	1 litter	RC1

4.1.6 Test Compound

Pre-study analysis of the identity, purity, stability, strength, and composition of SC-19129 were determined by the Sponsor.

At commencement of the study a 10 g aliquot of SC-19129 was retained and stored under conditions as similar as possible to those pertaining to the major part of the sample supplied.

On completion of treatment, all residual SC-19129 was returned to the Sponsor for confirmation of identity, purity, stability, strength and composition.

4.1.7 Treatment

Before commencement of treatment, animals of each sex were divided into bodyweight groups (5 g range) and allocated to four treatment groups by selecting animals from each bodyweight range in rotation. Surplus animals were discarded from amongst those with outlying bodyweights and those showing minor clinical signs (hair loss).

Each animal was assigned a number and identified by an ear-notch corresponding to the last three digits of the identity number.

The four groups, consisting of a control group and three treatment groups, were treated as follows:

Group	Treatment	Dose level (mg/kg/day)	Number of animals		Animal numbering	
			M	F	M	F
1	Control	0	34	34	1001-1034	1137-1170
2	SC-19129	250	34	34	1035-1068	1171-1204
3	SC-19129	500	34	34	1069-1102	1205-1238
4	SC-19129	750	34	34	1103-1136	1239-1272

For the F_1 generation, the number of animals and numbering was as follows:

Group	Number of animals		Animal numbering	
	M	F	M	F
1	40	40	2001-2040	2161-2200
2	40	40	2041-2080	2201-2240
3	40	40	2081-2120	2241-2280
4	40	40	2121-2160	2281-2320

4.1.8 Treatment schedules

F_0 males received the appropriate diets for 71 days before pairing, throughout the mating period and until successful littering had been achieved. F_0 females received the diets for 15 days before pairing and throughout the mating period, gestation and lactation until termination after weaning on Day 21 post partum.

F_1 animals received the diets continuously from the time of weaning for a minimum of 10 weeks before pairing, and throughout pairing, gestation and lactation until termination.

4.1.9 Test diets

4.1.9.1 Concentrations

Dietary concentrations were calculated weekly for each sex to achieve close approximation to the dose levels specified, using bodyweight and food consumption data from the previous week and from background control data. Exceptions to this occurred during mating, when males received diets prepared to the female specification, and during the last week of lactation, when concentrations were not adjusted from the preceding week's values as no accurate estimation of the relative intakes of dam and litter could be made.

4.1.9.2 Preparation

The test substance was incorporated into powdered rodent diet and milled through a 1 mm screen to produce a pre-mix containing between 1.5 and 5.0% w/w SC-19129 as appropriate.

The pre-mix was further diluted with powdered rodent diet and mixed for 15 minutes in a double-cone mixer to achieve the desired concentrations of SC-19129 in the final diets.

Batches of each test diet were prepared weekly and issued in sealed polythene bags. Diets unused at the end of each week were usually incinerated. However, during mating and for occasional animals during gestation and lactation, diets were fed for periods of up to approximately 1½ weeks before being discarded, to maintain continuity of a specified concentration. 100 g aliquots of each test diet, other than those being analysed for achieved concentration in accordance with Section 4.1.9.3, were sealed into aluminium foil laminate sachets and stored at room temperature. The aliquots were discarded following authorisation from the Sponsor.

4.1.9.3 Quality control

On each day that quantities of test substance were weighed out for test diet preparation, the stock container was weighed before the first and after the last removal of part of its contents. The reduction in the weight of the stock container was documented as an independent check that the correct weight of the test substance was used. Diet samples were taken as shown in Text Table 1.

Text Table 1 : Dietary sampling schedule

Formulation week	Study status	Number and size of samples taken	Sex	Assay purpose
1	F ₀ maturation	18 x 10 g/group	M	Homogeneity
4	F ₀ maturation	2 x 10 g/group	M	Achieved concentration
9	F ₀ maturation	2 x 10 g/group/sex	M and F	Achieved concentration
12	Week 2 gestation (F ₀ -F ₁)	2 x 10 g/group/sex	M and F	Achieved concentration
14	Week 1 lactation (F ₀ -F ₁)	2 x 10 g/group	M	Stability after 7 days in animal room
15	Week 2 lactation (F ₀ -F ₁)	2 x 10 g/group/sex	M and F	Achieved concentration
17	Week 1 F ₁ maturation	2 x 10 g/group/sex	M and F	Achieved concentration
20	Week 4 F ₁ maturation	6 x 10 g/group/sex	M and F	Achieved concentration
25	Week 9 F ₁ maturation	6 x 10 g/group/sex	M and F	Achieved concentration
28	Week 2 gestation (F ₁ -F ₂)	6 x 10 g/group/sex 2 x 10 g/group/sex	M and F M and F	Achieved concentration Stability after 14 days in animal room
31	Week 2 lactation (F ₁ -F ₂)	6 x 10 g/group	F	Achieved concentration

For homogeneity analysis, duplicate samples were taken from nine positions in the mixture and one duplicate set was despatched to the Sponsor for analysis. On the other occasions half of the samples taken were returned to the Sponsor for analysis. All samples were stored deep frozen until despatch to the Sponsor. The results of analyses of the diet samples will be the subject of a separate report produced by the Sponsor.

4.1.10 Mating procedure

After the appropriate treatment period the females were paired on a one-to-one basis with males from the same treatment group. Each morning following pairing, the trays beneath the cages were checked for ejected copulation plugs, and a vaginal smear prepared from each female and examined for the presence of spermatozoa. The day on which evidence of mating was found was designated Day 0 of gestation.

Once mating had been confirmed, the males and females were separated and vaginal smearing discontinued. At F_0 - F_1 pairing two pairs failed to mate within 7 days of pairing but mating occurred in the next week without male changeover.

The same mating procedure was adopted with the F_1 animals after 10 weeks of treatment (13-14 weeks of age). F_1 males and females were paired within treatment groups avoiding sibling matings. One pair failed to mate within the first week but mating occurred, without male changeover in the next week. One male failed to mate within 14 days of pairing and was replaced by a proven male from the same treatment group. Mating occurred within 7 days of second pairing.

4.2 Serial observations (F_0) (paternal and maternal, pre-natal)

4.2.1 Signs

Each animal was examined daily throughout the study and any visible signs of reaction to treatment were recorded, with details of type, severity, time of onset and duration.

4.2.2 Bodyweight

Males were weighed at commencement of treatment and weekly until termination. Females were weighed at commencement of treatment, weekly until paired for mating, and on Days 0, 6, 13 and 20 post coitum.

4.2.3 Food consumption

Food consumption was recorded for each generation throughout the study with the exception of the mating periods.

4.2.4 Oestrous cycle

A vaginal smear was taken daily from each female for 10 days before pairing in order to assess the regularity and duration of the oestrous cycle.

4.2.5 Pre-coital interval (females)

The time elapsing between initial pairing and detection of mating was recorded.

4.3 Teratology phase

On Day 20 of gestation, twelve females from each group were killed by inhaled carbon dioxide and first examined macroscopically for evidence of disease or adverse reaction to treatment. Specimens of tissues considered to be abnormal were retained in an appropriate fixative. The reproductive tract, complete with ovaries, was dissected out and the following recorded:

- a) Number of corpora lutea in each ovary;
- b) Number of implantation sites;
- c) Number of resorption sites (classified as early or late);
- d) Number and distribution of live and dead fetuses in each uterine horn;
- e) Weight and sex of individual fetuses;
- f) Individual placental weights;
- g) External abnormalities of individual fetuses;
- h) Any morphological abnormality of the maternal reproductive tract;
- i) Skeletal examinations: the neck, thoracic and abdominal cavities of approximately half of the fetuses from each litter were dissected and examined. Following examination and evisceration, the fetuses were placed in industrial methylated spirit (74 o.p.) before processing, which utilised a modification of the Dawson staining technique (J.M. Tesh, Ph.D. Thesis, University of Liverpool, 1968) and subsequent skeletal examination;
- j) Visceral examination: the remaining fetuses were placed in Bouin's fixative for subsequent free-hand sectioning following the technique of Wilson (in Teratology: Principles and Techniques, p. 251, University of Chicago Press, 1965).

4.4 Post-natal phase (Maternal)

The remaining 22 females were allocated to deliver and raise their young naturally to Day 21 post partum.

4.4.1 Maternal signs

From Day 20 post coitum females were examined three times each day (twice at weekends) for the onset and progress of parturition and subsequently for any clinical signs post partum.

4.4.2 Duration of gestation

The time elapsing between the detection of mating and the commencement of parturition was recorded.

4.4.3 Bodyweight

Females were weighed on Days 1, 4, 7, 14 and 21 post partum.

4.5 Post-natal observations (litters)

4.5.1 Observations on Day 1 post partum

All litters were observed at approximately 24 hours after birth and pups were toe-marked for individual identification.

4.5.2 Signs

Litters were observed daily for evidence of treatment-related clinical signs.

4.5.3 Mortality and litter size

Daily records were maintained of mortality and consequent changes in litter size. On Day 4 post partum litter size was reduced to eight to give, where possible, four males and four females per litter. Offspring within each sex were selected randomly. Where litter size was eight or less no adjustment was made.

Offspring culled on Day 4 or found dead were examined externally and internally for abnormalities. Specimens of abnormal tissues were retained.

4.5.4 Bodyweight

Offspring were weighed individually on Days 1, 4, 7, 14 and 21 post partum. Animals continuing the study from this point were weighed weekly after selection.

4.5.5 Sex ratio

The offspring were sexed on Days 1, 4 (before and after culling), 14 and 21 post partum.

4.5.6 Physical development

The speed of physical development of the offspring was assessed on an individual offspring basis by recording the days on which the onset of the following parameters occurred:

- a) Pinna unfolding - detachment of the edge of the pinna.
- b) Hair growth - macroscopic observation of generalised growth of body hair.
- c) Tooth eruption - eruption of the upper incisors through the gum.
- d) Eye opening - separation of the upper and lower eyelids.
- e) Testicular descent - testes were palpable in the scrotum.
- f) Vaginal opening - separation of vaginal edges.

Data was reported as the onset and completion of each parameter within individual litters.

4.5.7 Auditory and visual function

After weaning at Day 21 post partum, auditory and visual responses of the progeny were examined in a qualitative manner by means of the following techniques:

a) Auditory function

Auditory function was assessed by using the startle response to a sudden sharp noise.

b) Visual function

Visual function was assessed by:

- i) examination of the pupil closure response to a bright point of light.
- ii) assessment of the visual placing response.

4.5.8 Behavioural studies

a) Activity

After Day 21 post partum, each litter was separated into males and females and placed in clear plastic cages; following a period of acclimatisation the activity of each litter was measured for 12 hours overnight. For this purpose a system incorporating a pair of infra-red light sources and detectors was used to monitor within-cage activity, the frequency with which the light beams were interrupted producing an activity score (Tesh J.M., in *Methods in Pre-natal Toxicology*, ed. Neubert et al, Thieme Verlag, Stuttgart, 1977).

b) Water-filled maze

A water-filled Y-maze was used to evaluate learning ability of the offspring (Tesh, J.M., ibid). The times taken by each animal to swim through the maze in six successive trials was measured. A maximum of 60 seconds was allowed for each trial; any animal exceeding this time was removed and was considered to have failed the test. Maintained improvement in swimming time was taken as an indication of learning.

4.6 Development and reproductive performance of the F₁ generation

4.6.1 Selection (Appendix 29)

Following weaning, 40 male and 40 female offspring were selected from each group using random number tables, to form the F₁ generation. Where possible, two males and two females were selected from each litter. Each animal was assigned a number and identified by ear-notching.

4.6.2 Serial observations

The procedures followed and observations made were as described for the first generation (Sections 4.1.10 - 4.5.5) except that twenty females in each group were killed on Day 20 of gestation, the remaining half being allowed to give birth naturally.

4.6.3 Mating procedure

When the selected F₁ progeny had been treated for 10 weeks after weaning (13-14 weeks of age) the animals were mated within groups following the procedures described in Section 4.1.10.

4.7 Terminal studies

4.7.1 Parental animals (F₀ and F₁)

Males were killed when the majority of females had littered successfully.

Females that littered and reared offspring to weaning were killed on Day 21 post partum. Females that littered but whose litters died before weaning were killed on the day that their last offspring died.

Females allocated to litter that mated but did not give birth were killed on Day 25 post coitum. Females that failed to mate were killed 25 days after the last day of pairing.

All parental animals were subjected to necropsy as described in Section 4.7.4.

4.7.2 Offspring (unselected F₁ and F₂)

F₁ offspring not selected for continuation of the study were killed on completion of behavioural studies and vaginal opening and examined externally and internally for macroscopic abnormalities. F₂ offspring were killed after weaning and examined externally and internally for macroscopic abnormalities. Specimens of abnormal tissues were retained.

4.7.3 Euthanasia

With the exception of offspring culled on Day 4 post partum, all animals were killed by carbon dioxide inhalation.

Culled offspring were killed by an intraperitoneal injection of pentobarbitone sodium B. Vet. C. Expiral : marketed by Ceva Limited, Watford, Hertfordshire.

4.7.4 Macroscopic pathology

All parental animals were subjected to a detailed necropsy.

The necropsy procedure included a review of the history of each animal and a detailed examination of the cranial, thoracic, abdominal and pelvic cavities and their viscera. The external and cut surfaces of the organs and tissues were examined either before or after weighing, as appropriate. The number of uterine implantation sites were recorded in all females. Abnormalities, interactions and changes were noted, the requisite organs weighed and the required tissue samples preserved in fixative (see Text Table 2).

Before disposal of the carcass, the retained tissues were checked against the Protocol and the Senior Prosector reviewed the necropsy report.

Text Table 2 : Pathology procedures.

LIST		A	B
Organ/tissue		Weigh	Fix
Abnormalities		T if possible	T
Epididymides	Left	M	M
	Right	M	M
Mammary glands	Cranial		O
	Caudal		O
Ovaries	Left	F	F
	Right	F	F
Pituitary			S
Prostate		M	M
Seminal vesicles ^a		M	M
Testes	Left	M	M
	Right	M	M
Uterus ^b		F	F
Vagina			F

T All animals (including offspring).

M All parental males.

F All females killed for teratological examination.

O Parental females with total litter loss.

S Parental animals with suspect fertility (samples only).

a Both lobes weighed and retained as single unit.

b Weighed gravid and after removal of foetuses.

4.7.5 Organ weights

The organs specified in column A of Text Table 2 (Pathology procedures) were dissected free of adjacent fat and other contiguous tissue and the weights recorded.

4.7.6 Tissues preserved in fixative

Samples of the tissues specified in column B of Text Table 2 (Pathology procedures) were preserved in buffered formol saline. In those cases where a lesion was not clearly delineated, contiguous tissue was fixed with the grossly affected region.

4.8 Treatment of data

Data were expressed as means with standard deviations (S.D.) calculated according to the formula:

$$\sqrt{\frac{\sum(x-\bar{x})^2}{n-1}}$$

where x = individual value
 \bar{x} = mean value
 n = number of observations

with the exception of resorption count, for which the standard deviation was calculated as:

$$\sqrt{\bar{x}}$$

This formula was used because resorptions approximate to a Poisson distribution.

4.8.1 Bodyweights

Group mean values (\pm S.D.) were calculated and tabulated for all bodyweights reported. Weight changes were plotted graphically with respect to start of treatment (Time 0 for F_0 ; Weaning for F_1) and relative to Day 0 of gestation and Day 1 of lactation for pregnant and lactating females respectively.

4.8.2 Food consumption

Group mean values (\pm S.D.) for food consumption were calculated as follows:

4.8.2.1 Group-housed animals

Food consumption per rat (g/rat/week) was calculated for each cage and the group mean (\pm S.D.) calculated from the formula:

$$\text{Group mean} = \frac{\text{Total of individual cage mean values}}{\text{Number of cages}}$$

4.8.2.2 Individually-housed animals

Food consumption (g/rat/day) was calculated individually for Days 0-5, 6-12 and 13-19 post coitum and 1-6, 7-13 and 14-20 post partum. Group mean data (\pm S.D.) was based on the number of pregnant/lactating animals as appropriate.

4.8.2.3 Littermates before selection (F₁)

Food consumption (g/rat/week) was calculated for each cage of littermates and was based on the total number of days elapsing between weaning and selection of individual litters (5-9 days). Group mean consumption was then calculated as in Section 4.8.2.1.

4.8.2.4 All cage and individual data were rounded to the nearest gram before group mean data or chemical intake data were calculated.

4.8.3 Food conversion efficiency (FCE)

FCE was calculated for males and for females before pairing according to the formula:

$$FCE = \frac{\text{Group mean bodyweight gain (g) in week}}{\text{Group mean food consumption (g/rat/day)}} \times 100$$

During gestation FCE was calculated as:

$$FCE = \frac{\text{Group mean bodyweight change (g) in period}}{\text{Group mean food intake (g/rat/day)} \times \text{no. days in period}} \times 100$$

4.8.4 Chemical intake

Chemical intake (mg/kg/day) was calculated as follows:

4.8.4.1 Group-housed animals

$$\text{Chemical intake} = \frac{\text{Group mean food intake (g/rat/week)} \times \text{ppm}}{\text{Group mean mid-period bodyweight} \times 7}$$

4.8.4.2 Individually-housed animals

Chemical intake was calculated for each animal during the periods of measurement Days 0-5, 6-12 and 13-19 post coitum and Days 1-6 and 7-13 post partum from the formula:

$$\text{Chemical intake} = \frac{\text{Food intake (g/rat/day)} \times \text{ppm}}{\text{Mid-period bodyweight}}$$

Group mean data (\pm S.D.) was based on the number of pregnant or lactating animals as appropriate.

Chemical intake for the period Days 14-20 post partum was not presented as the quantities of diet consumed by the offspring during this period could not be determined.

4.8.5 Mating performance and fertility

For each group and sex the following were calculated:

$$\text{Percentage mating} = \frac{\text{Animals mating}}{\text{Animals paired}} \times 100$$

$$\text{Fertility index} = \frac{\text{Animals achieving a pregnancy}}{\text{Animals paired}} \times 100$$

$$\text{Conception rate} = \frac{\text{Animals achieving a pregnancy}}{\text{Animals mating}} \times 100$$

$$\text{Gestation index} = \frac{\text{Number of live litters born}}{\text{Number pregnant}} \times 100$$

4.8.6 Pre-natal data

4.8.6.1 Pre-natal losses were considered separately for the pre- and post-implantation phases.

a) Pre-implantation loss

Pre-implantation loss included losses due to non-fertilisation of ova and very early post-implantation deaths (i.e. those occurring in the first 2 to 3 days post-implantation), in addition to true pre-implantation loss.

It was calculated from the formula:

$$\frac{\text{No. corpora lutea} - \text{No. implantations}}{\text{No. corpora lutea}} \times 100$$

b) Post-implantation loss

Post-implantation loss did not include the first 2 to 3 days post-implantation as any deaths that occurred in this phase would leave no remains visible at Day 20.

It was calculated from the formula:

$$\frac{\text{No implantations} - \text{No. live foetuses}}{\text{No. implantations}} \times 100$$

Group mean values (\pm S.D.) were calculated from the individual litter values.

4.8.6.2 Group mean foetal and placental weights and standard deviations were calculated as:

$$\frac{\text{Total of individual litter mean foetal/placental weights}}{\text{Number of litters}}$$

4.8.6.3 Foetal observations

Observations on F_1 and F_2 fetuses at necropsy and at skeletal evaluation or free-hand sectioning were calculated on a group basis for each observation as:

$$\frac{\text{Number of fetuses/litters with a particular observation}}{\text{Total number of fetuses/litters examined in group}} \times 100$$

4.8.7 Post-natal data (F_0 and F_1 generation)

Gestation length was calculated as the number of gestation days up to and including the day on which offspring were first observed. Where parturition started overnight, this value was adjusted by subtracting half a day.

Post-implantation survival index was calculated for each group on a litter basis as:

$$\frac{\text{Number of offspring born}}{\text{Number of uterine implantation sites}} \times 100$$

Group mean offspring weight was calculated as:

$$\frac{\text{Total of individual litter mean offspring weights}}{\text{Number of litters on day of examination}}$$

Group mean offspring bodyweight change was plotted graphically with respect to Day 1 post partum.

Live birth index was calculated for each group on a litter basis as:

$$\frac{\text{Number of live offspring at Day 1 post partum}}{\text{Total number of offspring born}} \times 100$$

Viability index was calculated for each group on a litter basis as:

$$\frac{\text{Number of live offspring on Day 4 post partum}}{\text{Number of live offspring at Day 1 post partum}} \times 100$$

Lactation index was calculated for each group on a litter basis as:

$$\frac{\text{Number of live offspring on Day of examination}}{\text{No. live offspring after culling on Day 4 post partum}} \times 100$$

Offspring development timing

A continuity correction of half a day was subtracted from the age (Day post partum) of litters born overnight.

Sex ratio

The ratio of male to female offspring was calculated at birth, and for live offspring at birth, before and after culling on Day 4 post partum and at weaning.

Group mean activity score was calculated for each sex as:

$$\frac{\text{Total of individual litter means}}{\text{Number of litters}}$$

Group mean swimming time in the water-filled Y-maze was calculated for each sex as:

$$\frac{\text{Summed individual litter mean swimming times}}{\text{Number of litters}}$$

4.8.8 Statistical evaluation

The significance of suggestive intergroup differences was tested, where deemed to be appropriate. The following statistical tests were available:-

A one-way analysis of variance, using pooled error variance was first performed. If 'F' was significant then two-tailed 't' tests were performed comparing the control group to the treated group

Mann-Whitney U-test

Chi-squared test,
Fisher's Exact
Probability test or
Mann-Whitney U-test

Bodyweights
Bodyweight change
Food consumption
Water-maze swimming times
Reproductive organ weights (relative and absolute)
Foetal and placental weights

Corpora lutea count
Implantation count
Resorption count
Pre-coital interval
Pre-implantation loss
Post-implantation loss
Litter size
Post-implantation survival index
Live birth index
Viability index
Lactation index
Gestation length
Physical activity scores
Sex ratio

Fertility index
Gestation index
Mating performance
Conception rate
Oestrous cycle distribution

Where significance was found, the statistical test used has been specified. Differences with an associated probability of $P < 0.05$ were considered to be statistically significant.

5. RESULTS

5.1 F₀ generation

5.1.1 Achieved dosages (Tables 1 and 2; Appendices 8 and 14)

Calculated group mean dosages for both males and females were within 10% of intended values throughout the F₀ generation.

5.1.2 General condition and mortality

The general condition of F₀ animals receiving diets containing SC-19129 was similar to that of the controls and no deaths occurred.

5.1.3 Bodyweight of males (Figure 1; Table 3; Appendix 1)

Bodyweight gain of males from Groups 3 and 4 (500 and 750 mg/kg/day) was slightly reduced compared with that of the controls, but the difference was not statistically significant, no dose response occurred, and the slight decrease in bodyweight gains tended to parallel slight decreases in food intake (see Section 5.1.5). Bodyweight gain of Group 2 males (250 mg/kg/day) was unaffected.

5.1.4 Bodyweight of females (Figures 2, 5 and 7; Tables 4, 12 and 20; Appendices 2, 6 and 12)

There were some slight inter-group variations in bodyweight gains of females before pairing and during gestation and lactation, but no treatment-related trends were apparent.

5.1.5 Food consumption (Tables 5, 6, 13 and 21; Appendices 3, 4, 7 and 13)

Although not significantly different, weekly food consumption values of males in Groups 3 and 4 (500 and 750 mg/kg/day) occasionally showed slight decreases. Food consumption of females was essentially unaffected.

5.1.6 Food conversion efficiency (Tables 7, 8 and 14)

Food conversion efficiency in treated males and females was similar to that of the controls.

5.1.7 Oestrous cycles (Figure 3; Table 9; Appendix 5)

The regularity and duration of oestrous cycles were unaffected by treatment with SC-19129.

5.1.8 Mating performance and fertility (Figure 4; Tables 10 and 11; Appendix 5)

Mating performance and fertility showed no adverse effects of treatment with SC-19129.

5.2 Litter responses

5.2.1 Females killed on Day 20 of gestation

5.2.1.1 Necropsy of females (Table 31; Appendix 24)

No macroscopic changes were observed that could be attributed to treatment with SC-19129.

5.2.1.2 Litter responses (Table 15; Appendix 9)

There were some inter-group variations in the numbers of corpora lutea, implantations and viable young and in the extent of pre- and post-implantation losses, but no indication of any treatment-related response was apparent.

Foetal and placental weight analysis detected no adverse effects of treatment with SC-19129.

5.2.1.3 Foetal evaluation (Tables 16-18; Appendices 9-11)

Examination of foetuses at necropsy and after free-hand serial sectioning or skeletal processing, revealed a number of observations in all groups, the majority of which were of types and incidences previously recorded in this strain in these laboratories.

One grossly abnormal foetus with craniofacial malformations, craniorrhachischisis and subsequent displacement of the viscera was observed in Group 4 (750 mg/kg/day). The isolated nature of this finding was not suggestive of any treatment-related aetiology.

Compared with the concurrent controls, at free-hand serial sectioning all treated groups showed a slight increase in the incidence of hepatic haemorrhage, the highest value being recorded in Group 3 (500 mg/kg/day). As no dosage-relationship was apparent, and as all values were within the background control range it was considered that the increase was unrelated to treatment. The foetal incidence for displaced testis in Group 4 (750 mg/kg/day) appeared to be slightly high. However, these data were calculated on the basis of male foetuses and therefore represented two foetuses only, one of which had multiple malformations (see previously). Again, it was considered that there was no involvement with treatment.

5.2.2 Females allowed to litter

5.2.2.1 Gestation length and index (Figure 6; Table 19; Appendix 5)

Gestation length was within the normal range of 22 to 23¹/₂ days in all groups. All pregnant animals in the treated groups gave birth successfully, with no evidence of dystocia. One control animal, which failed to give birth, was found to have a single, large, resorbing foetus retained in utero when examined post mortem on Day 25 post coitum.

5.2.2.2 General condition of offspring

The general condition of the offspring was unaffected by the presence of SC-19129 in the diet.

5.2.2.3 Litter size and viability indices (Tables 22 and 23, Appendix 15)

Litter size at birth was similar in all groups. Two litters in Group 3 (500 mg/kg/day) showed high perinatal mortality resulting in a slightly reduced viability index at Day 4 post partum. However, after culling, there was no evidence of any treatment-related effect upon offspring viability.

5.2.2.4 Bodyweight of offspring (Figure 8; Table 24; Appendix 16)

Mean bodyweight at Day 1 post partum and growth of the offspring to Day 21 post partum were similar in all groups.

5.2.2.5 Sex ratio (Table 25; Appendix 17)

Sex ratios showed some minor inter-group variations but there was no indication of any treatment-related effect.

5.2.2.6 Physical development (Figures 9-14; Appendix 18)

Physical development, as assessed by the times of onset and completion of pinna unfolding, hair growth, testicular descent, tooth eruption, eye opening and vaginal opening, showed no adverse effects of treatment.

5.2.2.7 Auditory and visual functions (Table 26; Appendix 19)

Auditory and visual functions of the F₁ offspring were unaffected by treatment with SC-19129.

5.2.2.8 Activity monitoring (Figures 15 and 16; Table 27; Appendix 20)

The activity scores for male and female offspring were similar in treated and control groups.

5.2.2.9 Learning performance (Figures 17 and 18; Table 28; Appendix 21)

Mean swimming times of females from Group 4 (750 mg/kg/day) at the initial trial was slightly greater than that of controls, although the effect was largely due to a small number of litters. Subsequent performances of females and that of males throughout were similar in all groups.

5.3 Terminal studies

5.3.1 Macroscopic observations - F₁ offspring (Table 29; Appendix 22)

Examination of offspring that died before weaning, and of offspring culled at Day 4 or killed after weaning revealed no abnormalities that were considered to be related to treatment with SC-19129. The majority of offspring that died in the lactation period were found to have no milk in their stomachs.

5.3.2 Macroscopic observations - F₀ adults (Tables 30 and 31; Appendices 23 and 24)

Examination of F₀ adults at the end of the treatment period revealed no abnormalities that were considered to be related to treatment.

5.3.3 Male reproductive organ weights (Tables 32 and 33; Appendices 25 and 26)

Group mean absolute and relative weights of testes, epididymides, prostate gland and seminal vesicles showed no significant inter-group variations.

5.3.4 Female reproductive organ weights (Tables 34 and 35; Appendices 27 and 28)

There were no significant intergroup differences in the absolute and relative weights of the reproductive organs.

5.4 F₁ generation

5.4.1 Achieved dosages (Tables 36 and 37; Appendices 39 and 45)

For the majority of the treatment period the mean achieved dosage for all groups fell within 10% of the intended dosage. Dosages fell outside the 10% range during Weeks 1 and 3 of treatment (both sexes), and during the first week of lactation (females); in all cases this was due to animals eating a different amount of food from that which had been estimated.

5.4.2 General condition and mortality

The general condition of F₁ animals was unaffected by treatment, and no deaths occurred.

5.4.3 Bodyweight of males (Figure 19; Table 38; Appendix 30)

Initial mean bodyweight was similar in all groups of males, but by the time of pairing, weight gain was slightly reduced in all treated groups, although statistical significance was achieved only in Group 4 (750 mg/kg/day; $P < 0.01$). However, no dose response in bodyweight changes was observed and the decreased bodyweight gain in Group 4 (750 mg/kg/day) in males tended to parallel a slight decrease in food consumption (see Section 5.4.5).

5.4.4 Bodyweight of females (Figures 20, 23 and 25; Tables 39, 47 and 55; Appendices 31, 37 and 43)

Initial mean bodyweight of selected females and bodyweight gain up to pairing and during gestation were unaffected by treatment.

During the lactation period, treated females showed a slightly lower rate of bodyweight gain than that of the controls, but no dosage-related effect was apparent, and none of the slight differences were significant.

5.4.5 Food consumption (Tables 40, 41 48 and 56; Appendices 32-35, 38 and 44)

Although not significantly different, weekly food consumption values of males in Group 4 (750 mg/kg/day) showed slight decreases from Weeks 7 through to 10 and in Weeks 13 and 14. Food consumption of females was essentially unaffected.

5.4.6 Food conversion efficiency (Tables 42, 43 and 49)

Food conversion efficiency was unaffected by treatment.

5.4.7 Oestrous cycles (Figure 21; Table 44; Appendix 36)

The regularity and duration of oestrous cycles were similar in all groups.

5.4.8 Mating performance and fertility (Figure 22; Tables 45 and 46; Appendix 36)

Mating performance and fertility were unaffected by treatment with SC-19129.

5.5 Litter responses

5.5.1 Females killed on Day 20 of gestation

5.5.1.1 Necropsy of females (Table 63; Appendix 51)

No macroscopic changes were observed that could be attributed to treatment with SC-19129.

5.5.1.2 Litter responses (Table 50; Appendix 40)

The numbers of corpora lutea, implantations, viable young and resorptions showed some inter-group variations, but no effects of treatment were apparent. Pre-implantation loss was high in all groups, including the controls, and this was due to an unusually high incidence of unilateral implantation.

Foetal and placental weights showed no adverse effects of treatment with SC-19129.

5.5.1.3 Foetal examination (Tables 51-53; Appendices 40-42)

Examination of fetuses at necropsy, after free-hand serial sectioning, or skeletal processing revealed a number of observations in all groups, the majority of which were of types and incidences previously recorded in this strain in these laboratories.

One foetus in the control group had bilateral microphthalmia, and a second foetus had a possible hairline septal defect. In Group 3 (500 mg/kg/day) one foetus had no innominate artery, the right carotid and subclavian arteries arose directly from the aortic arch, whilst in Group 4 (750 mg/kg/day) one foetus had unilateral microphthalmia with an associated reduction in the thickness of the retinal layer, and a second foetus had unilateral anophthalmia, severe internal hydrocephaly and a reduced pituitary gland.

One conjoined foetus was seen in Group 4 (750 mg/kg/day), with the smaller foetus presenting major skeletal malformations.

There were no indications that any of these abnormalities were associated with treatment with SC-19129.

5.5.2 Females allowed to litter

5.5.2.1 Gestation length and index (Figure 24; Table 54; Appendix 36)

With the exception of one female from Group 2 (250 mg/kg/day) which gave birth to a single foetus after a gestation period of 24¹/₂ days, all females gave birth successfully within the normal range of 22 to 23¹/₂ days of gestation. There was no evidence of dystocia and gestation index was unaffected by treatment.

5.5.2.2 General condition of offspring

The general condition of the F₂ offspring was unaffected by treatment.

5.5.2.3 Litter size and viability indices (Tables 57 and 58; Appendix 46)

Litter size at Day 1 post partum and subsequent offspring survival were similar in all groups.

5.5.2.4 Bodyweight of offspring (Figure 26; Table 59; Appendix 47)

Treatment with SC-19129 had no effect upon initial bodyweight of offspring or upon bodyweight gain to weaning at Day 21 post partum.

5.5.2.5 Sex ratio (Table 60; Appendix 48)

The ratio of male to female offspring was similar in all groups.

5.6 Terminal studies

5.6.1 Macroscopic observations - F₂ offspring (Table 61; Appendix 49)

Examination of offspring that died before weaning, and of offspring culled at Day 4 or killed after weaning revealed no macroscopic abnormalities that were considered to be related to treatment.

The majority of offspring that died during the lactation period were found to have no milk in their stomachs.

5.6.2 Macroscopic observations - F₁ adults (Tables 62 and 63; Appendices 50 and 51)

Macroscopic examination of F₁ adults at the end of study revealed no abnormalities that could be associated with treatment.

5.6.3 Male reproductive organ weights (Tables 64 and 65; Appendices 52 and 53)

There were no significant inter-group differences in the absolute weights of the reproductive organs.

Group mean relative weight of the testes and seminal vesicles was slightly increased in Group 4 (750 mg/kg/day) and relative weight of the epididymides was increased in all treated groups as a consequence of slight reductions in bodyweight.

5.6.4 Female reproductive organ weights (Tables 66 and 67; Appendices 54 and 55)

There were no intergroup differences in the absolute and relative weights of the reproductive organs.

FIGURE 1

Bodyweight change (g) of males (F_0)

- Group 1 : Control
——— Group 2 : SC-19129 : 250 mg/kg/day (intended)
——— Group 3 : SC-19129 : 500 mg/kg/day (intended)
----- Group 4 : SC-19129 : 750 mg/kg/day (intended)

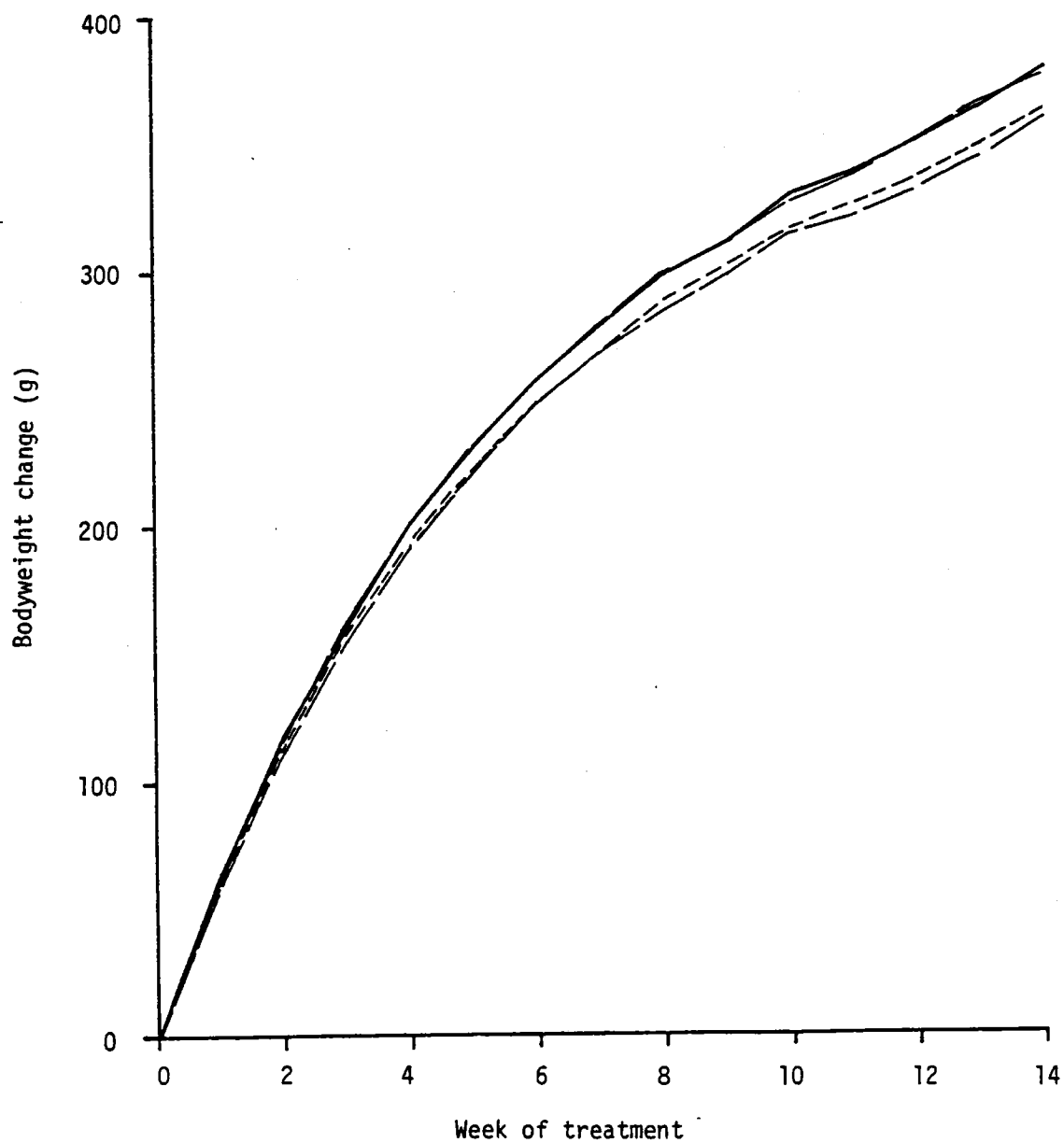


FIGURE 2

Bodyweight change (g) of females before pairing (F_0)

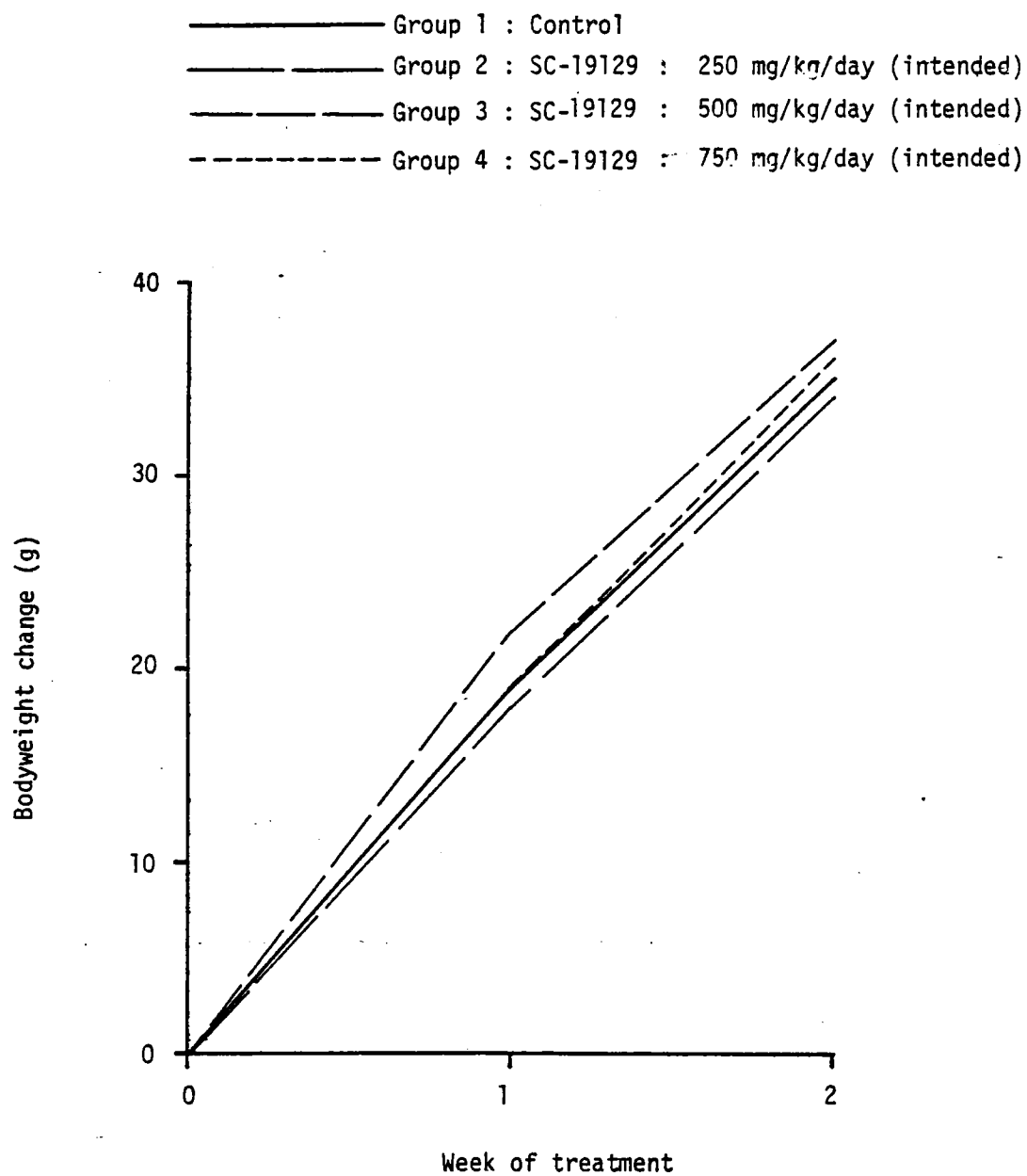


FIGURE 3

Oestrous cycles (F₀)

Group	:	1	2	3	4
Compound	:	Control	---SC-19129---		
Intended dosage (mg/kg/day)	:	0	250	500	750

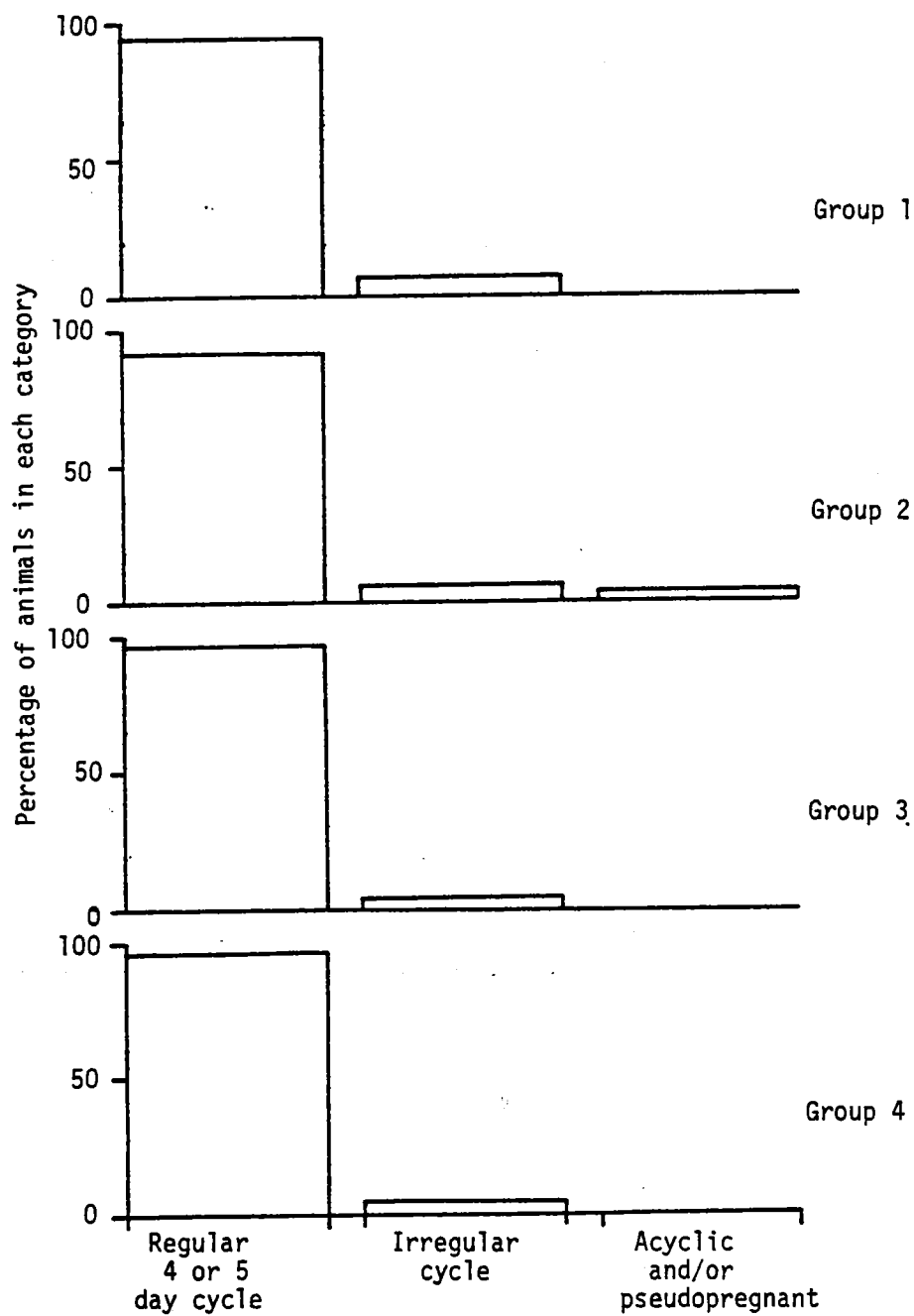


FIGURE 4

Pre-coital interval ($F_0 - F_1$)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

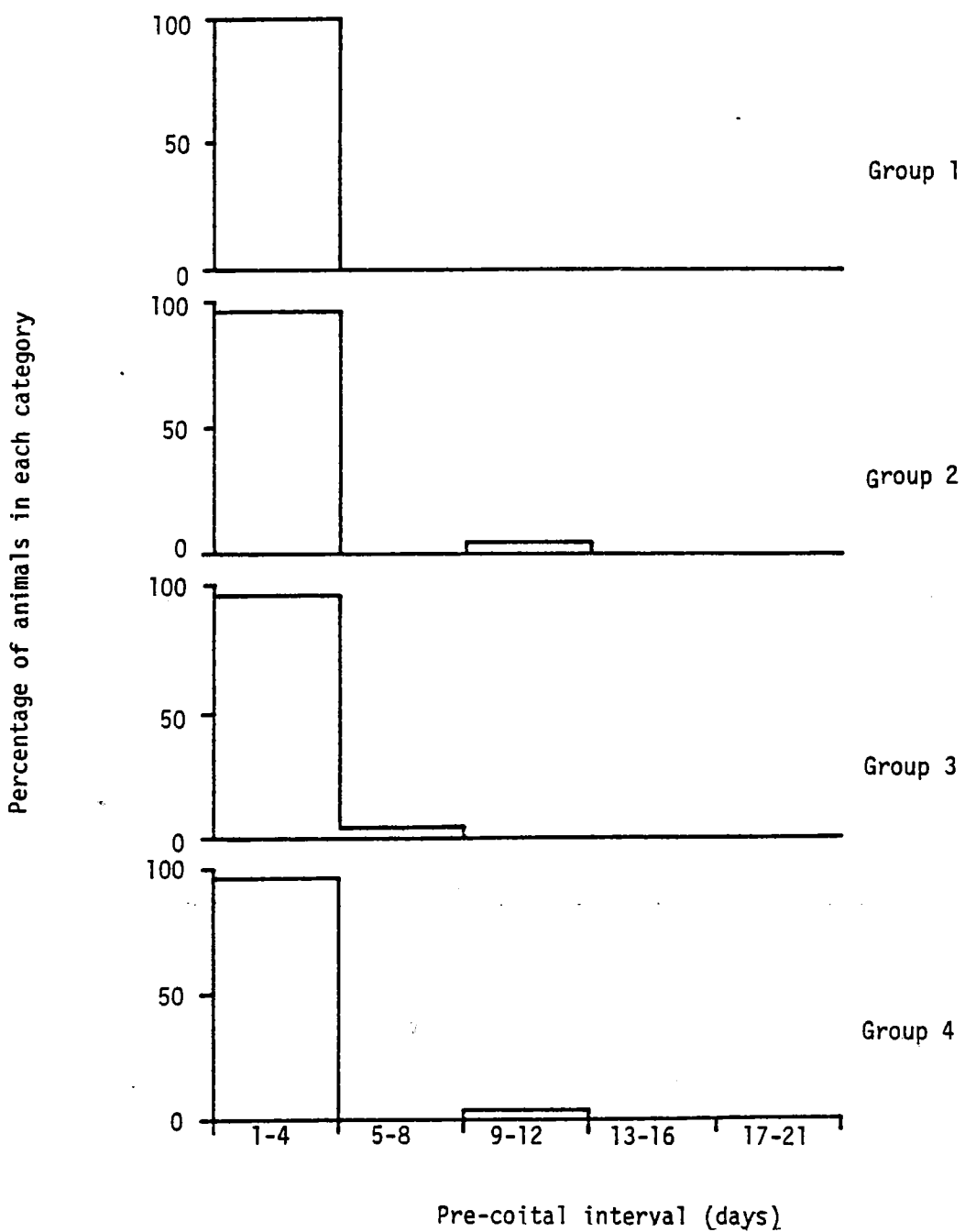


FIGURE 5

Bodyweight change (g) of females during gestation ($F_0 - F_1$)

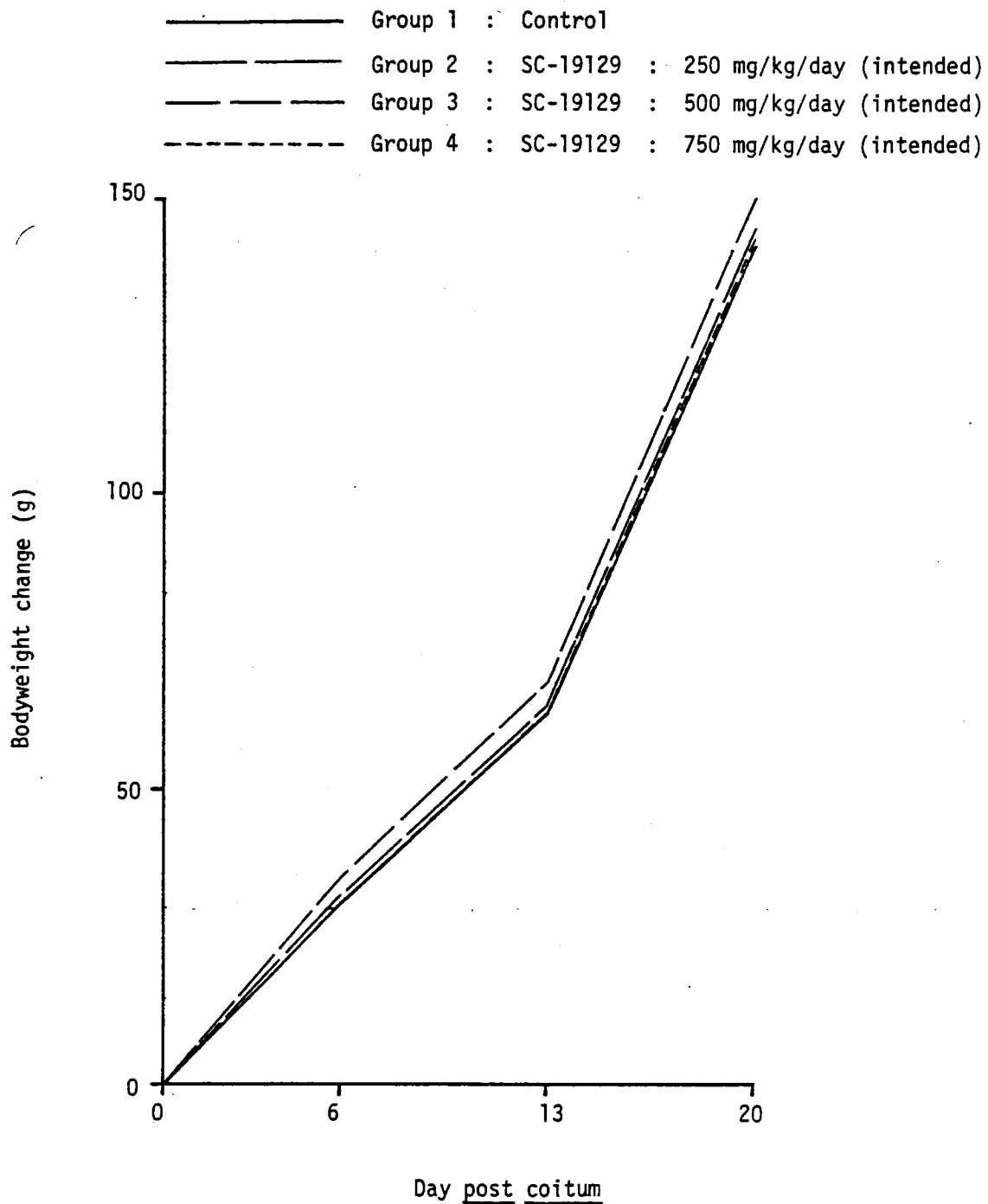


FIGURE 6

Gestation length ($F_0 - F_1$)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

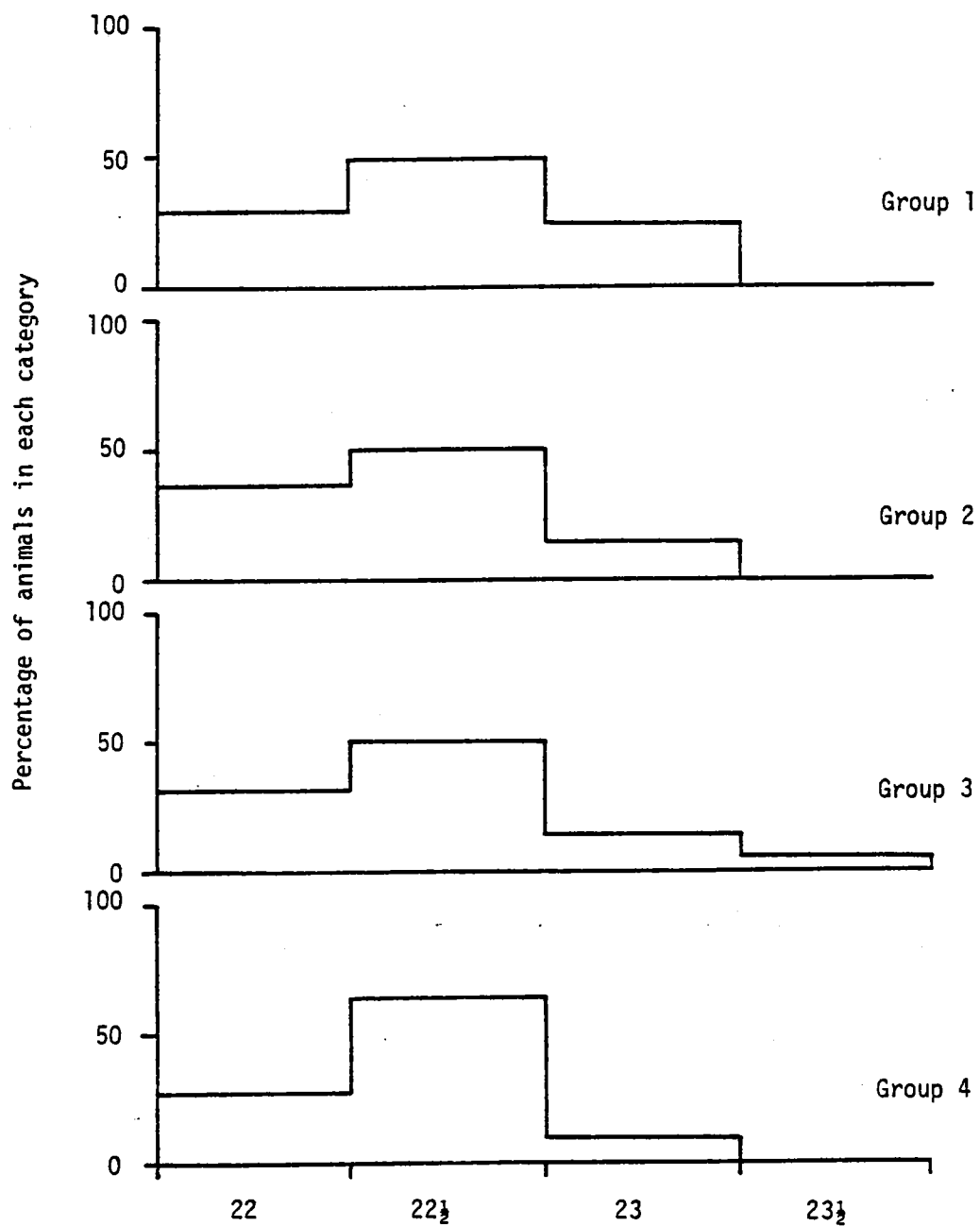


FIGURE 7

Bodyweight change (g) of females during lactation (F_0 - F_1)

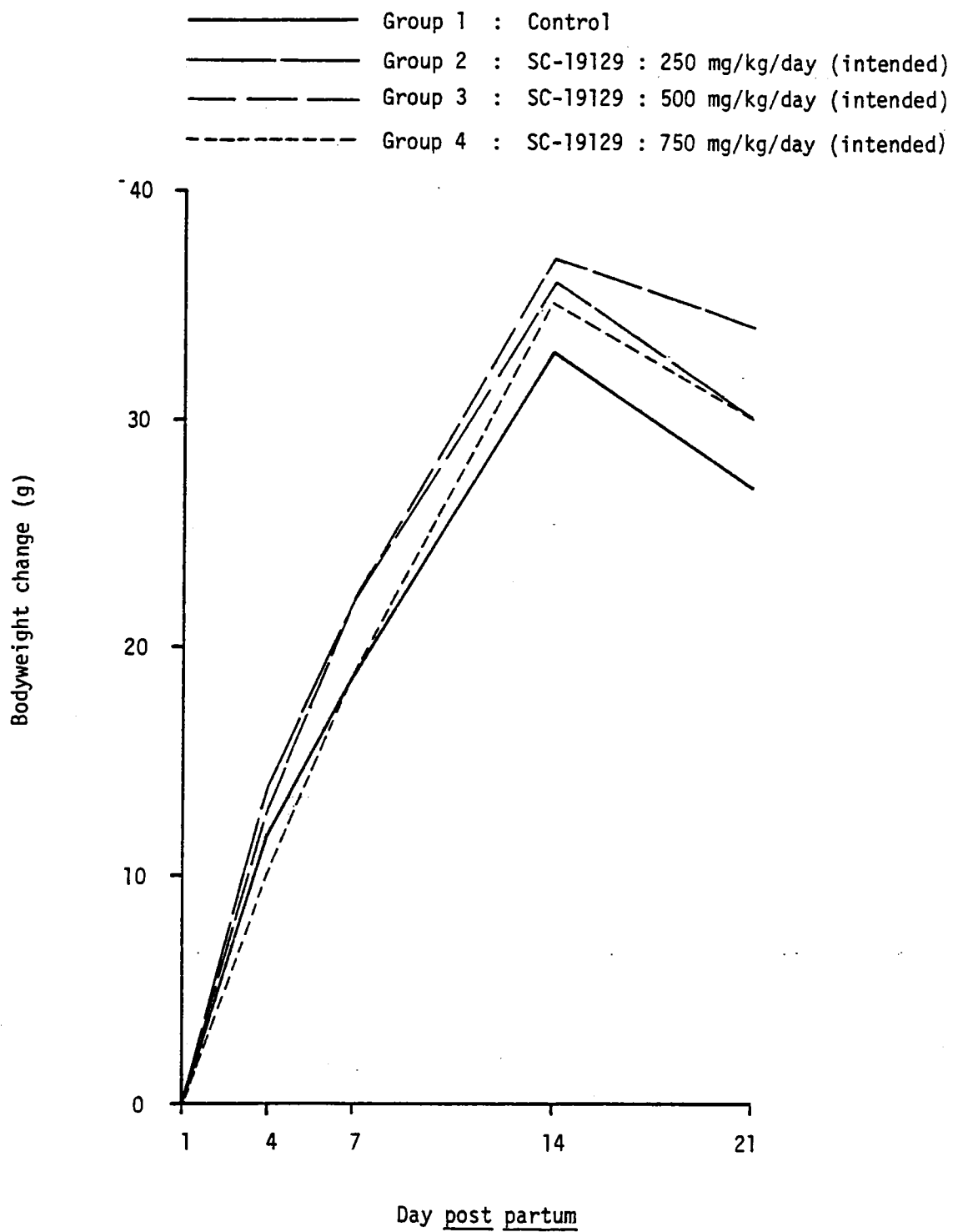


FIGURE 8

Bodyweight change (g) of offspring (F_1)

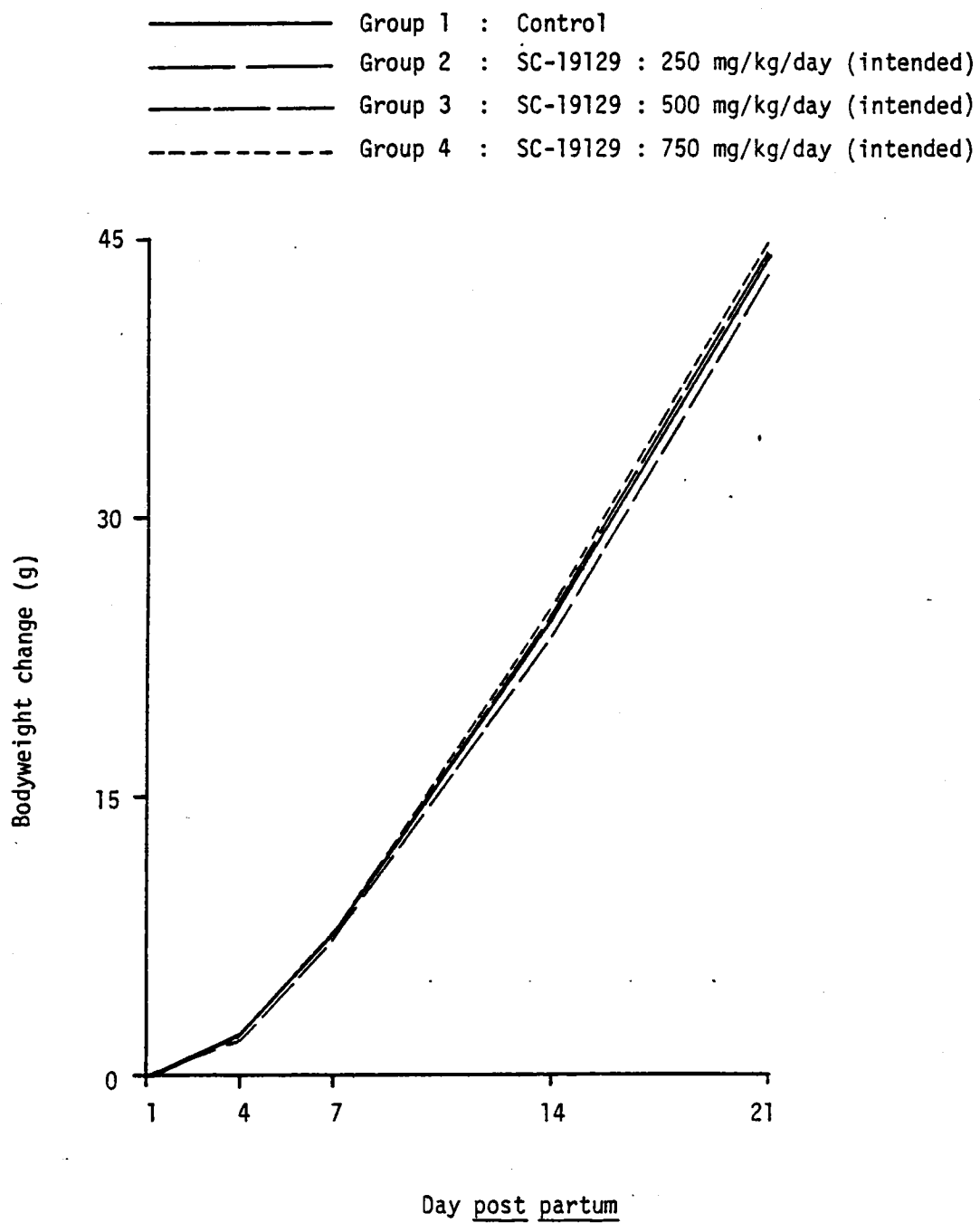


FIGURE 9

Offspring development - pinna unfolding (F_1)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

————— Represents one litter

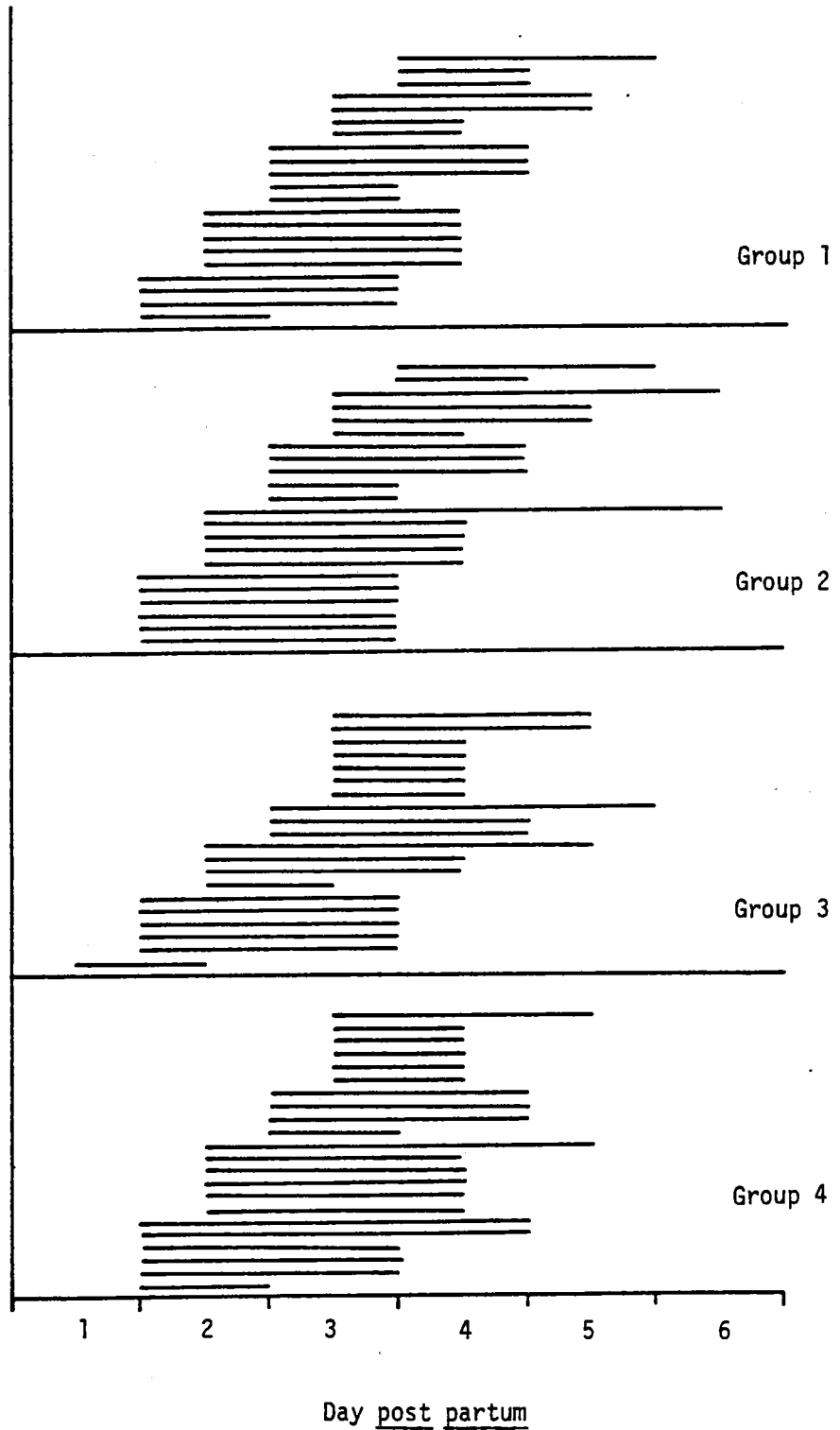


FIGURE 10

Offspring development - hair growth (F_1)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

————— Represents one litter

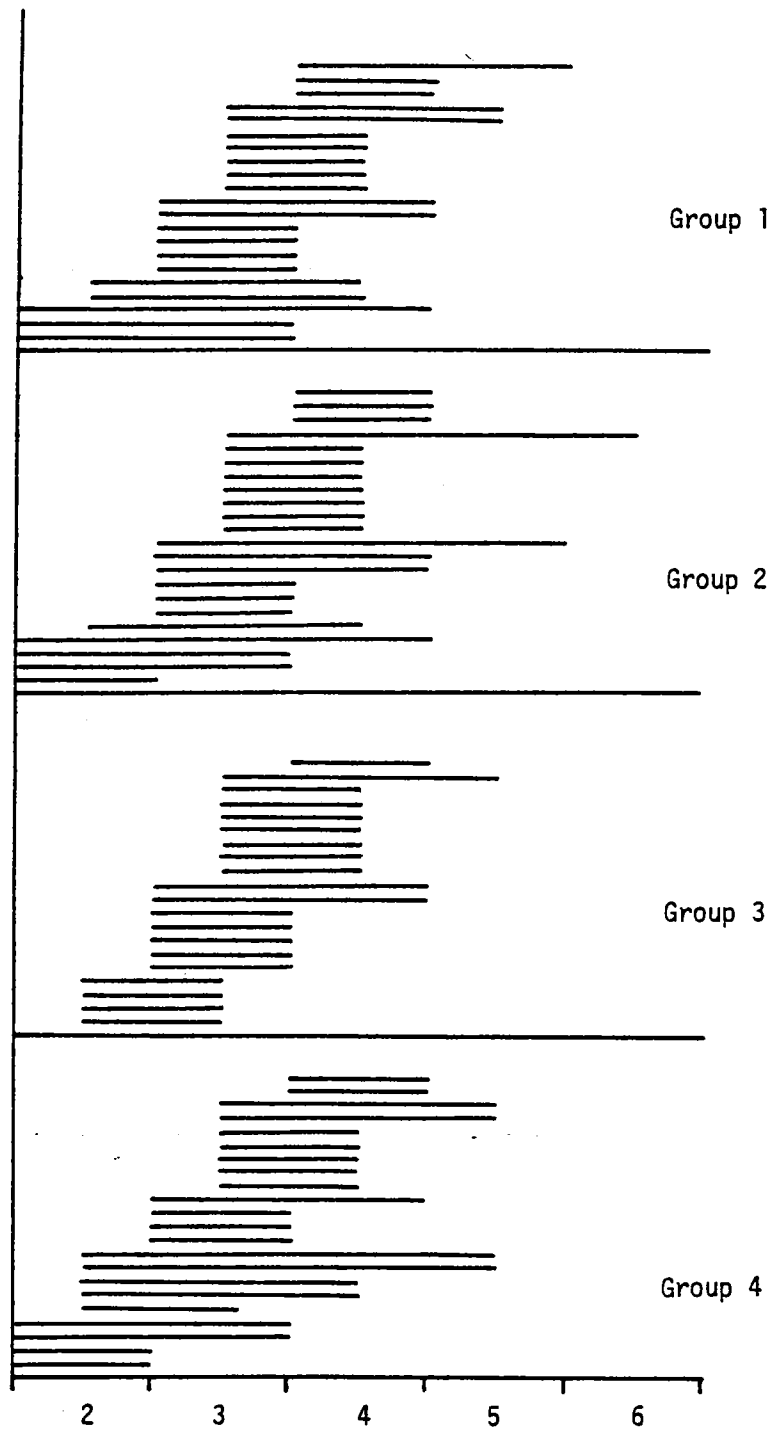


FIGURE 11

Offspring development - testes descent (F_1)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

————— Represents one litter

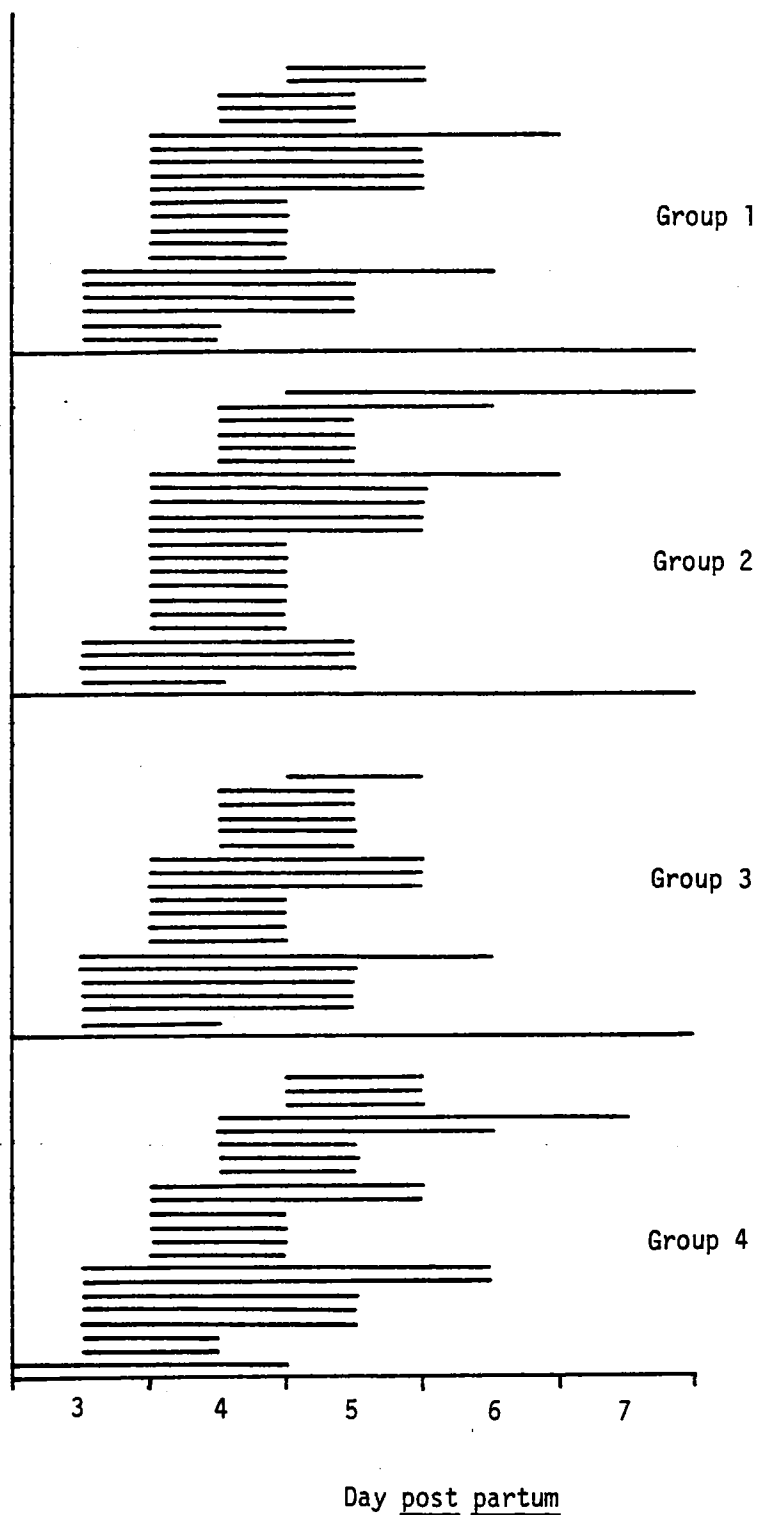


FIGURE 12

Offspring development - tooth eruption (F_1)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

————— Represents one litter

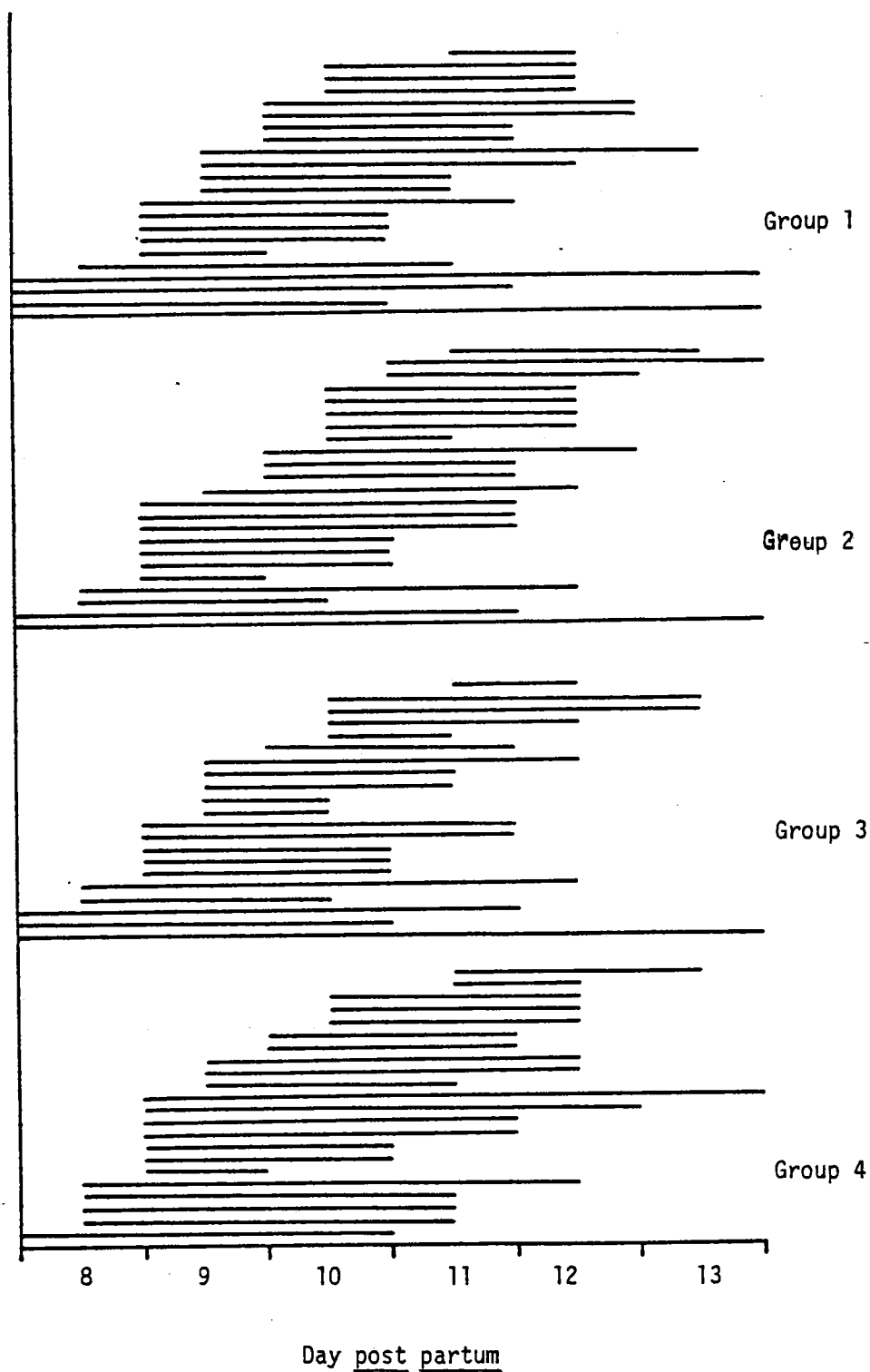
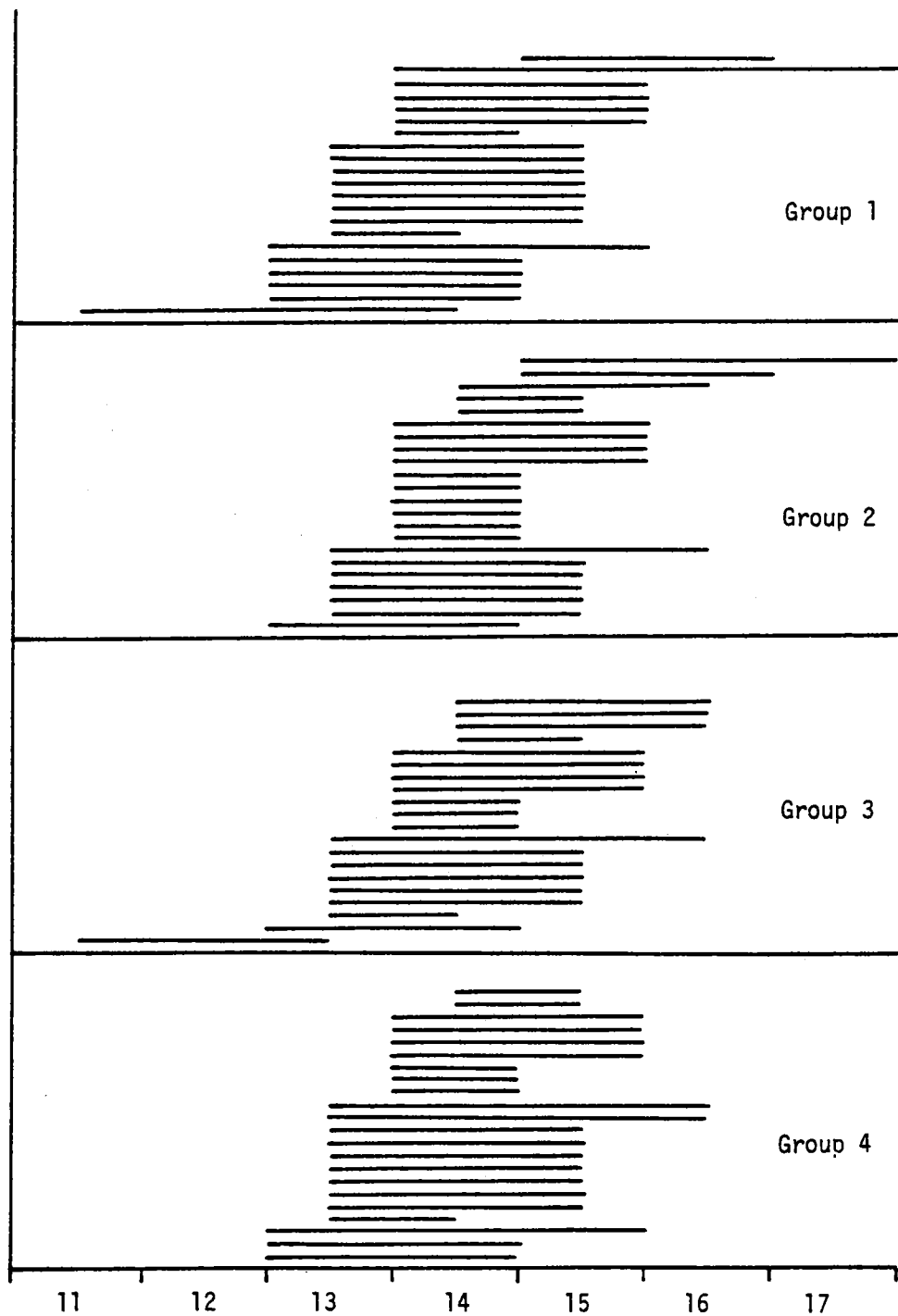


FIGURE 13

Offspring development - eye opening (F_1)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day):		0	250	500	750

————— Represents one litter



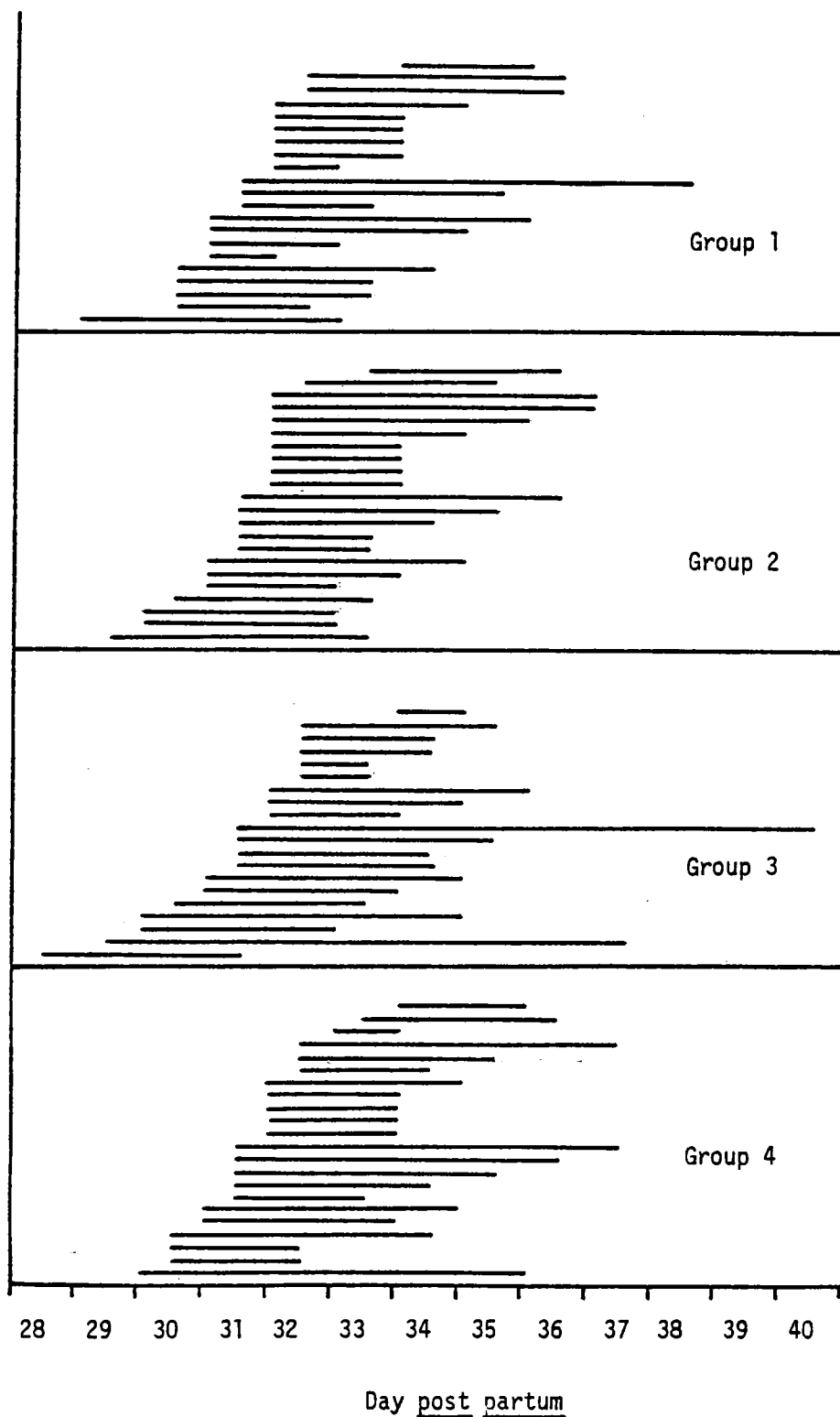
Day post partum

FIGURE 14

Offspring development - vaginal opening (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day):		0	250	500	750

— Represents one litter.



FIGURES 15 and 16

Key to categories for activity scores (F_1)

<u>Category</u>	<u>Activity scores</u>
1	751 - 1000
2	1001 - 1250
3	1251 - 1500
4	1501 - 1750
5	1751 - 2000
6	2001 - 2250
7	2251 - 2500

FIGURE 15

Litter mean activity scores of males (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

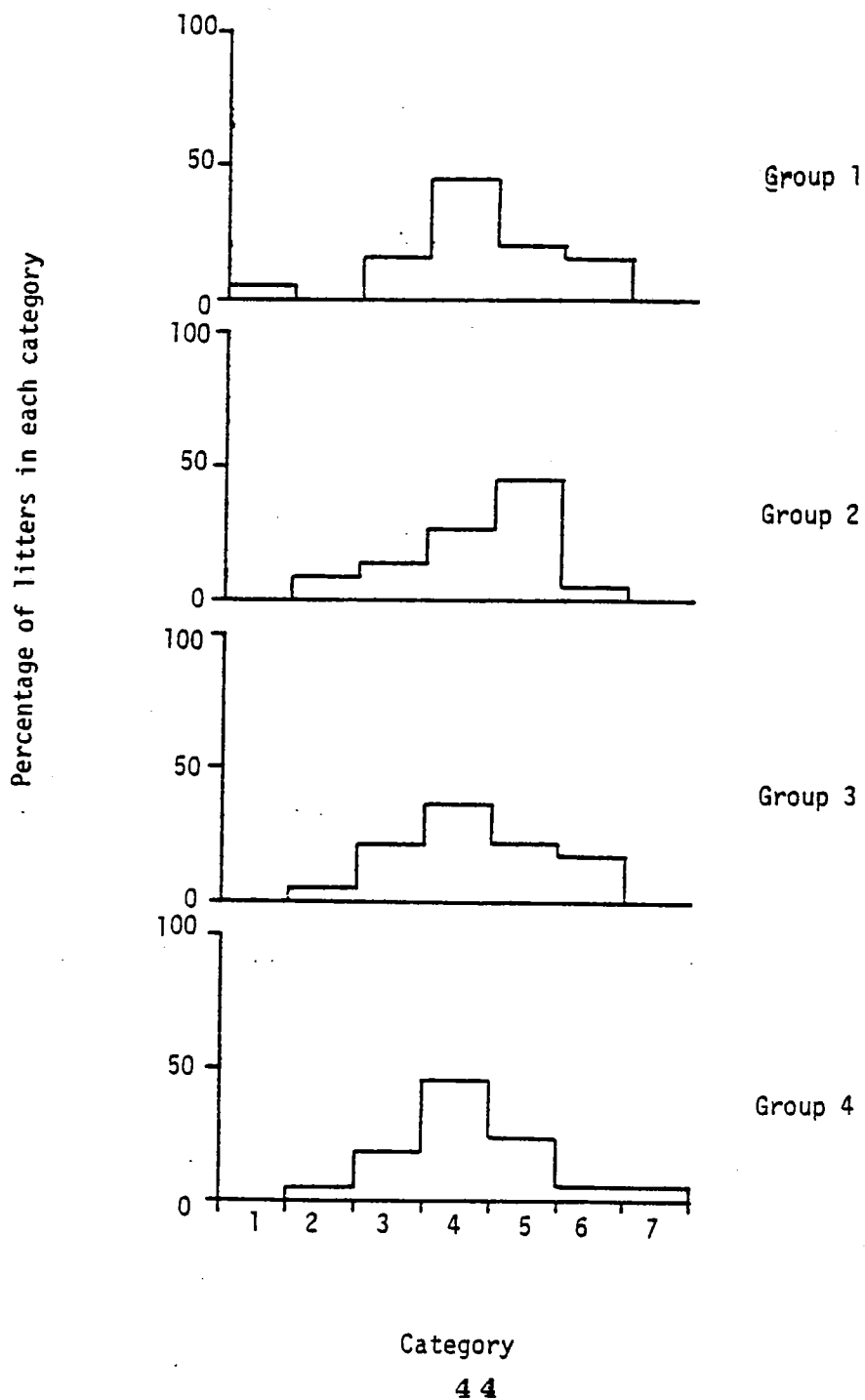


FIGURE 16

Litter mean activity scores of females (F_1)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

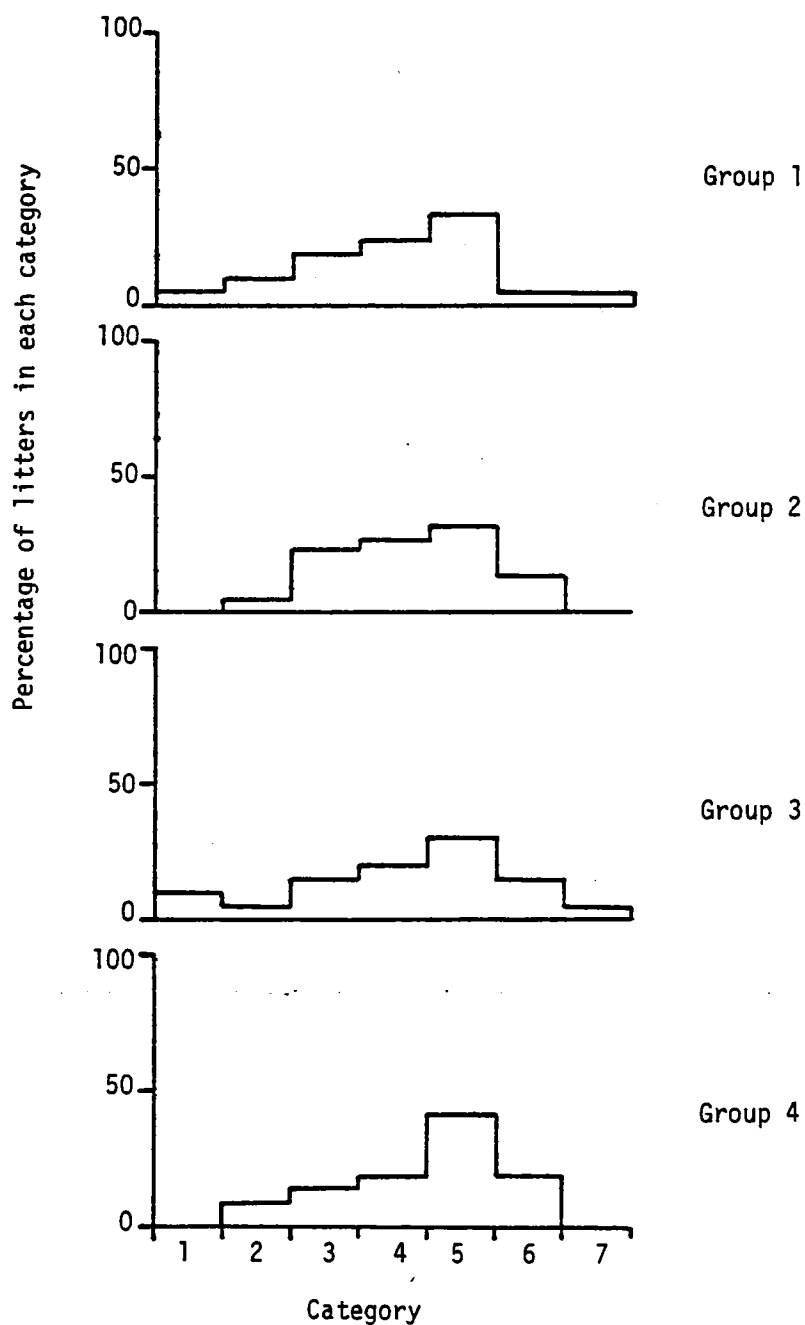


FIGURE 17

Water maze - group mean swimming times of males (F_1)

———— Group 1 : Control
———— Group 2 : SC-19129 : 250 mg/kg/day (intended)
———— Group 3 : SC-19129 : 500 mg/kg/day (intended)
----- Group 4 : SC-19129 : 750 mg/kg/day (intended)

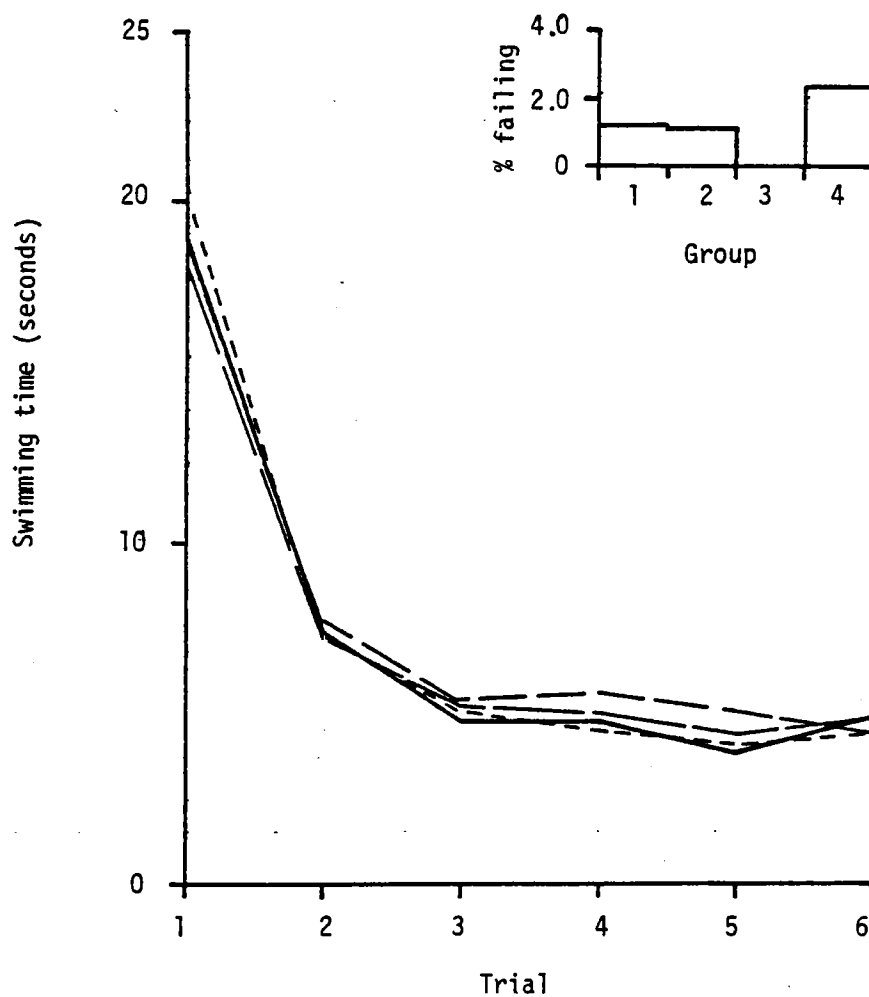


FIGURE 18

Water maze - group mean swimming times of females (F₁)

———— Group 1 : Control
———— Group 2 : SC-19129 : 250 mg/kg/day (intended)
—— ——— Group 3 : SC-19129 : 500 mg/kg/day (intended)
----- Group 4 : SC-19129 : 750 mg/kg/day (intended)

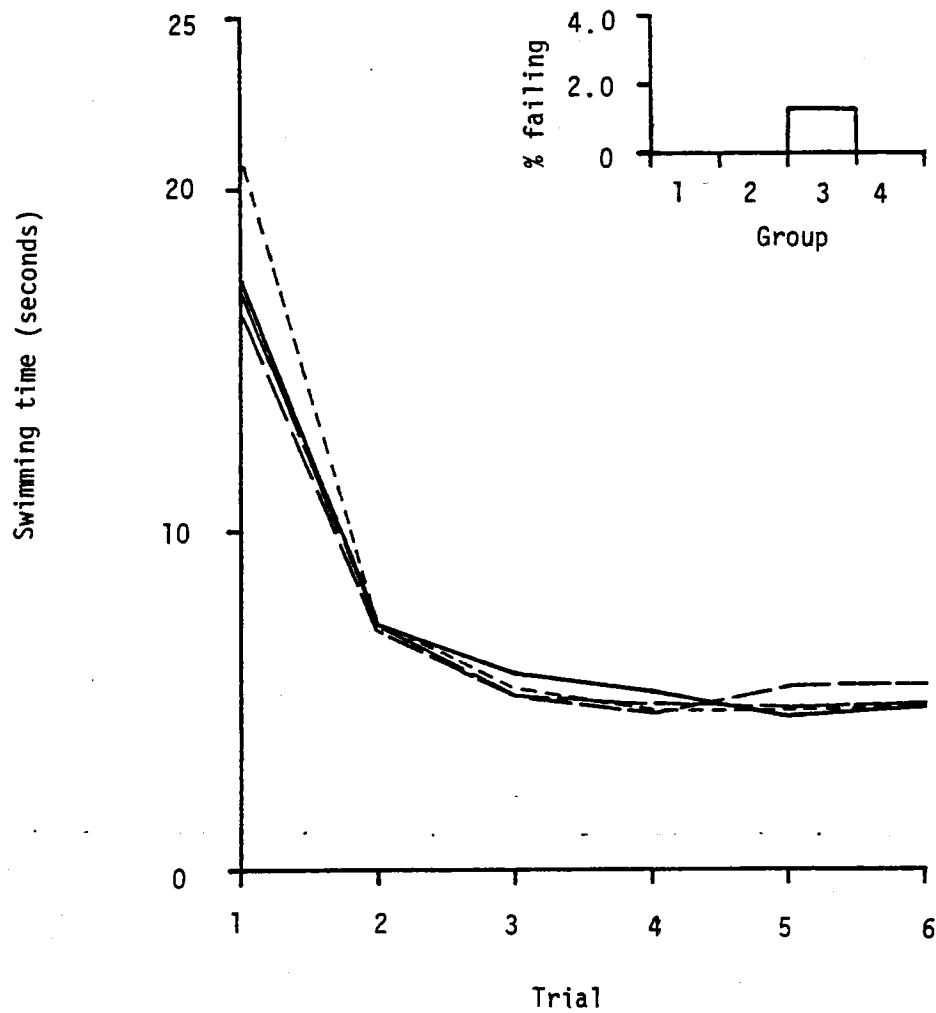


FIGURE 19

Bodyweight change (g) of males (F₁)

- Group 1 : Control
- Group 2 : SC-19129 : 250 mg/kg/day (intended)
- Group 3 : SC-19129 : 500 mg/kg/day (intended)
- - - Group 4 : SC-19129 : 750 mg/kg/day (intended)

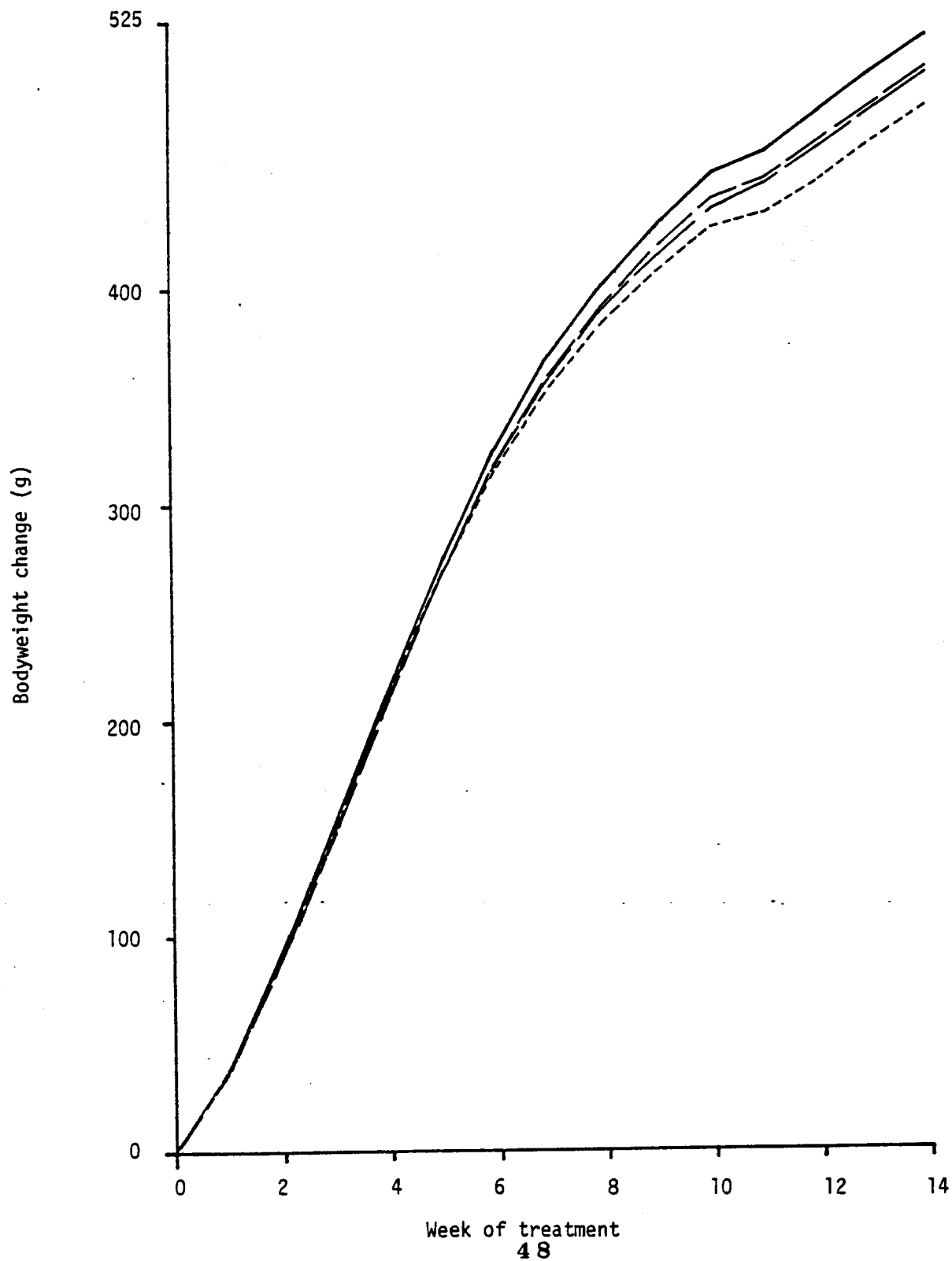


FIGURE 20

Bodyweight change (g) of females before pairing (F₁)

- Group 1 : Control
- Group 2 : SC-19129 : 250 mg/kg/day (intended)
- Group 3 : SC-19129 : 500 mg/kg/day (intended)
- Group 4 : SC-19129 : 750 mg/kg/day (intended)

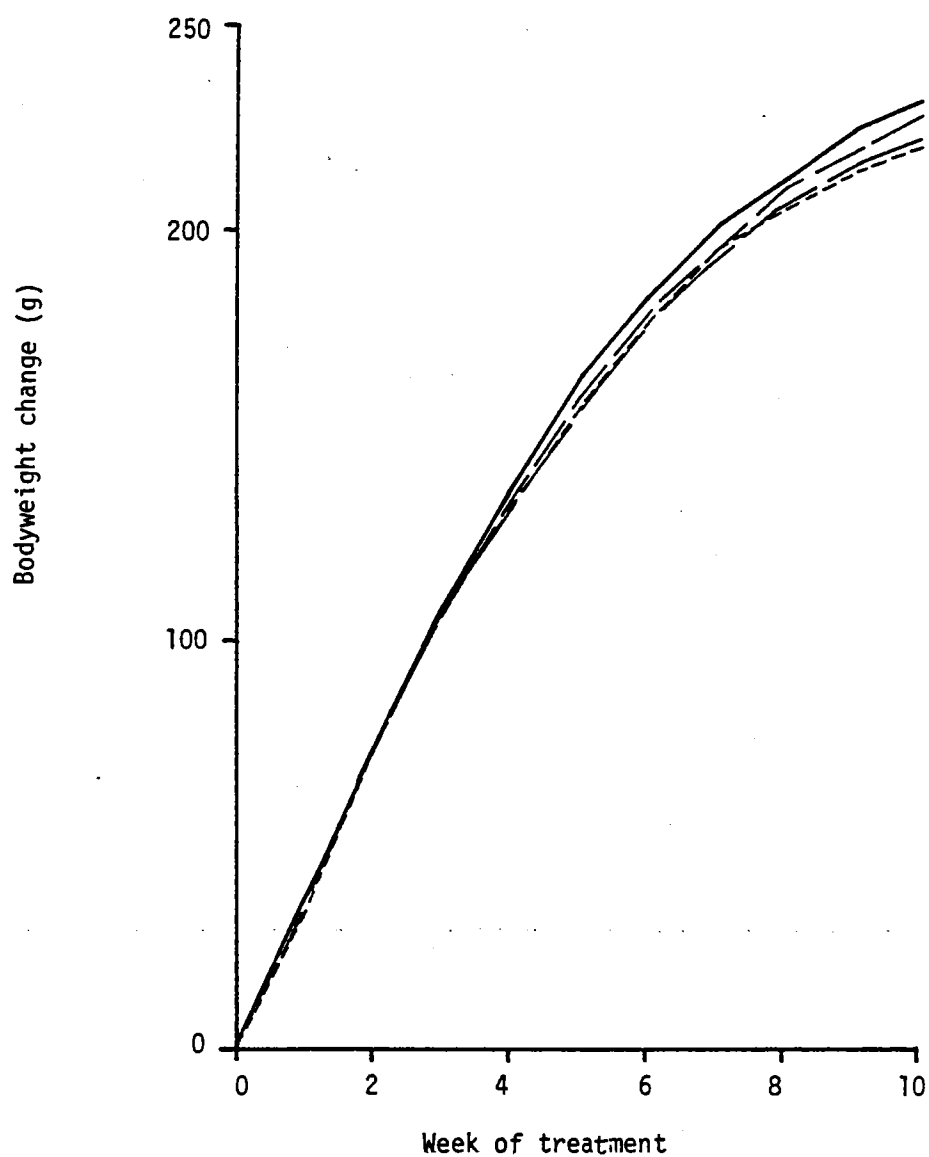


FIGURE 21

Oestrous cycles (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

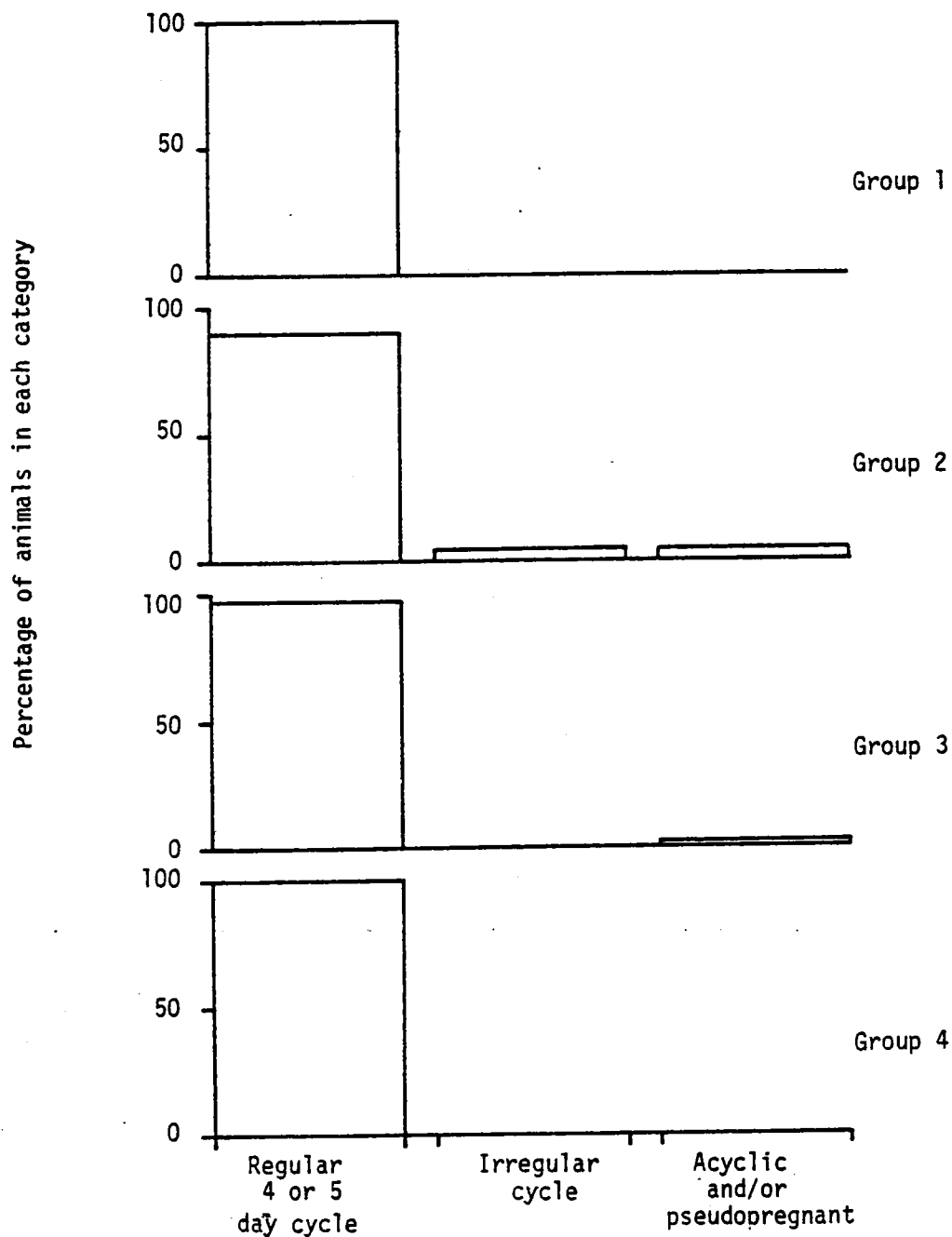


FIGURE 22

Pre-coital interval ($F_1 - F_2$)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

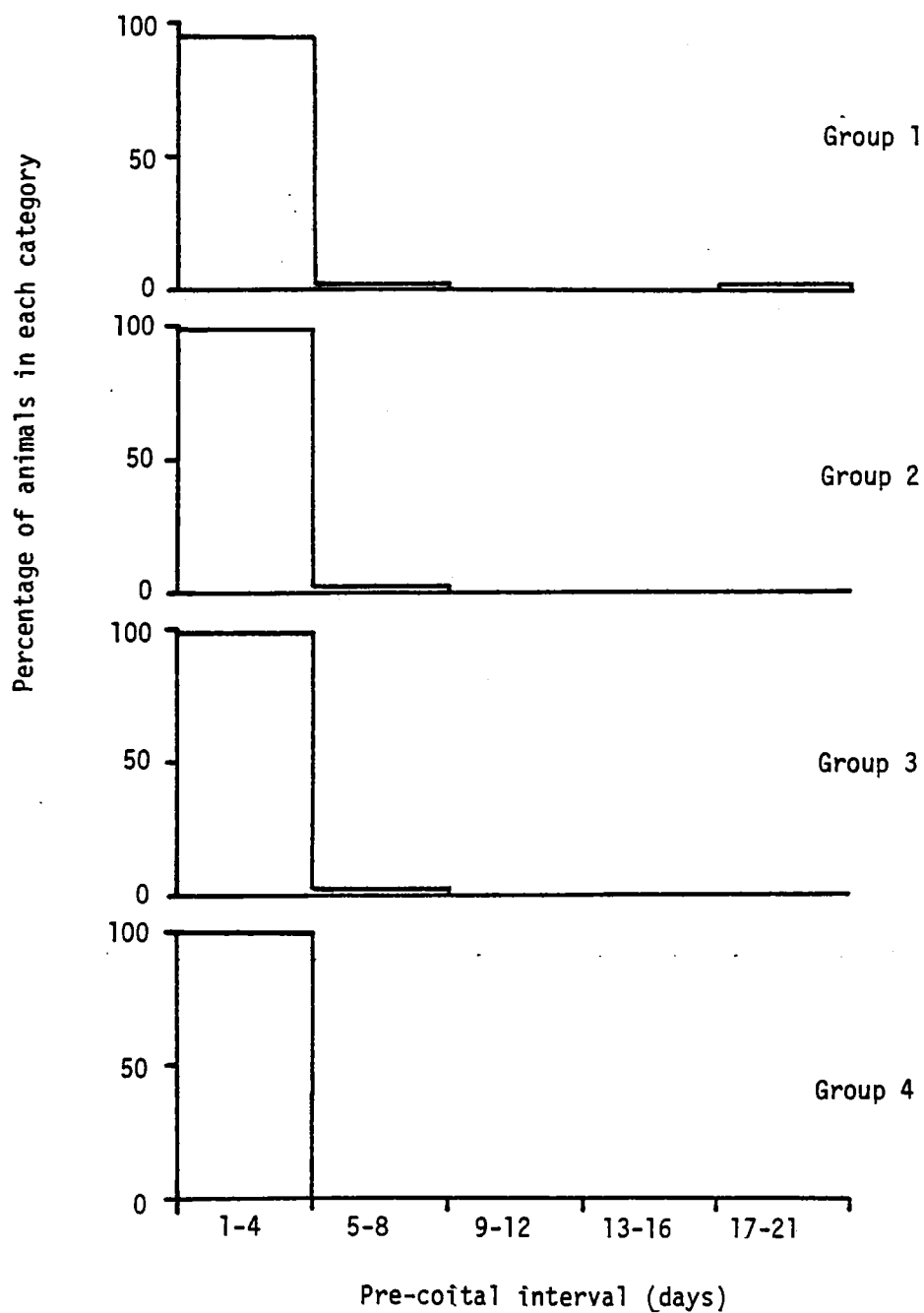


FIGURE 23

Bodyweight change (g) of females during gestation (F₁ - F₂)

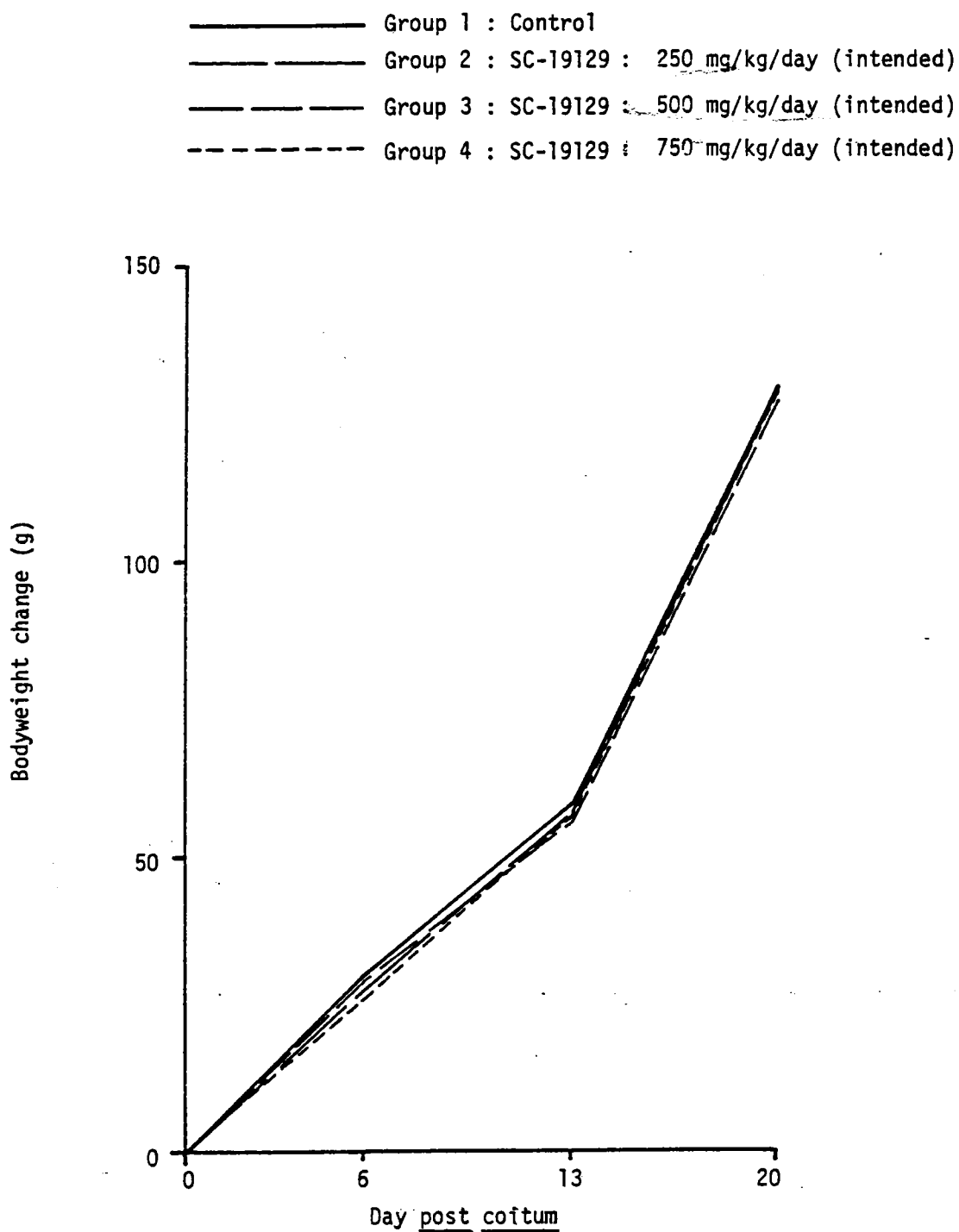


FIGURE 24

Gestation length (F₁- F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

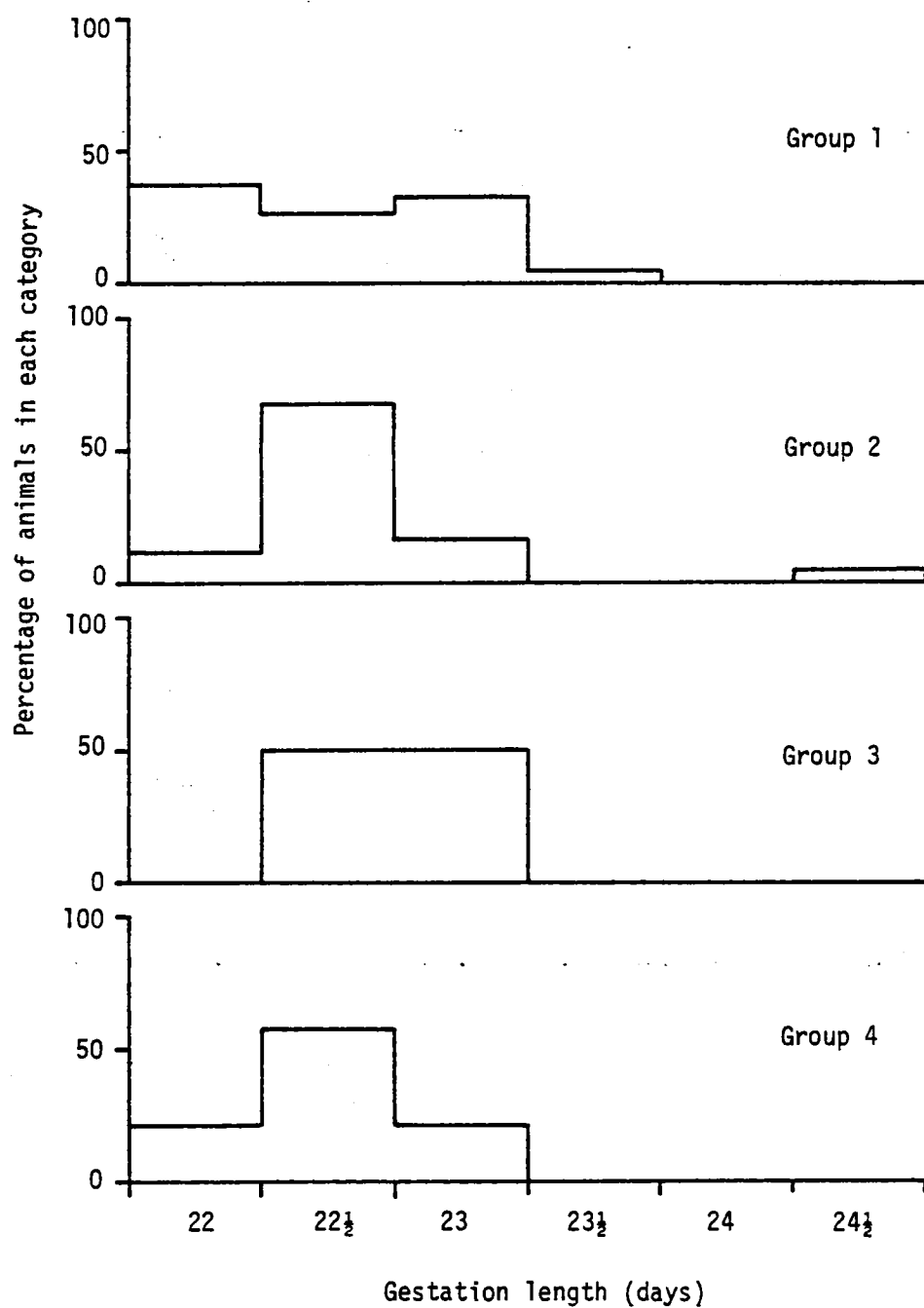


FIGURE 25

Bodyweight change (g) of females during lactation (F₁- F₂)

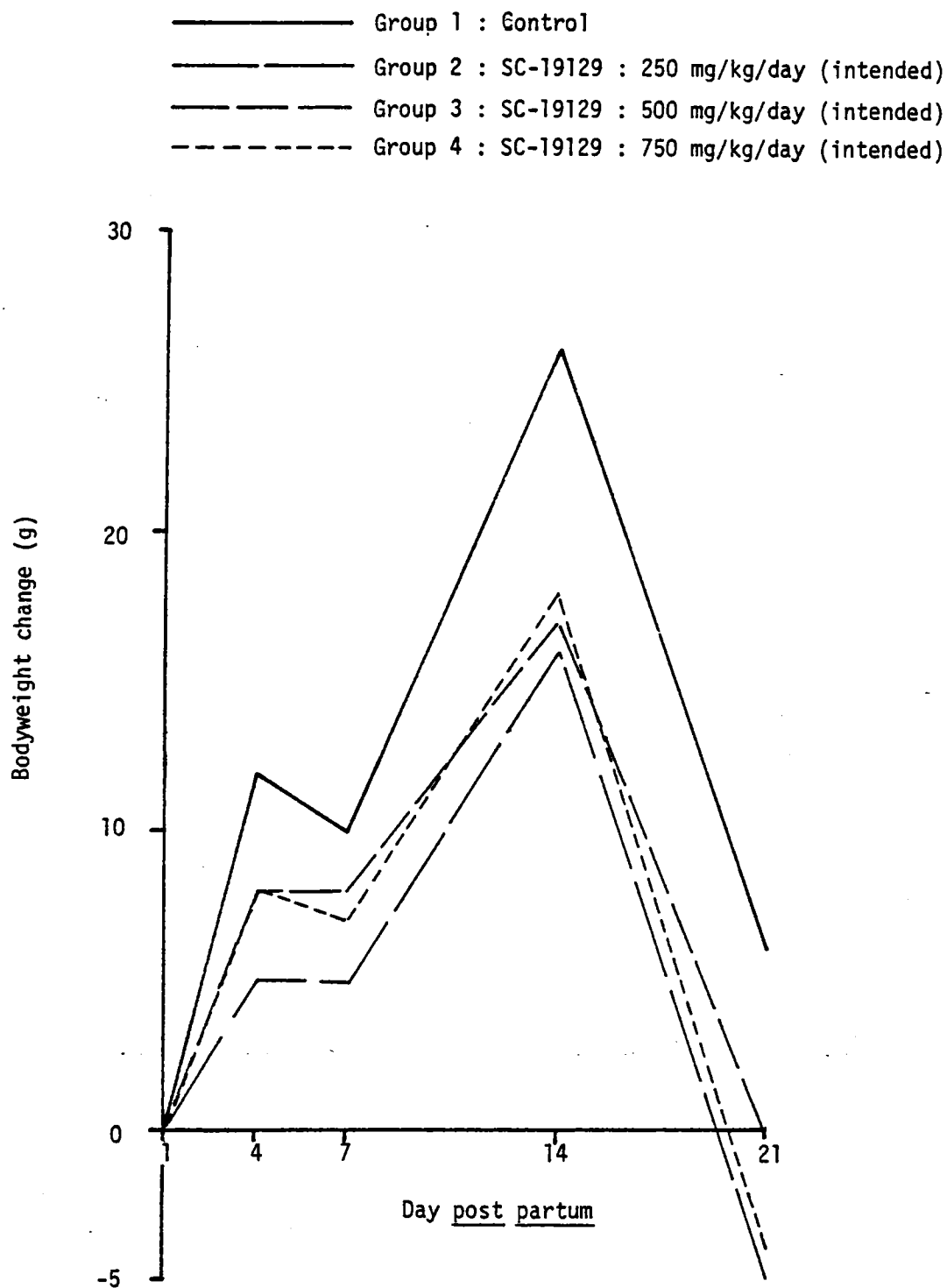


FIGURE 26

Bodyweight change (g) of offspring (F₂)

- Group 1 : Control
- Group 2 : SC-19129 : 250 mg/kg/day (intended)
- Group 3 : SC-19129 : 500 mg/kg/day (intended)
- Group 4 : SC-19129 : 750 mg/kg/day (intended)

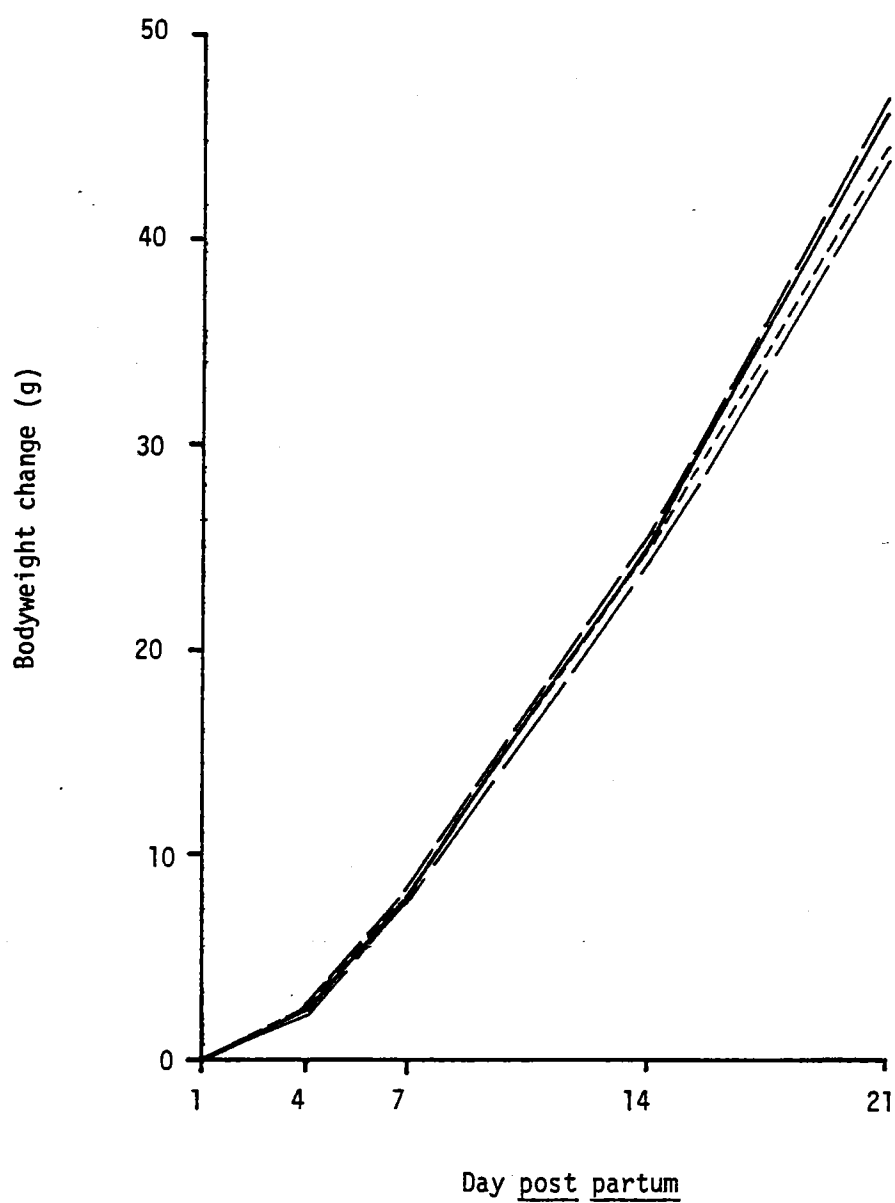


TABLE 1

Achieved dosage (mg/kg/day) - group mean values for males (F₀)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment													
	1	2	3	4	5	6	7	8	9	10	11A	12	13	14
2	249	259	247	234	251	254	253	252	253	247		241	256	266
% of intended	100	104	99	94	100	102	101	101	101	99		96	102	106
3	473	496	487	480	505	500	498	495	487	500		475	503	533
% of intended	95	99	97	96	101	100	100	99	97	100		95	101	107
4	735	756	745	714	754	757	763	744	726	759		711	761	809
% of intended	98	101	99	95	101	101	102	99	97	101		95	101	108

A Animals paired for mating - food intake not recorded.

TABLE 2

Achieved dosages (mg/kg/day) - group mean values for females (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Before pairing ^A Week of treatment		During gestation Days <u>post coitum</u>			During lactation Days <u>post partum</u>		
		1	2	0-5	6-12	13-19	1-6	7-13	14-20 ^B
2	Mean	265	239	253	252	265	233	249	
	S.D.	-	-	16	23	26	42	25	
	n	-	-	34	34	34	22	22	
	% of intended	106	96	101	101	106	93	100	
3	Mean	532	466	509	512	541	461	482	
	S.D.	-	-	35	35	47	76	73	
	n	-	-	34	34	34	20	20	
	% of intended	106	93	102	102	108	92	96	
4	Mean	792	700	763	745	795	691	734	
	S.D.	-	-	77	58	80	103	64	
	n	-	-	34	34	34	22	22	
	% of intended	106	93	102	99	106	92	98	

A Values based on group mean bodyweights and group mean food intake.

B Offspring consuming diet : concentration of compound in diet maintained at level set for Days 7-13 post partum.

S.D. Standard deviation.

n Number of animals.

TABLE 3

Group mean bodyweights (g) of males (F_0)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
1	Mean	166	229	284	329	367	397	423	444	464	478	496	504	516	529	544
	S.D.	6	9	15	22	27	31	34	37	42	44	47	48	51	52	56
	n	34	34	34	34	34	34	34	34	34	34	34	34	34	34	34
2	Mean	164	229	283	328	365	396	421	443	463	476	492	501	514	528	539
	S.D.	9	10	17	22	27	30	33	38	42	44	47	45	49	52	55
	n	34	34	34	34	34	34	34	34	34	34	34	34	34	34	34
3	Mean	166	226	278	321	358	388	413	434	451	464	479	487	497	509	524
	S.D.	8	11	15	20	24	27	29	32	35	37	39	39	41	42	45
	n	34	34	34	34	34	34	34	34	34	34	34	34	34	34	34
4	Mean	165	228	281	325	357	389	412	433	453	466	481	490	501	514	526
	S.D.	9	10	15	19	21	26	27	30	32	35	37	37	37	39	42
	n	34	34	34	34	34	34	34	34	34	34	34	34	34	34	34

S.D. Standard deviation.
 n Number of animals.

TABLE 4

Group mean bodyweights (g) of females before pairing (F_0)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Week of treatment		
		0	1	2
1	Mean	202	221	237
	S.D.	8	10	13
	n	34	34	34
2	Mean	203	221	237
	S.D.	8	12	13
	n	34	34	34
3	Mean	199	221	236
	S.D.	8	10	11
	n	34	34	34
4	Mean	202	221	238
	S.D.	8	10	12
	n	34	34	34

S.D. Standard deviation.

n Number of animals.

TABLE 5

Food intake (g/rat/week) - group mean values for males (F_0)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment													
	1	2	3	4	5	6	7	8	9	10	11 ^A	12	13	14
1	Mean	160	176	189	186	192	192	188	189	184	184	180	190	191
	S.D.	6	7	5	6	4	6	5	5	5	3	5	3	5
	n	7	7	7	7	7	7	7	7	7	7	7	7	7
2	Mean	165	181	191	186	187	190	189	187	186	185	179	190	192
	S.D.	4	6	6	6	4	3	4	8	4	4	5	7	7
	n	7	7	7	7	7	7	7	7	7	7	7	7	7
3	Mean	156	173	183	183	185	185	184	183	179	181	172	181	185
	S.D.	7	6	6	5	6	8	7	7	9	11	6	7	5
	n	7	7	7	7	7	7	7	7	7	7	7	7	7
4	Mean	162	176	187	184	185	186	187	184	178	181	172	183	187
	S.D.	4	5	9	10	5	6	6	9	6	3	7	9	6
	n	7	7	7	7	7	7	7	7	7	7	7	7	7

A Animals paired for mating.

S.D. Standard deviation.

n Number of cages.

TABLE 6

Food intake (g/rat/week) - group mean values for females before pairing (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Week of treatment	
		1	2
1	Mean	138	134
	S.D.	4	5
	n	7	7
2	Mean	138	134
	S.D.	6	9
	n	7	7
3	Mean	137	130
	S.D.	6	5
	n	7	7
4	Mean	137	131
	S.D.	6	6
	n	7	7

S.D. Standard deviation.
n Number of cages.

TABLE 7

Food conversion efficiency^A for males (F₀)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment													
	1	2	3	4	5	6	7	8	9	10	11 ^A	12	13	14
1	39	31	24	20	16	14	11	11	8	10		7	7	8
2	39	30	24	20	17	13	12	11	7	9		7	7	6
3	38	30	23	20	16	14	11	9	7	8		6	7	8
4	39	30	24	17	17	12	11	11	7	8		6	7	6

^A Animals paired for mating :- food intake not recorded.

$$\Delta \text{ FCE} = \frac{\text{Group mean bodyweight gain (g) in week}}{\text{Group mean food intake (g/rat/week) in week}} \times 100$$

TABLE 8

Food conversion efficiency^Δ for females before pairing (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Week of treatment	
	1	2
1	14	12
2	13	12
3	16	12
4	14	13

$$\Delta \text{ FCE} = \frac{\text{Group mean bodyweight gain (g) in week}}{\text{Group mean food intake (g/rat/week) in week}} \times 100$$

TABLE 9

Oestrous cycles (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Number of animals	Regular 4 or 5 day cycle	Irregular cycle	Acyclic and/or pseudopregnant
1	34	32	2	0
2	34	31	2	1
3	34	33	1	0
4	34	33	1	0

TABLE 10

Pre-coital interval (F₀ females)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Number of animals	Pre-coital interval (days)				
		1-4	5-8	9-12	13-16	17-21
1	34	34	0	0	0	0
2	34	33	0	1	0	0
3	34	33	1	0	0	0
4	34	33	0	1	0	0

TABLE 11

Mating performance and fertility(F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group and sex	Number paired	Number mating	Number achieving pregnancy	Percentage mating	Conception rate (%)	Fertility index (%)
1M	34	34	34	100	100	100
2M	34	34	34	100	100	100
3M	34	34	34	100	100	100
4M	34	34	34	100	100	100
1F	34	34	34	100	100	100
2F	34	34	34	100	100	100
3F	34	34	34	100	100	100
4F	34	34	34	100	100	100

TABLE 12

Group mean bodyweights (g) of females during gestation (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Day <u>post coitum</u>			
		0	6	13	20
1	Mean	247	278	310	389
	S.D.	16	14	18	19
	n	33	33	33	33
2	Mean	245	277	309	390
	S.D.	15	19	23	26
	n	34	34	34	34
3	Mean	244	279	312	394
	S.D.	12	17	20	23
	n	34	34	34	34
4	Mean	246	277	309	389
	S.D.	15	15	21	28
	n	34	34	34	34

S.D. Standard deviation.

n Number of animals.

TABLE 13

Food intake (g/rat/day) - group mean values for females during gestation (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Days <u>post coitum</u>		
		0-5	6-12	13-19
1	Mean	24	26	28
	S.D.	2	3	3
	n	33	33	33
2	Mean	24	26	28
	S.D.	2	3	3
	n	34	34	34
3	Mean	24	27	29
	S.D.	2	3	3
	n	34	34	34
4	Mean	24	25	28
	S.D.	3	3	3
	n	34	34	34

S.D. Standard deviation.

n Number of animals.

TABLE 14

Food conversion efficiency^Δ for females during gestation (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Days <u>post coitum</u>		
	0-5	6-12	13-19
1	22	18	40
2	22	18	41
3	24	17	40
4	22	18	41

$$\Delta \text{ FCE} = \frac{\text{Group mean bodyweight change (g) in period}}{\text{Group mean food intake (g/rat/day) x no. days in period}} \times 100$$

TABLE 15

Group mean litter data - females killed on Day 20 of gestation (F_0-F_1)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Number of pregnant animals	Corpora lutea count	Implan- tations	Viable young			Resorptions			Implantation loss(%)		Foetal weight (g)	Placental weight (g)	
				M	F	Total	Early	Late	Total	Pre-	Post-			
1	12	Mean S.D.	16.3 1.3	14.8 1.7	6.7 2.0	7.1 1.2	13.8 1.5	0.75 0.87	0.33 0.58	1.08 1.04	8.6 9.4	7.2 5.4	3.26 0.14	0.51 0.04
2	12	Mean S.D.	17.3 2.4	14.9 2.1	5.9 1.9	8.3 2.5	14.2 2.1	0.42 0.65	0.33 0.58	0.75 0.87	12.7 14.5	4.9 5.5	3.39 0.19	0.50 0.04
3	12	Mean S.D.	17.3 1.8	16.2 2.0	8.1 2.0	7.7 1.5	15.8 1.9	0.33 0.58	0.08 0.29	0.42 0.65	7.2 6.0	2.5 4.1	3.20 0.17	0.50 0.05
4	12	Mean S.D.	15.7 2.3	13.7 3.2	6.7 2.6	6.1 2.2	12.8 3.1	0.50 0.71	0.42 0.65	0.92 0.96	11.2 20.3	6.5 6.1	3.43* 0.27	0.52 0.06
Background		Overall mean	15.9	14.5	6.7	6.9	13.7	0.65	0.21	0.86	8.84 ^A	5.92 ^A	3.33	0.49
data from 97 studies		Recorded ranges	13.0-18.1	12.0-16.1	5.2-8.1	5.6-8.3	11.1-14.8	0.05-1.47	0.00-0.58	0.25-1.65	1.6-13.8	1.7-12.7	3.06-3.55	0.43-0.54

A Background data for pre- and post-implantation losses based on grand totals instead of means of individual animal data.
 S.D. Standard deviation.

* Significantly different from Control : $P < 0.05$ (Analysis of variance and Student's t-test).

TABLE 16

Summary of foetal observations at necropsy (F₁)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data
<u>External examination</u>					
Number of foetuses (litters) examined:	165 (12)	170 (12)	189 (12)	153 (12)	23937
Number of male : female foetuses:	80 : 85	71 : 99	97 : 92	80 : 73	foetuses 98 studies
<u>Observations: % incidence^o (litters)</u>					
Small foetus (less than 2.70 g)	3.6 (33.3)	1.2 (8.3)	7.4 (66.7)	3.3 (16.7)	Mean 3.57 Study range 0.4 - 18.4
Large foetus (more than 4.00 g)	-	-	-	0.7 (8.3)	1.61 0.0 - 8.7
Grossly abnormal foetus; face cleft; vertebral column exposed; ears displaced caudally; amniotic fluid red	-	-	-	0.7 (8.3)	0.36 0.0 - 4.1
Shiny skin	0.6 (8.3)	-	-	-	0.06 0.0 - 0.7
Subcutaneous haemorrhage on head	-	-	1.1 (16.7)	-	0.03 0.0 - 0.7
Subcutaneous haemorrhage on body	-	-	0.5 (8.3)	-	0.14 0.0 - 6.9
Pale-green area on placenta	-	-	0.5 (8.3)	-	1.04 0.0 - 6.2
Large placenta (more than 0.70 g)	3.0 (25.0)	1.2 (16.7)	1.1 (16.7)	2.0 (25.0)	

continued on next page

- o One foetus may have more than one observation.
 * No record in background control data.

TABLE 16 - continued

Summary of foetal observations at necropsy (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	1	2	3	4	Control data
<u>Internal examination</u>					
Number of foetuses (litters) examined:	85 (12)	87 (12)	95 (12)	80 (12)	12036
Number of male : female foetuses:	45 : 40	35 : 52	47 : 48	41 : 39	foetuses 83 studies
<u>Observations: % incidence⁰ (litters)</u>					
Thyroid glands dark/haemorrhagic	1.2 (8.3)	-	1.1 (8.3)	-	Mean 0.06
Haemorrhagic area on wall of innominate artery	-	-	1.1 (8.3)	-	0.02
Free blood in abdominal cavity	-	1.1 (8.3)	-	-	0.36
Adrenal glands increased in size	3.5 (8.3)	-	-	-	0.02
Adrenal glands dark	1.2 (8.3)	-	-	-	0.02
Unilateral hydronephrosis	-	3.4 (25.0)	-	1.3 (8.3)	1.16
Bilateral hydronephrosis	1.2 (8.3)	-	-	-	0.68
Unilateral hydroureter	2.4 (16.7)	2.3 (16.7)	2.1 (16.7)	3.8 (25.0)	5.38
Bilateral hydroureter	2.4 (16.7)	1.1 (8.3)	1.1 (8.3)	6.3 (25.0)	3.86
Right horn of uterus thread-like ^Δ	-	-	-	2.6 (8.3)	0.0 - 15.8
					0.0 - 2.0
					0.0 - 1.0
					0.0 - 7.6
					0.0 - 7.6
					1.0 - 16.3
					0.0 - 15.8

Δ Expressed as a percentage of females.

0 One foetus may have more than one observation.

π No record in background control data.

TABLE 17

Summary of foetal observations after free-hand serial sectioning (F₁)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data
Number of foetuses (litters) examined :	80 (12)	83 (12)	94 (12)	73 (12)	7083
Number of male : female foetuses:	35 : 45	36 : 47	50 : 44	39 : 34	foetuses studies
<u>Observations: % foetal incidence^o (% litters)</u>					
affected:					Mean Study range
Head:					
Blood in mouth	1.3 (8.3)	-	-	-	0.23 0.0 - 3.3
Intra-muscular nasal haemorrhage	1.3 (8.3)	1.2 (8.3)	1.1 (8.3)	1.4 (8.3)	0.55 0.0 - 3.0
Intra-muscular haemorrhage - lower jaw	6.3 (33.3)	9.6 (50.0)	5.3 (25.0)	9.6 (33.3)	0.86 0.0 - 10.7
Slight unilateral microphthalmia	1.3 (8.3)	-	-	-	0.08 0.0 - 2.3
Slight dilatation of lateral ventricles	-	-	2.1 (16.7)	-	3.13 0.0 - 18.0

continued on next page

o One foetus may have more than one observation.

TABLE 17 - continued

Summary of foetal observations after free-hand serial sectioning (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	1	2	3	4	Control data	
Number of foetuses (litters) examined :	80 (12)	83 (12)	94 (12)	73 (12)	7083	78
Number of male : female foetuses:	35 : 45	36 : 47	50 : 44	39 : 34	foetuses	studies
Observations: % foetal incidence ^σ (% litters) affected :						Mean
Thorax and abdomen:						Study range
Space between bodywall and organs	2.5 (16.7)	-	8.5 (58.3)	1.4 (8.3)	15.91	1.0 - 47.4
Pulmonary haemorrhage	-	-	1.1 (8.3)	-	0.07	0.0 - 1.7
Haemorrhage on surface of lung lobes	-	-	1.1 (8.3)	-	0.07	0.0 - 1.7
Slightly increased quantity of flocculent pleural fluid	-	-	-	1.4 (8.3)	0.17	0.0 - 7.1
Hepatic haemorrhage	10.0 (50.0)	16.9 (58.3)	20.2 (83.3)	15.1 (41.7)	10.74	0.0 - 25.7
Unilateral hydronephrosis	-	-	2.1 (16.7)	1.4 (8.3)	3.74	0.0 - 11.7
Bilateral hydronephrosis	-	1.2 (8.3)	-	1.4 (8.3)	1.29	0.0 - 9.8
Unilateral hydroureter	1.3 (8.3)	1.2 (8.3)	1.1 (8.3)	2.7 (16.7)	7.43	0.7 - 24.2
Bilateral hydroureter	-	-	-	1.4 (8.3)	5.22	0.0 - 16.0
Haemorrhagic peritoneal fluid	1.3 (8.3)	3.6 (16.7)	1.1 (8.3)	1.4 (8.3)	2.63	0.0 - 12.2
Localised internal abdominal haemorrhage	5.0 (33.3)	2.4 (16.7)	-	-	0.78	0.0 - 4.7
Haemorrhagic abdomen	-	-	-	1.4 (8.3)	2.06	0.0 - 8.0
Testis displaced towards midline/cranially ⁺	-	-	2.0 (8.3)	5.1 (16.7)	1.34	0.0 - 9.1
Genital tubercle slightly elongated	-	-	1.1 (8.3)	-	0.27	0.0 - 3.6
Slightly kinked tip of tail	-	-	1.1 (8.3)	-	0.08	0.0 - 2.1

^σ One foetus may have more than one observation.

+ Percentage calculated on total number of males.

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TABLE 17 - continued

Summary of foetal observations after free-hand serial sectioning (F₁)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data	
Number of foetuses (litters) examined :	80 (12)	83 (12)	94 (12)	73 (12)	7083	78
Number of male : female foetuses:	35 : 45	36 : 47	50 : 44	39 : 34	foetuses	studies
Observations: % foetal incidence ^σ (% litters)						
affected :					Mean	Study range
Others :						
Subcutaneous haemorrhages:						
Nasal	2.5 (16.7)	1.2 (8.3)	2.1 (16.7)	-	1.31	0.0 - 5.9
Cranial	-	1.2 (8.3)	-	-	2.36	0.0 - 8.2
Submandibular	1.3 (8.3)	-	2.1 (8.3)	1.4 (8.3)	1.38	0.0 - 8.8
Cervical	17.5 (66.7)	-	1.1 (8.3)	1.4 (8.3)	0.32	0.0 - 5.1
Scapular	1.3 (8.3)	10.8 (50.0)	21.3 (75.0)	16.4 (58.3)	32.11	6.4 - 90.5
Thoracic	1.3 (8.3)	-	1.1 (8.3)	-	0.96	0.0 - 5.6
Abdominal	1.3 (8.3)	-	1.1 (8.3)	1.4 (8.3)	0.49	0.0 - 3.8
Tail	3.8 (16.7)	-	2.1 (8.3)	1.4 (8.3)	0.07	0.0 - 2.1
Fore/hind limb(s)	12.5 (41.7)	7.2 (50.0)	11.7 (50.0)	12.3 (50.0)	3.06	0.0 - 14.4
Subcutaneous oedema - trunk	1.3 (8.3)	-	-	2.7 (8.3)	6.32 ^Δ	0.0 - 17.9 ^Δ
Cleft face, unilateral ablepheron, unilateral anophthalmia, craniorrachischisis	-	-	-	1.4 (8.3)	π	π

^σ One foetus may have more than one observation.

^π No record in background control data.

^Δ Derived from 2058 foetuses; 18 studies.

TABLE 18

Summary of foetal observations at skeletal examination (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	1	2	3	4	Control data	
Number of foetuses (litters) examined:	85 (12)	87 (12)	95 (12)	80 (12)	11503 foetuses	79 studies
Observations: % foetal incidence ^a : (% litter incidence)						
Head					Mean	Study range
Size of anterior fontanelle	3.5 (25.0)	-	2.1 (16.7)	-	1.06	0.0 - 6.5
	94.1 (100.0)	97.7 (100.0)	96.8 (100.0)	98.8 (100.0)	96.87	85.8 - 100.0
Incomplete ossification of supraoccipital bone	2.4 (16.7)	2.3 (16.7)	1.1 (8.3)	1.3 (8.3)	2.01	0.0 - 13.3
Incomplete ossification of interparietal bone	4.7 (33.3)	6.9 (41.7)	6.3 (33.3)	11.3 (33.3)	13.49	0.0 - 29.2
Incomplete ossification of one or both parietal bones	12.9 (50.0)	19.5 (58.3)	16.8 (58.3)	21.3 (50.0)	20.53	7.1 - 50.5
Incomplete ossification of squamosal bones	-	1.1 (8.3)	-	5.0 (25.0)	1.31	0.0 - 7.1
Small additional plaque of bone in parietal suture	-	1.1 (8.3)	-	6.3 (25.0)	0.81	0.0 - 4.7
Small discrete unossified area in frontal bone	-	-	1.1 (8.3)	1.3 (8.3)	0.28	0.0 - 2.4
Incomplete ossification of hyoid bone	4.7 (33.3)	9.2 (50.0)	6.3 (25.0)	5.0 (33.3)	7.87	1.0 - 25.0
Absence of hyoid bone	8.2 (33.3)	2.3 (16.7)	8.4 (41.7)	7.5 (33.3)	8.76	0.7 - 18.3

continued on next page

^a One foetus may have more than one observation.

TABLE 18 - continued

Summary of foetal observations at skeletal examination (F₁)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data	
Number of foetuses (litters) examined:	85 (12)	87 (12)	95 (12)	80 (12)	11503 foetuses	79 studies
<u>Observations: % foetal incidence^σ: (% litter incidence)</u>						
<u>Rib cage and vertebral column:</u>						
Number of ribs	13/13				Mean	Study range
	13/14					
	14/14					
13th rib(s) reduced in length	98.8 (100.0)	100.0 (100.0)	97.9 (100.0)	100.0 (100.0)	98.24	92.5 - 100.0
Incomplete ossification of sternbrae:					1.20	0.0 - 4.0
	1.2 (8.3)	-	2.1 (16.7)	-	0.50	0.0 - 3.5
	1.2 (8.3)	-	3.2 (16.7)	1.3 (8.3)	1.46	0.0 - 8.2
	5.9 (25.0)	10.3 (33.3)	5.3 (33.3)	16.3 (58.3)	16.49	0.0 - 40.0
	74.1 (100.0)	75.9 (100.0)	74.7 (100.0)	71.3 (100.0)	63.25	43.3 - 83.3
Number of bones affected	15.3 (50.0)	10.3 (58.3)	11.6 (41.7)	3.8 (16.7)	11.25	1.1 - 23.3
	4.7 (16.7)	2.3 (16.7)	7.4 (33.3)	2.5 (16.7)	3.70	0.0 - 17.5
	-	-	-	1.3 (8.3)	0.60	0.0 - 3.3
1st sternebra cleft	3.5 (8.3)	1.1 (8.3)	1.1 (8.3)	3.8 (8.3)	0.58	0.0 - 6.7
			2.1 (8.3)		0.32	0.0 - 2.8

σ One foetus may have more than one observation.

continued on next page

TABLE 18 - continued

Summary of foetal observations at skeletal examination (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	1	2	3	4	Control data	
Number of foetuses (litters) examined:	85 (12)	87 (12)	95 (12)	80 (12)	11503 foetuses	79 studies
Observations: % foetal incidence ^a : (% litter incidence)						
Rib cage and vertebral column - continued:						
Ossification of ventral arch of 1st cervical vertebra	10.6 (50.0)	12.6 (41.7)	4.2 (25.0)	10.0 (33.3)	6.09	0.0 - 23.2
Ossification of all cervical vertebral centra	-	3.4 (25.0)	-	-	0.84	0.0 - 4.1
Incomplete ossification of one or more cervical vertebral arches	-	1.1 (8.3)	4.2 (25.0)	3.8 (16.7)	0.24	0.0 - 3.1
Incomplete ossification of one or more thoracic vertebral centra	23.5 (83.3)	21.8 (66.7)	27.4 (91.7)	23.8 (75.0)	24.02	0.0 - 58.3
Incomplete ossification of one or more lumbar vertebral centra	-	-	-	1.3 (8.3)	0.34	0.0 - 2.1
Incomplete ossification of one or more sacral and/or lumbar vertebral arches	-	2.3 (16.7)	-	2.5 (8.3)	0.84	0.0 - 6.2
Incomplete ossification of caudal vertebrae, less than 5 vertebrae ossified	2.4 (16.7)	-	2.1 (16.7)	-	2.78	0.0 - 14.5
25 pre-sacral vertebrae	1.2 (8.3)	-	1.1 (8.3)	2.5 (8.3)	0.43	0.0 - 4.5

^a One foetus may have more than one observation.

continued on next page

TABLE 18 - continued

Summary of foetal observations at skeletal examination (F₁)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data	
Number of foetuses (litters) examined:	85 (12)	87 (12)	95 (12)	80 (12)	11503 foetuses	79 studies
Observations: % foetal incidence ^σ : (% litter incidence)						
Limbs, pectoral and pelvic girdles						
Number of metacarpals/metatarsals	60.0 (91.7)	59.8 (100.0)	68.4 (91.7)	47.5 (91.7)	65.56	28.6 - 86.7
3/4	38.8 (83.3)	40.2 (83.3)	31.6 (66.7)	48.8 (83.3)	31.55	6.2 - 71.4
4/4						
Incomplete ossification or absence of metacarpals/metatarsals	1.2 (8.3)	1.1 (8.3)	1.1 (8.3)	6.3 (25.0)	2.25	0.0 - 9.3
Ossification of one or more phalangeal bones	-	3.4 (16.7)	1.1 (8.3)	3.8 (25.0)	1.77	0.0 - 9.9
Apparent absence of inner corners of one or both scapulae	-	5.7 (41.7)	3.2 (25.0)	3.8 (25.0)	2.41	0.0 - 8.1
Incomplete ossification or absence of one or both pubic bones	9.4 (33.3)	10.3 (25.0)	4.2 (25.0)	5.0 (25.0)	6.75	0.0 - 18.6
Incomplete ossification of ischial bones	-	3.4 (16.7)	1.1 (8.3)	1.3 (8.3)	0.94	0.0 - 4.7
Asymmetric pelvis, ilia associated with different sacral vertebrae.	-	-	1.1 (8.3)	1.3 (8.3)	0.24	0.0 - 1.8

^σ One foetus may have more than one observation.

TABLE 19

Gestation length and gestation index (F_0 - F_1)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Number of animals	Gestation length (days)				Gestation index (%)
		22	22 ¹ / ₂	23	23 ¹ / ₂	
1	21	6	10	5	0	95
2	22	8	11	3	0	100
3	22	7	11	3	1	100
4	22	6	14	2	0	100

TABLE 20

Group mean bodyweights (g) of females during lactation (F_0 - F_1)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Day post partum				
		1	4	7	14	21
1	Mean	294	306	313	327	321
	S.D.	22	18	18	20	13
	n	21	21	21	21	21
2	Mean	293	307	315	329	323
	S.D.	26	20	20	23	26
	n	22	22	22	22	22
3	Mean	296	309	318	333	330
	S.D.	25	22	24	29	26
	n	22	22	20	20	20
4	Mean	295	305	314	330	325
	S.D.	22	20	19	21	22
	n	22	22	22	22	22

S.D. Standard deviation.

n Number of animals.

TABLE 21

Food intake (g/rat/day) - group
 mean value for females during lactation (F_0 - F_1)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Days post partum		
		1-6	7-13	14-20 ^A
1	Mean	37	51	69
	S.D.	7	6	6
	n	21	21	21
2	Mean	37	53	69
	S.D.	5	5	6
	n	22	22	22
3	Mean	37	52	70
	S.D.	6	9	10
	n	20	20	20
4	Mean	37	52	69
	S.D.	5	5	7
	n	22	22	22

S.D. Standard deviation.

n Number of females.

A Includes direct intake by litter.

TABLE 22

Group mean litter sizes (F₁)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group		Implan- tation sites	Total at Day 1 <u>post partum</u>	Number alive on Day <u>post partum</u>					
				1	4	4 ⁺	7	14	21
1	Mean	14.9	13.8	13.3	12.5	8.0	8.0	8.0	8.0
	S.D.	1.9	1.9	1.9	1.7	0.0	0.0	0.0	0.0
	n	21	21	21	21	21	21	21	21
2	Mean	15.0	14.1	13.9	13.1	8.0	8.0	8.0	8.0
	S.D.	1.7	1.9	1.9	2.1	0.0	0.2	0.2	0.2
	n	22	22	22	22	22	22	22	22
3	Mean	14.6	13.0	12.9	10.5	7.2	7.7	7.7	7.7
	S.D.	2.8	2.8	2.7	3.9	2.1	1.3	1.3	1.3
	n	22	22	22	22	22	20	20	20
4	Mean	15.8	14.5	14.0	13.0	8.0	8.0	7.8	7.8
	S.D.	2.5	2.4	2.4	2.1	0.2	0.2	0.5	0.5
	n	22	22	22	22	22	22	22	22

S.D. Standard deviation.

n Number of litters.

+ Following litter size adjustment.

TABLE 23

Group mean post-implantation survival,
live birth, viability and lactation indices (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Post- implantation survival index (%)	Live birth index (%)	Viability index Day 4 (%)	Lactation index Day <u>post partum</u> (%)		
				7	14	21
1	93	97	94	100	100	100
2	94	99	95	99	99	99
3	89	99	82	91	90	90
4	92	96	93	100	98	98

TABLE 24

Group mean bodyweights (g) of offspring (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Day <u>post partum</u>				
		1	4	7	14	21
1	Mean	6.1	8.4	13.8	30.5	50.1
	S.D.	0.6	1.2	2.0	3.4	5.2
	n	21	21	21	21	21
2	Mean	6.1	8.2	13.7	30.9	50.3
	S.D.	0.7	1.5	2.2	3.1	5.0
	n	22	22	22	22	22
3	Mean	6.0	7.9	13.3	29.6	49.1
	S.D.	0.7	1.6	2.2	3.7	5.7
	n	22	22	20	20	20
4	Mean	6.0	8.1	13.5	31.0	50.8
	S.D.	0.7	1.4	1.9	3.0	5.2
	n	22	22	22	22	22

S.D. Standard deviation.
n Number of litters.

TABLE 25

Sex ratios (F_1)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Total at Day 1			Number alive at Day 1			Number alive Day 4 (pre-cull)			Number alive Day 4 (post-cull)			Number alive Day 21		
	M F		Ratio	M F		Ratio	M F		Ratio	M F		Ratio	M F		Ratio
	M	F	Ratio	M	F	Ratio	M	F	Ratio	M	F	Ratio	M	F	Ratio
1	142	148	1 : 1.04	138	142	1 : 1.03	128	135	1 : 1.05	82	86	1 : 1.05	82	86	1 : 1.05
2	147	163	1 : 1.11	145	161	1 : 1.11	138	151	1 : 1.09	88	88	1 : 1.00	88	87	1 : 0.99
3	145	141	1 : 0.97	143	141	1 : 0.99	116	114	1 : 0.98	80	78	1 : 0.98	80	73	1 : 0.91
4	150	170	1 : 1.13	145	164	1 : 1.13	130	155	1 : 1.19	87	88	1 : 1.01	86	85	1 : 0.99

TABLE 26

Group mean auditory and visual responses (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	1	2	3	4
Number of animals examined	168	175	153	171
<u>Observations</u> : (% incidence)				
Normal auditory response	100.0	100.0	100.0	100.0
Normal visual placing response	100.0	100.0	100.0	100.0
Normal pupil closure response	99.4	100.0	99.3	100.0
Pupils failed to dilate : failed pupil closure test	0.6	-	-	-
Small cloudy area over both pupils : failed pupil closure test	0.6	-	-	-
Small pale area in centre of one or both pupils : passed pupil closure test	0.6	0.6	-	0.6
Small pup, unable to assess in pupil closure test : classed as failure	-	-	0.7	-

TABLE 27

Group mean activity scores (F_1)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group and sex	Number of offspring	Number of litters	Mean activity score	S.D.
1M	79	20	1682	306
2M	88	22	1680	240
3M	80	19	1685	260
4M	86	22	1670	273
1F	85	21	1621	332
2F	87	22	1699	285
3F	72	20	1686	397
4F	85	22	1734	302

S.D. Standard deviation.

TABLE 28

Water maze - group mean swimming times (seconds) (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day) :		0	250	500	750

Group and sex	Number of litters		Trial						Number of offspring failing (%)
			1	2	3	4	5	6	
1M	21	Mean	19.0	7.3	4.8	4.8	3.8	4.9	1.2
		S.D.	4.5	3.1	1.1	2.6	0.9	2.6	
2M	22	Mean	18.3	7.2	5.2	5.0	4.4	4.8	1.1
		S.D.	4.8	2.5	1.6	2.3	2.4	2.2	
3M	19	Mean	18.9	7.8	5.4	5.6	5.1	4.4	0.0
		S.D.	4.7	2.7	1.9	2.4	2.7	1.5	
4M	22	Mean	20.3	7.3	5.1	4.5	4.1	4.4	2.3
		S.D.	5.3	3.1	1.9	1.3	1.1	2.2	
1F	21	Mean	17.2	7.2	5.8	5.3	4.5	4.8	0.0
		S.D.	4.2	1.8	3.5	2.1	2.1	2.1	
2F	22	Mean	16.9	7.2	5.2	4.9	4.8	4.9	0.0
		S.D.	4.7	2.2	1.8	2.1	1.9	2.5	
3F	20	Mean	16.4	7.0	5.2	4.6	5.4	5.4	1.3
		S.D.	5.1	4.8	2.1	1.6	3.1	3.3	
4F	22	Mean	20.7*	7.3	5.4	4.7	4.7	4.8	0.0
		S.D.	4.9	3.3	1.8	1.6	1.8	1.6	

* Significantly different from Controls, $P < 0.05$ (Student's t-test).
S.D. Standard deviation.

TABLE 29

Summary of observations at necropsy of offspring (F₁)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Offspring dying before weaning ^Δ				Offspring killed at Day 4				Offspring killed after weaning			
	1	2	3	4	1	2	3	4	1	2	3	4
Number examined:	24	17	50	32	95	113	72	110	88	95	71	91
Observations - % incidence:												
Appearance - small pup for age	-	-	-	-	1.1	1.8	1.4	3.6	-	-	-	1.1
Brain - one or both lateral ventricles dilated	-	-	-	-	-	-	-	-	2.3	-	1.4	1.1
Eye - one pupil constricted, partially red-rimmed	-	-	-	-	-	-	-	-	1.1	-	-	-
Eye - opacity in centre of eye, haemorrhage on retina	-	-	-	-	-	-	-	-	-	-	-	1.1
Head - haemorrhage/wound on head	-	-	4.0	-	-	-	-	-	-	-	-	-
Jaw - apparent agenesis of lower jaw, no mouth	-	-	-	3.1	-	-	-	-	-	-	-	-
Kidney - unilateral hydronephrosis	12.5	5.9	-	9.4	-	0.9	1.4	3.6	1.1	2.1	-	1.1
Kidney - bilateral hydronephrosis	4.2	-	-	12.5	-	-	1.4	3.6	-	-	-	1.1
Kidney - several punctate cysts on surface of one kidney	-	-	-	-	-	-	-	-	-	1.1	-	-
Kidney - single large kidney	-	-	2.0	-	-	-	-	-	-	-	-	-
Limb - right hind limb missshapen	-	-	-	-	1.1	-	-	-	-	-	-	-
Limb - loss of use of hind limbs, haemorrhaging on left hind limb	-	-	-	-	-	-	-	0.9	-	-	-	-
Palate - dark area(s) in palate	-	-	4.0	-	-	-	-	-	-	-	-	-

^Δ Excludes missing, autolysed and grossly cannibalised offspring.

continued on next page

TABLE 29 - continued

Summary of observations at necropsy of offspring (F₁)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Offspring dying before weaning ^Δ				Offspring killed at Day 4				Offspring killed after weaning			
	1	2	3	4	1	2	3	4	1	2	3	4
Number examined:	24	17	50	32	95	113	72	110	88	95	71	91
Observations - % incidence:												
Stomach - no milk or reduced amount of food in stomach	87.5	88.2	88.0	90.6	4.2	-	-	0.9	-	-	-	-
Tail - damaged, reddened, loss of part or all of tail	4.2	-	-	-	-	-	1.4	-	-	-	1.4	-
Ureter - unilateral hydroureter	-	5.9	-	-	4.2	0.9	-	2.7	-	-	-	-
Ureter - bilateral hydroureter	-	-	-	-	-	-	2.8	2.7	-	-	-	-
Urinary bladder - full	-	-	-	-	30.5	23.0	38.9	30.9	-	-	-	-
Urinary bladder - distended	-	-	-	-	2.1	1.8	-	0.9	-	-	-	-
Urinary bladder - contents cloudy	-	-	-	-	-	-	-	0.9	-	-	-	-
Died after weaning - small, no food in stomach	-	-	2.0	-	-	-	-	-	-	-	-	-
Died after weaning - red stain on snout, one eye misshapen, wound on abdomen; lungs congested, haemorrhagic area on one kidney	-	-	2.0	-	-	-	-	-	-	-	-	-

^Δ Excludes missing, autolysed and grossly cannibalised offspring.

TABLE 30

Summary of observations at necropsy of males (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	1	2	3	4
Number of animals:	34	34	34	34
Observations - % incidence:				
Caecum - contents - yellow mucoid material	-	-	2.9	-
Epididymis - small raised yellow body (1 mm diameter) attached to caput epididymis, unilateral	-	2.9	-	-
Epididymis - several small pale firm areas between head and tail of organ; cut surface - pale firm tissue, unilateral	-	2.9	-	-
Eye - red-rimmed	-	2.9	-	-
Intestines - section of wall near caecum reddened	2.9	-	-	-
Intestines - entire tract contents - green fluid	2.9	-	-	-
Intestines - generally devoid of contents	-	-	-	2.9
Jejunum - section of wall dark and haemorrhagic - contents red mucus	-	2.9	-	-
Lung - one or more lobes congested and/or consolidated	-	-	2.9	2.9
Rectum - devoid of pellets	-	-	2.9	-
Rectum - contents - soft faecal material	2.9	-	-	-
Skin - red stain on face/around nares	-	2.9	2.9	-
Skin - encrustations on cheeks/nose	2.9	2.9	-	-
Skin - firm swelling on left ear - cut surface - pale amorphous tissue	2.9	-	-	-
Skin - scabs at base of tail	-	-	-	2.9
Skull - subcutaneous haemorrhage overlying skull	5.9	-	-	2.9
Spleen - split into two parts	-	-	2.9	-
Stomach - devoid of contents	-	-	-	2.9
Thymus - firm and enlarged (8.5 g; 35 x 25 mm)	-	2.9	-	-

TABLE 31

Summary of observations at necropsy of females (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	1	2	3	4
Number of animals:	34	34	34	34
Observations - % incidence:				
Caecum - slightly enlarged/enlarged	2.9	8.8	2.9	5.9
Caecum- contents gassy	2.9	2.9	-	2.9
Caecum - contents fluid -	-	-	2.9	-
Eye - red-rimmed	-	2.9	2.9	-
Eye - pupil oval and constricted	-	-	2.9	-
Eye - haemorrhagic	-	2.9	-	-
Intestines - contents green/translucent/ mucoid	-	8.8	5.9	5.9
Intestines - areas of reddened walls and/or red mucus in contents	-	-	-	5.9
Jejunum - swollen with yellow mucoid material	2.9	-	-	-
Kidney - unilateral hydronephrosis	-	2.9	-	5.9
Kidney - bilateral hydronephrosis	2.9	-	-	-
Kidney - misshapen and/or enlarged	5.9	-	-	-
Kidney - contains cloudy material	2.9	-	-	-
Lung - pale foci/grey areas on lung tissue	8.8	2.9	-	2.9
Mammary tissue - pale and inactive	-	-	5.9	-
Rectum - contents soft faecal material/pellets	5.9	2.9	-	2.9
Rectum - devoid of faecal pellets	-	-	2.9	-
Skin - hairloss on snout	-	2.9	-	-
Skin - encrustations	-	2.9	-	-
Skull - subcutaneous haemorrhage overlying skull	2.9	-	2.9	-
Spleen - pale raised areas (<2 mm diameter) over surface	-	-	2.9	-
Stomach - contents yellow	2.9	-	2.9	-
Ureter - unilateral hydroureter	-	2.9	-	-
Ureter - bilateral hydroureter	2.9	-	-	2.9
Urinary bladder - contains stone(s) with or without purulent fluid	2.9	2.9	-	2.9
Urinary bladder - walls thickened	2.9	2.9	-	-
Uterus - unilateral implantation sites	2.9	-	-	2.9
Uterus - free blood in one horn	-	-	2.9	-
Uterus - fluid-filled cyst (3 mm diameter) in one horn	-	2.9	-	-
Uterus - single resorbing foetus retained in utero	2.9	-	-	-
Uterine fat/mesentery - small/hard/white bodies present	2.9	2.9	-	-

TABLE 32

Group mean absolute weights (g) of male reproductive organs (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Body weight (g)	Prostate	Testes	Seminal Vesicles	Epidid- ymides
----------------	-----------------------	----------	--------	---------------------	-------------------

1M	545	0.56	3.39	2.70	1.22
S.D.	57	0.16	0.26	0.33	0.10
n	34	34	34	34	34

2M	542	0.59	3.40	2.74	1.24
S.D.	58	0.14	0.32	0.32	0.11
n	34	34	34	34	33

3M	526	0.61	3.31	2.61	1.23
S.D.	48	0.18	0.27	0.32	0.10
n	34	34	34	34	34

4M	527	0.58	3.36	2.57	1.22
S.D.	42	0.19	0.28	0.35	0.11
n	34	34	34	31	34

S.D. Standard deviation.
n Number of animals.

TABLE 33

Group mean relative weights^Δ of male reproductive organs (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Body weight (g)	Prostate	Testes	Seminal Vesicles	Epidid- ymides
----------------	-----------------------	----------	--------	---------------------	-------------------

1M	545	0.10	0.63	0.50	0.23
S.D.	57	0.03	0.07	0.06	0.03
n	34	34	34	34	34
2M	542	0.11	0.63	0.51	0.23
S.D.	58	0.03	0.08	0.06	0.03
n	34	34	34	34	33
3M	526	0.12	0.63	0.50	0.24
S.D.	48	0.04	0.08	0.07	0.03
n	34	34	34	34	34
4M	527	0.11	0.64	0.49	0.23
S.D.	42	0.04	0.06	0.08	0.02
n	34	34	34	31	34

S.D. Standard deviation.

n Number of animals.

Δ Expressed as a percentage of bodyweight.

TABLE 34

Group mean absolute weights (g) of female
reproductive organs at Day 20 of gestation (F_0 - F_1)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Body weight (g)	Gravid Uterus	Uterus	Ovaries
1F	387	72	4.39	0.127
S.D.	23	8	0.41	0.024
n	12	11	12	12
2F	385	76	4.40	0.120
S.D.	27	12	0.51	0.021
n	12	12	12	12
3F	387	80	4.74	0.123
S.D.	22	11	0.57	0.013
n	12	12	12	12
4F	374	71	4.26	0.118
S.D.	26	16	0.76	0.012
n	12	12	12	12

S.D. Standard deviation.
n Number of animals.

TABLE 35

Group mean relative weights^Δ of female
reproductive organs at Day 20 of gestation (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Body weight (g)	Gravid Uterus	Uterus	Ovaries ⁺
1F	387	18.73	1.14	32.8
S.D.	23	2.39	0.11	5.4
n	12	11	12	12
2F	385	19.68	1.15	31.4
S.D.	27	2.78	0.13	6.2
n	12	12	12	12
3F	387	20.76	1.22	31.7
S.D.	22	2.51	0.12	3.4
n	12	12	12	12
4F	374	18.74	1.13	31.6
S.D.	26	3.63	0.16	3.1
n	12	12	12	12

S.D. Standard deviation.

n Number of animals.

Δ Expressed as a percentage of bodyweight
unless otherwise indicated.

+ Ovaries : percentage value multiplied by 1000.

TABLE 36

Achieved dosage (mg/kg/day) - group mean values for males (F₁)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment													
	1	2	3	4	5	6	7	8	9	10	11 ^A	12 ^A	13	14
2	179	234	275	249	261	265	250	247	246	240			225	245
% of intended	72	94	110	100	104	106	100	99	98	96			90	98
3	359	472	555	510	526	524	509	503	491	476			460	482
% of intended	72	94	111	102	105	105	102	101	98	95			92	96
4	540	715	836	759	783	777	760	757	739	695			706	738
% of intended	72	95	111	101	104	104	101	101	99	93			94	98

A Animals paired for mating - food intake not recorded.

TABLE 37

Achieved dosage (mg/kg/day) - group mean values for females (F_1)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment ^A										During gestation			During lactation		
	1	2	3	4	5	6	7	8	9	10	Days post coitum 0-5	6-12	13-19	Days post partum 1-6	7-13	14-20 ^B
2	193	227	285	256	259	252	247	255	242	235	267	245	235	205	253	-
Mean											43	33	29	51	41	
S.D.											36	37	37	17	17	
n											107	98	94	82	101	
% of intended	77	91	114	102	104	101	99	102	97	94						
3	414	458	583	512	498	505	495	505	490	469	529	477	478	445	518	-
Mean											83	87	77	65	71	
S.D.											39	39	39	20	20	
n											106	95	96	89	104	
% of intended	83	92	117	102	100	101	99	101	98	94						
4	614	685	853	801	764	758	742	784	742	697	822	745	741	650	781	-
Mean											115	112	99	127	114	
S.D.											36	37	37	18	18	
n											110	99	99	87	104	
% of intended	82	91	114	107	102	101	99	105	99	93						

S.D. Standard deviation.

n Number of animals.

A Values based on group mean bodyweights and group mean food intake.

B Offspring consuming diet : concentration of compound in diet maintained at level set for Days 7-13 post partum.

TABLE 38

Group mean bodyweights (g) of males (F_1)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
1	Mean	52	91	145	206	267	326	379	421	454	480	504	514	533	552	568
	S.D.	6	10	14	17	21	23	28	31	33	36	39	41	44	48	50
	n	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
2	Mean	53	90	144	203	266	324	372	412	443	467	488	500	516	535	551
	S.D.	6	9	14	16	20	22	28	31	35	38	42	42	48	51	54
	n	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
3	Mean	52	90	142	200	263	322	372	413	445	470	492	501	519	536	553
	S.D.	5	9	13	16	21	24	28	31	33	38	41	41	43	46	48
	n	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
4	Mean	52	90	143	202	265	321	369	406	435	458	478**	486	501	519	535**
	S.D.	5	11	14	16	19	23	27	31	35	38	41	42	42	48	51
	n	40	40	40	40	40	40	40	40	40	40	40	40	40	40	39

S.D. Standard deviation.

n Number of animals.

** Bodyweight change (Weeks 0-10/ Weeks 0-14) significantly different from Controls, $P < 0.01$ (Student's t-test).

TABLE 39

Group mean bodyweights (g) of females before pairing (F_1)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment											
	0	1	2	3	4	5	6	7	8	9	10	
1	Mean	48	84	121	156	185	212	232	249	261	272	279
	S.D.	6	10	12	13	15	18	20	22	22	25	26
	n	40	40	40	40	40	40	40	40	40	40	40
2	Mean	48	83	121	155	180	204	226	241	254	264	270
	S.D.	5	10	12	12	13	14	19	20	21	22	25
	n	40	40	40	40	40	40	40	40	40	40	40
3	Mean	46	81	119	153	180	205	226	242	256	265	273
	S.D.	7	9	12	15	17	19	20	21	23	23	24
	n	40	40	40	40	40	40	40	40	40	40	40
4	Mean	49	83	123	156	182	206	227	244	254	263	269
	S.D.	6	11	12	12	14	16	17	20	22	23	24
	n	40	40	40	40	40	40	40	40	40	40	40

S.D. Standard deviation.
 n Number of animals.

TABLE 40

Food intake (g/rat/week) - group mean values for males (F_1)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment													
	1 ^A	2	3	4	5	6	7	8	9	10	11 ^B	12 ^B	13	14
1 Mean	73	128	159	178	198	207	212	211	208	199			192	202
S.D.	7	6	4	7	7	13	13	8	7	10			12	12
n	21	8	8	8	8	8	8	8	8	8			8	8
2 Mean	74	127	161	177	200	209	208	205	204	195			183	202
S.D.	7	5	2	7	5	4	5	8	13	10			12	11
n	22	8	8	8	8	8	8	8	8	8			8	8
3 Mean	74	127	160	179	200	207	210	211	206	200			190	202
S.D.	9	4	4	5	4	6	7	4	7	8			12	12
n	19	8	8	8	8	8	8	8	8	8			8	8
4 Mean	74	129	162	179	199	204	205	206	200	189			186	197
S.D.	10	10	3	6	6	9	9	9	11	9			11	10
n	22	8	8	8	8	8	8	8	8	8			8	8

A Animals housed as littermates for approximately one week after weaning.

B Animals paired for mating.

S.D. Standard deviation.

n Number of cages.

TABLE 41

Food intake (g/rat/week) - group mean values for females before pairing (F_1)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment									
	1 ^A	2	3	4	5	6	7	8	9	10
1 Mean	70	110	134	143	148	148	148	147	147	138
S.D.	8	7	6	6	10	9	9	9	9	5
n	21	8	8	8	8	8	8	7	8	8
2 Mean	71	112	137	137	147	147	144	147	140	137
S.D.	9	7	3	4	5	6	8	7	9	8
n	22	8	8	8	8	8	8	8	8	8
3 Mean	74	111	138	136	143	146	144	146	142	136
S.D.	12	5	6	10	7	10	6	6	10	7
n	20	8	8	8	8	8	8	8	8	8
4 Mean	76	114	138	144	146	147	145	151	142	136
S.D.	9	7	5	9	8	7	8	8	6	5
n	22	8	8	8	8	8	8	8	8	8

A Animals housed as littermates for approximately one week after weaning.

S.D. Standard deviation.

n Number of cages.

TABLE 42

Food conversion efficiency^A for males (F_1)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment													
	1 ^A	2	3	4	5	6	7	8	9	10	11 ^B	12 ^B	13	14
1	53	42	38	34	30	26	20	16	13	12			10	8
2	50	43	37	36	29	23	19	15	12	11			10	8
3	51	41	36	35	30	24	20	15	12	11			9	8
4	51	41	36	35	28	24	18	14	12	11			10	8

A Animals housed as littermates for approximately one week after weaning.

B Animals paired for mating - food intake not recorded.

$$A \quad FCE = \frac{\text{Group mean bodyweight gain (g) in week}}{\text{Group mean food intake (g/rat/week) in week}} \times 100$$

TABLE 43

Food conversion efficiency^Δ for females before pairing(F₁)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Week of treatment									
	1	2	3	4	5	6	7	8	9	10
1	51	34	26	20	18	14	11	8	7	5
2	49	34	25	18	16	15	10	9	7	4
3	47	34	25	20	17	14	11	10	6	6
4	45	35	24	18	16	14	12	7	6	4

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$$\Delta \text{ FCE} = \frac{\text{Group mean bodyweight gain (g) in week}}{\text{Group mean food intake (g/rat/week) in week}} \times 100$$

TABLE 44

Oestrous cycles (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Number of animals	Regular 4 or 5 day cycle	Irregular cycle	Acyclic and/or pseudopregnant
1	40	40	0	0
2	40	36	2	2
3	40	39	0	1
4	40	40	0	0

TABLE 45

Pre-coital interval (F₁ females)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Number of animals	Pre-coital interval (days)				
		1-4	5-8	9-12	13-16	17-21
1	40	38	1	0	0	1
2	40	39	1	0	0	0
3	40	39	1	0	0	0
4	40	40	0	0	0	0

TABLE 46

Mating performance and fertility (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group and sex	Number paired	Number mating	Number achieving pregnancy	Percentage mating	Conception rate (%)	Fertility index (%)
1M	40	39	36	98	92	90
2M	40	40	37	100	93	93
3M	40	40	39	100	98	98
4M	40	40	37	100	93	93
1F	40	40	37	100	93	93
2F	40	40	37	100	93	93
3F	40	40	39	100	98	98
4F	40	40	37	100	93	93

TABLE 47

Group mean bodyweights (g) of females during gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Day <u>post coitum</u>			
		0	6	13	20
1	Mean	283	313	342	413
	S.D.	28	28	30	31
	n	37	37	37	37
2	Mean	275	303	332	405
	S.D.	26	26	25	26
	n	37	37	37	37
3	Mean	278	307	334	406
	S.D.	24	26	30	35
	n	39	39	39	39
4	Mean	272	298	329	401
	S.D.	25	26	30	35
	n	37	37	37	37

S.D. Standard deviation.
n Number of animals.

TABLE 48

Food intake (g/rat/day) - group mean values for females during gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Days <u>post coitum</u>		
		0-5	6-12	13-19
1	Mean	23	25	26
	S.D.	3	3	3
	n	37	37	37
2	Mean	22	26	26
	S.D.	4	3	3
	n	36	37	37
3	Mean	22	26	26
	S.D.	4	5	4
	n	39	39	39
4	Mean	23	27	27
	S.D.	3	4	4
	n	36	37	37

S.D. Standard deviation.

n Number of animals.

TABLE 49

Food conversion efficiency^Δ for females during gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Days <u>post coitum</u>		
	0-5	6-12	13-19
1	22	17	39
2	21	16	40
3	22	15	40
4	19	16	38

$$\Delta \text{ FCE} = \frac{\text{Group mean bodyweight change (g) in period}}{\text{Group mean food intake (g/rat/day) x no. days in period}} \times 100$$

TABLE 50

Group mean litter data - females killed on Day 20 of gestation (F_1 - F_2)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Number of pregnant animals	Corpora lutea count	Implan- tations	Viable young			Resorptions			Implantation loss(%)		Foetal weight (g)	Placental weight (g)
				M	F	Total	Early	Late	Total	Pre-	Post-		
1	18	Mean 16.4 S.D. 2.1	12.8 3.3	5.8 2.1	5.8 2.1	11.6 3.4	0.72 0.85	0.50 0.71	1.22 1.10	22.5 18.0	9.5 12.3	3.23 0.26	0.51 0.08
2	18	Mean 16.3 S.D. 3.4	14.4 2.9	7.8 2.5	5.9 2.0	13.7 3.0	0.67 0.82	0.06 0.24	0.72 0.85	11.1 16.7	5.0 6.3	3.13 0.30	0.50 0.07
3	19	Mean 15.8 S.D. 1.8	12.7 3.8	5.9 2.2	6.0 2.3	11.9 3.5	0.58 0.76	0.21 0.46	0.79 0.89	19.2 24.5	5.9 6.7	3.18 0.30	0.49 0.06
4	18	Mean 15.8 S.D. 2.0	13.3 3.5	5.7 2.0	6.6 2.9	12.3 3.3	1.00 1.00	0.06 0.24	1.06 1.03	15.1 21.1	8.4 8.2	3.21 0.21	0.50 0.06
Background		Overall 15.9 mean	14.5	6.7	6.9	13.7	0.65	0.21	0.86	8.84 ^A	5.92 ^A	3.33	0.49
data from		Recorded 13.0-	12.0-	5.2	5.6	11.1	0.05-	0.00-	0.25-	1.6-	1.7-	3.06-	0.43
97 studies		ranges 18.1	16.1	8.1	8.3	14.8	1.47	0.58	1.65	13.8	12.7	3.55	-0.54

A Background data for pre- and post-implantation losses based on grand totals instead of means of individual animal data.
 S.D. Standard deviation.

TABLE 51

Summary of foetal observations at necropsy (F_1 - F_2)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	1	2	3	4	Control data
<u>External examination</u>					
Number of foetuses (litters) examined:	208 (18)	246 (18)	227 (19)	221 (18)	23937
Number of male : female foetuses:	104 : 104	140 : 106	113 : 114	103 : 118	foetuses studies
<u>Observations: % incidence^σ (% litters)</u>					
Small foetus (less than 2.70 g)	7.2 (38.9)	11.4 (50.0)	6.2 (31.6)	7.7 (55.6)	Mean Study range
Large foetus (more than 4.00 g)	0.5 (5.6)	0.4 (5.6)	-	1.4 (16.7)	3.57 0.4 - 18.4
Shiny skin	1.0 (5.6)	1.2 (5.6)	0.4 (5.3)	0.5 (5.6)	1.61 0.0 - 8.7
Abnormal pup (Siamese twin)	-	-	-	0.5 (5.6)	0.36 0.0 - 4.1
Subcutaneous haemorrhage on one ear	0.5 (5.6)	-	-	-	π
Haemorrhage on palate	-	0.4 (5.6)	-	-	0.06 0.0 - 0.7
Haemorrhage on limb	-	-	-	0.5 (5.6)	0.01 0.0 - 0.4
Subcutaneous haemorrhage on tail	0.5 (5.6)	-	-	-	0.07 0.0 - 0.7
Small placenta (less than 0.30 g)	-	-	0.9 (10.5)	0.5 (5.6)	0.07 0.0 - 0.7
Large placenta (more than 0.70 g)	1.9 (11.1)	1.2 (11.1)	0.9 (10.5)	-	0.24 0.0 - 2.7
Missshapen placenta	2.9 (5.6)	-	-	-	1.04 0.0 - 6.2
Conjoined placentae	-	-	0.4 (5.3)	0.5 (5.6)	π
Placenta with pale edges	-	-	4.0 (5.3)	-	0.02 0.0 - 0.5
					0.14 0.0 - 6.9

continued on next page

σ One foetus may have more than one observation.

π No record in background control data.

TABLE 51 - continued

Summary of foetal observations at necropsy (F_1 - F_2)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data
<u>Internal examination</u>					
Number of foetuses (litters) examined:	109 (18)	127 (18)	119 (19)	116 (18)	12036 83
Number of male : female foetuses:	58 : 51	69 : 58	65 : 54	48 : 68	foetuses studies
Observations: % incidence ^{σ} (% litters)					Mean Study range
One thyroid haemorrhagic	-	-	0.8 (5.3)	-	0.06 0.0 - 0.9
Ductus arteriosus 50% closed. Lung not inflated	0.9 (5.6)	-	-	-	0.14 0.0 - 4.3
Clotted blood in abdomen	-	0.8 (5.6)	-	-	0.36 0.0 - 2.0
Unilateral hydroureter	4.6 (22.2)	3.1 (11.1)	0.8 (5.3)	6.0 (22.2)	5.38 1.0 - 16.3
Bilateral hydroureter	2.8 (16.7)	0.8 (5.6)	1.7 (10.5)	6.0 (27.8)	3.86 0.0 - 15.8
Unilateral hydronephrosis	1.8 (11.1)	1.6 (5.6)	-	1.7 (11.1)	1.16 0.0 - 7.6
Bilateral hydronephrosis	1.8 (11.1)	1.6 (11.1)	0.8 (5.3)	3.4 (16.7)	0.68 0.0 - 7.6

σ One foetus may have more than one observation.

TABLE 52

Summary of foetal observations after free-hand serial sectioning (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data	
Number of foetuses (litters) examined:	99 (18)	119 (18)	108 (19)	105 (18)	7083	78
Number of male : female foetuses	46 : 53	71 : 48	48 : 60	55 : 50	foetuses	studies
Observations: % foetal incidence ^σ						
(% litters) affected:						
Head:						
Depression on underside of tongue	1.0 (5.6)	-	0.9 (5.3)	-	π	π
Intra-muscular haemorrhage - tongue	-	0.8 (5.6)	-	-	0.01	0.0 - 0.7
Intra-muscular haemorrhage - nasal region	-	0.8 (5.6)	-	-	0.55	0.0 - 3.0
Intra-muscular haemorrhage - lower/side of jaw	-	1.7 (11.1)	0.9 (5.3)	1.9 (11.1)	0.86	0.0 - 10.7
Blood in nasal sinuses/nasopharynx/trachea	-	0.8 (5.6)	0.9 (5.3)	1.9 (5.6)	0.23	0.0 - 3.3
Snail haemorrhage - left eye lid	-	0.8 (5.6)	-	-	π	π
Unilateral slight microphthalmia; reduction in thickness of retinal layer	-	-	-	1.0 (5.6)	0.08	0.0 - 2.3 ^A
Bilateral microphthalmia	1.0 (5.6)	-	-	-	0.03	0.0 - 1.1
Unilateral anophthalmia; severe internal hydrocephaly; pituitary gland reduced in size	-	-	-	1.0 (5.6)	0.03	0.0 - 1.7 ^B
Unilateral dilated orbital sinus	-	-	0.9 (5.3)	-	0.52	0.0 - 7.0
Slightly increased dilatation of brain ventricle(s)	2.0 (11.1)	3.4 (11.1)	-	-	3.13	0.0 - 18.0
Haemorrhage between cerebral hemisphere and pia mater	-	0.8 (5.6)	-	1.0 (5.6)	0.10	0.0 - 3.9
Haemorrhage surrounding dorsal cerebellar region	-	-	-	1.0 (5.6)	0.03	0.0 - 1.0

continued on next page

^σ One foetus may have more than one observation.
 A Control data for unilateral microphthalmia.

π No record in background control data.
 B Control data for hydrocephaly.

TABLE 52 - continued

Summary of foetal observations after free-hand serial sectioning (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data
Number of foetuses (litters) examined:	99 (18)	119 (18)	108 (19)	105 (18)	7083
Number of male : female foetuses	46 : 53	71 : 48	48 : 60	55 : 50	foetuses studies
Observations: % foetal incidence^σ					
(% litters) affected:					
Thorax and abdomen:					
Intra-muscular haemorrhage - lateral cervical region	-	0.8 (5.6)	0.9 (5.3)	-	π
Slightly distended lateral cervical lymph ducts	-	-	0.9 (5.3)	-	π
Space between body wall and organs	13.1 (38.9)	24.4 (55.6)	12.0 (36.8)	18.1 (66.7)	15.91
Intra-muscular haemorrhage - scapular region	1.0 (5.6)	-	-	-	0.04
Absence of innominate artery	-	-	0.9 (5.3)	-	0.03
Blood in thoracic lymph duct at aortic arch level	1.0 (5.6)	-	-	-	π
Possible hairline septal defect	1.0 (5.6)	-	-	-	π
Slightly increased amount of pericardial fluid	-	-	-	1.0 (5.6)	π
Petechial haemorrhages on right lower lung lobe	-	0.8 (5.6)	-	-	0.07
Lower ribs appear unattached at sternal end	1.0 (5.6)	-	-	-	π
Hepatic haemorrhage	20.2 (50.0)	13.4 (44.4)	7.4 (42.1)	11.4 (44.4)	10.74
Vacuole in adrenal gland without/containing blood	-	-	1.9 (10.5)	-	0.03
Unilateral hydronephrosis	2.0 (11.1)	-	2.8 (15.8)	-	3.74
Bilateral hydronephrosis	1.0 (5.6)	-	1.9 (10.5)	2.9 (16.7)	1.28
Unilateral hydroureter	3.0 (16.7)	5.9 (22.2)	11.1 (36.8)	7.6 (16.7)	7.43
Bilateral hydroureter	1.0 (5.6)	1.7 (11.1)	6.5 (26.3)	2.9 (16.7)	5.22
					0.0 - 11.7
					0.0 - 9.8
					0.7 - 24.2
					0.0 - 16.0

σ One foetus may have more than one observation. π No record in background control data.

continued on next page

TABLE 52 - continued

Summary of foetal observations after free-hand serial sectioning (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data	
Number of foetuses (litters) examined:	99 (18)	119 (18)	108 (19)	105 (18)	7083	78
Number of male : female foetuses	46 : 53	71 : 48	48 : 60	55 : 50	foetuses	studies
Observations: % foetal incidence ^σ						
(% litters) affected:						
Thorax and abdomen - continued						
Haemorrhagic peritoneal fluid	3.0 (16.7)	0.8 (5.6)	1.9 (10.5)	1.0 (5.6)	2.63	0.0 - 12.2
Localised internal abdominal haemorrhage	1.0 (5.6)	2.5 (16.7)	0.9 (5.3)	-	0.78	0.0 - 4.7
Haemorrhagic abdomen	6.1 (27.8)	0.8 (5.6)	0.9 (5.3)	1.9 (11.1)	2.06	0.0 - 8.0
Slightly distended bladder	1.0 (5.6)	-	1.9 (5.3)	-	0.24	0.0 - 8.2
Dilated umbilical arteries	1.0 (5.6)	2.5 (16.7)	0.9 (5.3)	1.0 (5.6)	0.48	0.0 - 9.8
Testis(es) displaced towards midline/cranially/ventrally ⁺	4.3 (11.1)	5.6 (22.2)	4.2 (10.5)	1.8 (5.6)	1.34	0.0 - 9.1
Slightly elongated genital tubercle	3.0 (16.7)	3.4 (11.1)	-	-	0.27	0.0 - 3.6
Blood in anus	1.0 (5.6)	0.8 (5.6)	-	1.0 (5.6)	0.01	0.0 - 1.0

continued on next page

σ One foetus may have more than one observation.

+ Calculated as a percentage of males.

TABLE 52 - continued

Summary of foetal observations after free-hand serial sectioning (F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	1	2	3	4	Control data	
Number of foetuses (litters) examined:	99 (18)	119 (18)	108 (19)	105 (18)	7083	78
Number of male : female foetuses	46 : 53	71 : 48	48 : 60	55 : 50	foetuses	studies
Observations: % foetal incidence ^σ						
(% litters) affected:						
Others						
Subcutaneous haemorrhages :						
- Dorsal cervical	5.1 (22.2)	2.5 (11.1)	0.9 (5.3)	1.0 (5.6)	0.32	0.0 - 5.1
- Scapular	26.3 (77.8)	22.7 (77.8)	12.0 (47.4)	22.9 (66.7)	32.11	6.4 - 94.5
- Nasal	2.0 (11.1)	1.7 (11.1)	-	2.9 (16.7)	1.31	0.0 - 5.9
- Lower jaw	1.0 (5.6)	0.8 (5.6)	-	-	1.38	0.0 - 8.8
- Cranial	6.1 (27.8)	2.5 (16.7)	2.8 (15.8)	3.8 (16.7)	2.36	0.0 - 8.2
- Dorsal/lateral/ventral thoracic	2.0 (11.1)	0.8 (5.6)	1.9 (10.5)	3.8 (16.7)	0.94	0.0 - 5.6
- Dorsal/lateral abdominal	1.0 (5.6)	3.4 (22.2)	-	-	0.49	0.0 - 3.8
- Fore/hind limb(s)	19.2 (44.4)	14.3 (50.0)	8.3 (42.1)	8.6 (44.4)	3.06	0.0 - 14.4
- Tail	3.0 (16.7)	0.8 (5.6)	-	-	0.07	0.0 - 2.1
Subcutaneous oedema - trunk	2.0 (11.1)	0.8 (5.6)	0.9 (5.3)	6.7 (11.1)	6.32	0.0 - 17.9 ^Δ

^σ One foetus may have more than one observation.

^Δ Derived from 2058 foetuses; 18 studies.

TABLE 53

Summary of foetal observations at skeletal examination (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data	
Number of foetuses (litters) examined:	109 (18)	127 (18)	119 (19)	116 (18)	11503 foetuses	79 studies
Observations: % foetal incidence ^a : (% litter incidence)						
Head	Mean Study range					
Size of anterior fontanelle	2.8 (11.1) 94.5 (100.0)	0.8 (5.6) 98.4 (100.0)	0.8 (5.3) 98.3 (100.0)	-	1.06 96.87	0.0 - 6.5 85.8 - 100.0
Incomplete ossification of supraoccipital bone	2.8 (11.1)	0.8 (5.6)	0.8 (5.3)	1.7 (11.1)	2.01	0.0 - 13.3
Incomplete ossification of interparietal bone	15.6 (50.0)	7.1 (38.9)	10.9 (42.1)	9.5 (44.4)	13.49	0.0 - 29.2
Incomplete ossification of one or both parietal bones	19.3 (55.6)	25.2 (66.7)	13.4 (52.6)	15.5 (61.1)	20.53	7.1 - 50.5
Incomplete ossification of squamosal bones	0.9 (5.6)	-	-	-	1.31	0.0 - 7.1
Small discrete unossified area in frontal bone	0.9 (5.6)	-	-	0.9 (5.6)	0.81	0.0 - 4.7
Small discrete unossified area in basioccipital bone	-	0.8 (5.6)	-	-	0.22	0.0 - 2.6
Incomplete ossification of palatine bones (not cleft palate)	-	-	-	0.9 (5.6)	0.03	0.0 - 2.5
Incomplete ossification of basisphenoid	-	-	-	-	0.02	0.0 - 1.1
Small additional plaque of bone in parietal suture	0.9 (5.6)	-	-	0.9 (5.6)	0.02	0.0 - 0.7
Frontal/ nasal suture enlarged	2.8 (11.1)	0.8 (5.6)	2.5 (10.5)	1.7 (11.1)	0.28	0.0 - 2.4
Incomplete ossification of hyoid bone	-	3.1 (22.2)	1.7 (10.5)	1.7 (11.1)	1.07	0.0 - 5.3
Absence of hyoid bone	6.4 (22.2)	1.6 (11.1)	7.6 (26.3)	8.6 (27.8)	7.87	1.0 - 25.0
					8.76	0.7 - 18.3

continued on next page

^a One foetus may have more than one observation.

TABLE 53 - continued

Summary of foetal observations at skeletal examination (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data
Number of foetuses (litters) examined:	109 (18)	127 (18)	119 (19)	116 (18)	11503 foetuses 79 studies
Observations: % foetal incidence ^a : (% litter incidence)					
Ribcage and vertebral column:					
Number of ribs	96.3 (100.0)	97.6 (100.0)	99.2 (100.0)	100.0 (100.0)	98.24 (92.5 - 100.0)
13th rib(s) reduced in length or absent	1.8 (11.1)	1.6 (11.1)	0.8 (5.3)	-	1.20 (0.0 - 4.0)
Slight medial thickening of right 9th and left 10th ribs	0.9 (5.6)	0.8 (5.6)	-	-	0.50 (0.0 - 3.5)
Incomplete ossification of sternbrae:	2.8 (16.7)	0.8 (5.6)	0.8 (5.3)	1.7 (11.1)	1.46 (0.0 - 8.2)
	-	0.8 (5.6)	-	-	1.7 (11.1)
Number of bones affected	2.8 (11.1)	3.9 (22.2)	4.2 (21.1)	6.0 (33.3)	16.49 (0.0 - 40.0)
1st sternbra cleft	78.9 (100.0)	67.7 (100.0)	73.9 (100.0)	67.2 (100.0)	63.25 (43.3 - 83.3)
One or more sternbrae offset	10.1 (27.8)	20.5 (72.2)	14.3 (52.6)	14.7 (61.1)	11.25 (1.1 - 23.3)
Two or more sternbrae fused	4.6 (16.7)	6.3 (22.2)	6.7 (31.6)	6.9 (38.9)	3.70 (0.0 - 17.5)
Ossification of ventral arch of 1st cervical vertebra	0.9 (5.6)	-	-	1.7 (11.1)	0.60 (0.0 - 3.3)
Incomplete ossification of one or more cervical vertebral arches	1.8 (11.1)	0.8 (5.6)	0.8 (5.3)	0.9 (5.6)	0.58 (0.0 - 6.7)
	2.8 (5.6)	2.4 (11.1)	-	3.4 (16.7)	0.32 (0.0 - 2.8)
	2.8 (11.1)	0.8 (5.6)	0.8 (5.3)	1.7 (11.1)	1.47 (0.0 - 5.2)
	1.8 (5.6)	-	-	-	0.02 (0.0 - 0.5)
	13.8 (44.4)	4.7 (11.1)	8.4 (26.3)	9.5 (44.4)	6.09 (0.0 - 23.2 ^a)
	3.7 (16.7)	1.6 (11.1)	3.4 (5.3)	3.4 (16.7)	0.24 (0.0 - 3.1)

continued on next page

^a One foetus may have more than one observation.
 a 11281 foetuses from 77 studies.

TABLE 53 - continued

Summary of foetal observations at skeletal examination (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data	
Number of foetuses (litters) examined:	109 (18)	127 (18)	119 (19)	116 (18)	11503 foetuses	79 studies
<u>Observations: % foetal incidence^σ: (% litter incidence)</u>						
Rib cage and vertebral column :- continued					Mean	Study range
Ossification of all cervical vertebral centra	-	0.8 (5.6)	-	-	0.84	0.0 - 4.1
Incomplete ossification of one or more thoracic vertebral centra	31.2 (88.9)	16.5 (55.6)	23.5 (68.4)	35.3 (83.3)	24.02	0.0 - 58.3
Incomplete ossification of one or more lumbar vertebral centra	-	-	-	0.9 (5.6)	0.34	0.0 - 2.1
Incomplete ossification of one or more sacral and/or lumbar vertebral arches	-	-	-	1.7 (11.1)	0.84	0.0 - 6.2
25 pre-sacral vertebrae	1.8 (11.1)	1.6 (11.1)	-	1.7 (11.1)	0.43	0.0 - 4.5
Incomplete ossification of caudal vertebrae, less than 5 vertebrae ossified	7.3 (33.3)	7.9 (33.3)	5.0 (15.8)	2.6 (16.7)	2.78	0.0 - 14.5

^σ One foetus may have more than one observation.

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TABLE 53 - continued

Summary of foetal observations at skeletal examination (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data
Number of foetuses (litters) examined:	109 (18)	127 (18)	119 (19)	116 (18)	11503 foetuses 79 studies
Observations: % foetal incidence ^a : (% litter incidence)					
Limbs, pectoral and pelvic girdles					
Number of metacarpals/metatarsals	3/4				
Number of metacarpals/metatarsals	58.7 (100.0)	62.2 (94.4)	64.7 (100.0)	72.4 (100.0)	65.56 28.6 - 86.7
Incomplete ossification or absence of metacarpals/metatarsals	38.5 (77.8)	36.2 (72.2)	31.1 (73.7)	25.9 (77.8)	31.55 6.2 - 71.4
Ossification of one or more phalangeal bones	2.8 (11.1)	2.4 (16.7)	4.2 (15.8)	2.6 (11.1)	2.25 0.0 - 9.3
Apparent absence of inner corners of one or both scapulae	-	3.9 (16.7)	-	-	1.77 0.0 - 9.9
Incomplete ossification or absence of one or both pubic bones	5.5 (33.3)	7.1 (27.8)	9.2 (42.1)	3.4 (16.7)	2.41 0.0 - 8.1
Incomplete ossification of ischial bones	11.0 (33.3)	11.0 (44.4)	7.6 (21.1)	8.6 (33.3)	6.75 0.0 - 18.6
Asymmetric pelvis, ilia associated with different sacral vertebrae	0.9 (5.6)	-	-	0.9 (5.6)	0.94 0.0 - 4.7
		1.6 (11.1)	-	1.7 (11.1)	0.24 0.0 1.8

continued on next page

or One foetus may have more than one observation.

TABLE 53 - continued

Summary of foetal observations at skeletal examination (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	1	2	3	4	Control data
Number of foetuses (litters) examined:	109 (18)	127 (18)	119 (19)	116 (18)	11503 foetuses 79 studies
Observations: % foetal incidence ^σ : (% litter incidence)					
Limbs, pectoral and pelvic girdles :- continued					
Conjoined foetuses :- two foetuses joined ventrally between 2nd sternbra and umbilicus of major foetus, resulting in sternbral cleft with sternbral fusion. Minor foetus has no cranial structures no sternbrae, vertebrae or ribs; hindlimbs normal, pubic bones absent; front limbs fused to radius - single fused scapula rudiment, fused humeri, fused and reduced radii, separate ulnae and forefeet. Major foetus otherwise normal					
	-	-	-	0.9 (5.6)	π π
					Mean Study range

^σ One foetus may have more than one observation.
^π No previous record in background control data.

TABLE 54

Gestation length and gestation index (F_1-F_2)

Group : 1 2 3 4
 Compound: : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Number of animals	Gestation length (days)						Gestation index (%)
		22	22 ¹ / ₂	23	23 ¹ / ₂	24	24 ¹ / ₂	
1	19	7	5	6	1	0	0	100.0
2	19	2	13	3	0	0	1	100.0
3	20	0	10	10	0	0	0	100.0
4	19	4	11	4	0	0	0	100.0

TABLE 55

Group mean bodyweights (g) of females during lactation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Day <u>post partum</u>				
		1	4	7	14	21
1	Mean	321	333	331	347	327
	S.D.	30	24	24	24	20
	n	19	18	18	18	18
2	Mean	325	330	330	341	320
	S.D.	31	25	23	20	18
	n	19	18	17	17	17
3	Mean	322	330	330	339	322
	S.D.	30	25	23	25	20
	n	20	20	20	20	20
4	Mean	315	323	322	333	311
	S.D.	41	34	32	29	22
	n	19	18	18	18	18

S.D. Standard deviation.
n Number of animals.

TABLE 56

Food intake (g/rat/day) -
group mean values for females during lactation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Days post partum		
		1-6	7-13	14-20 ^A
1	Mean	32	50	64
	S.D.	5	8	6
	n	18	18	18
2	Mean	32	52	61
	S.D.	6	8	7
	n	17	17	17
3	Mean	35	53	64
	S.D.	5	6	8
	n	20	20	20
4	Mean	33	52	61
	S.D.	6	5	4
	n	18	18	18

S.D. Standard deviation.

n Number of litters.

A Includes direct intake by litter.

TABLE 57

Group mean litter sizes (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group		Implan- tation sites	Total at Day 1 <u>post partum</u>	Number alive on Day <u>post partum</u>					
				1	4	4 ⁺	7	14	21
1	Mean	14.3	13.1	13.0	12.2	7.6	7.5	7.4	7.4
	S.D.	4.0	3.7	3.7	3.7	1.3	1.3	1.3	1.3
	n	19	19	19	18	18	18	18	18
2	Mean	13.2	12.3	12.3	11.7	7.4	7.6	7.6	7.6
	S.D.	4.0	4.2	4.1	4.0	1.7	0.8	0.8	0.8
	n	19	19	19	18	18	17	17	17
3	Mean	14.4	13.1	13.1	12.7	7.9	7.6	7.5	7.5
	S.D.	2.2	2.2	2.2	2.5	0.4	1.2	1.2	1.2
	n	20	20	20	20	20	20	20	20
4	Mean	13.7	12.7	12.7	12.4	7.9	7.9	7.9	7.9
	S.D.	2.5	2.7	2.7	2.7	0.5	0.5	0.5	0.5
	n	19	19	19	18	18	18	18	18

S.D. Standard deviation.

n Number of litters.

+ Following litter size adjustment.

TABLE 58

Group mean post-implantation survival,
live birth, viability and lactation indices (F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Post- implantation survival index (%)	Live birth index (%)	Viability index Day 4 (%)	Lactation index on		
				Day 7	Day 14	Day 21
1	92	100	89	99	99	99
2	93	100	86	93	93	93
3	91	100	97	96	95	95
4	93	100	92	100	100	100

TABLE 59

Group mean bodyweights (g) of offspring (F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group		Day <u>post partum</u>				
		1	4	7	14	21
1	Mean	6.0	8.3	13.9	31.2	52.2
	S.D.	0.7	1.4	2.2	3.4	5.5
	n	19	18	18	18	18
2	Mean	6.1	8.1	14.0	30.4	50.1
	S.D.	0.9	2.0	2.4	3.3	5.8
	n	19	18	17	17	17
3	Mean	6.3	8.7	14.8	32.2	53.1
	S.D.	0.6	1.5	2.2	3.5	6.4
	n	20	20	20	20	20
4	Mean	6.0	8.5	14.3	31.0	50.6
	S.D.	0.7	1.1	1.5	2.1	3.4
	n	19	18	18	18	18

S.D. Standard deviation.
n Number of litters.

TABLE 60

Sex ratios (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Total at Day 1			Number alive at Day 1			Number alive Day 4 (pre-cull)			Number alive Day 4 (post-cull)			Number alive Day 21		
	M	F	Ratio	M	F	Ratio	M	F	Ratio	M	F	Ratio	M	F	Ratio
1	127	121	1 : 0.95	127	120	1 : 0.94	115	104	1 : 0.90	69	67	1 : 0.97	68	66	1 : 0.97
2	120	114	1 : 0.95	120	113	1 : 0.94	108	103	1 : 0.95	68	65	1 : 0.96	66	64	1 : 0.97
3	135	127	1 : 0.94	134	127	1 : 0.95	130	124	1 : 0.95	81	77	1 : 0.95	76	74	1 : 0.97
4	121	121	1 : 1.00	121	121	1 : 1.00	114	110	1 : 0.96	68	74	1 : 1.09	68	74	1 : 1.09

TABLE 61

Summary of observations at necropsy of offspring (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Offspring dying before weaning ^Δ				Offspring killed at Day 4				Offspring killed after weaning			
	1	2	3	4	1	2	3	4	1	2	3	4
Number examined :	17	21	12	8	83	78	96	82	134	130	150	142
Observations - % incidence:												
Appearance - small pup for age	-	-	-	12.5	1.2	1.3	-	-	-	1.5	2.0	-
Brain - unilateral dilation of lateral ventricles	-	-	-	-	-	-	-	-	-	-	0.7	-
Brain - hydrocephaly, head slightly domed	-	-	-	-	-	-	-	-	-	-	-	0.7
Epididymis - unilateral rudimentary organ	-	-	-	-	-	-	-	-	0.7	-	-	-
Eye - one eye missing	-	-	-	-	-	-	-	-	-	-	-	-
Eye - one eye constricted, both eyes cloudy	-	-	-	-	-	-	-	-	-	-	0.7	-
Head - wound above left eye	-	-	-	12.5	-	-	-	-	-	-	-	-
Kidney - unilateral hydronephrosis	23.5	9.5	-	-	1.2	-	-	-	0.7	1.5	0.7	1.4
Kidney - bilateral hydronephrosis	11.8	4.8	-	-	2.4	1.3	1.0	-	-	-	-	-
Kidney - punctate cyst(s) on surface of one kidney	-	-	-	-	-	-	-	-	-	0.8	0.7	-
Kidney - pale raised areas (to 5 mm diameter) on one kidney	-	-	-	-	-	-	-	-	0.7	-	-	-
Kidney - pale areas (to 2 mm diameter) on both kidneys	-	-	-	-	-	-	-	-	-	-	0.7	-
Liver - pale punctate areas on left median lobe	-	-	-	-	-	-	1.0	-	-	-	-	-
Palate - pale areas on palate	-	4.8	-	-	-	-	-	-	-	-	-	-
Palate - dark areas on palate	-	4.8	8.3	12.5	-	-	3.1	-	-	-	-	-
Palate - haemorrhage on one side of palate	5.9	-	-	-	-	-	-	-	-	-	-	-

continued on next page

Δ Excludes missing, autolysed and grossly cannibalised offspring.

TABLE 61 - continued

Summary of observations at necropsy of offspring (F₂)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group	Offspring dying before weaning ^Δ				Offspring killed at Day 4				Offspring killed after weaning			
	1	2	3	4	1	2	3	4	1	2	3	4
Number examined	17	21	12	8	83	78	96	82	134	130	150	142
Observations - % incidence:												
Stomach - no milk in stomach	70.6	85.7	83.3	100.0	-	-	6.3	-	-	-	-	-
Stomach/ Intestines - distended with gas	5.9	-	-	-	-	-	-	-	-	-	-	-
Testis - unilateral rudimentary organ	-	-	-	-	-	-	-	-	-	-	0.7	-
Ureter - unilateral hydroureter	-	-	-	-	4.8	-	-	2.4	-	-	-	-
Ureter - bilateral hydroureter	-	-	-	-	2.4	-	1.0	1.2	-	-	-	-
Urinary bladder - full	-	-	-	-	4.8	1.3	10.4	14.6	-	-	-	-
Urinary bladder - distended	-	-	-	-	-	-	3.1	3.7	-	-	-	-

^Δ Excludes missing, autolysed and grossly cannibalised offspring.

TABLE 62

Summary of observations at necropsy of males (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	1	2	3	4
Number of animals :	40	40	40	40
Observations - % incidence:				
Appearance - hairloss, face	-	-	-	2.5
Epididymis - blue and/or reduced, unilateral	5.0	7.5	2.5	5.0
Epididymis - slightly enlarged, unilateral	-	-	-	2.5
Fat pads - creamy or yellow body in testicular fat pad	2.5	2.5	2.5	2.5
Intestines - section of walls of small intestine red, contents yellow and fluid	2.5	-	-	-
Kidney - unilateral hydronephrosis	-	2.5	5.0	2.5
Pancreas - pedunculate body attached to pancreas	-	2.5	-	-
Prostate - reduced	-	5.0	-	2.5
Testis - small, blue and/or flaccid, unilateral	5.0	7.5	2.5	5.0
Testis - large, blue and flaccid, unilateral	2.5	-	-	-
Testis - large (1½ - 2 x normal), unilateral	7.5	5.0	2.5	-
Testis - large (2 x normal), bilateral	-	-	-	2.5
Testis - yellow body (2 x 2 mm) under tunica membrane	2.5	-	-	-

TABLE 63

Summary of observations at necropsy of females (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	1	2	3	4
Number of animals :	40	40	40	40
Observations - % incidence:				
Appearance - hairloss, ventral surface	2.5	-	5.0	2.5
Appearance - hairloss, limbs	2.5	-	2.5	-
Appearance - one ear missing	2.5	-	-	-
Heart - enlarged, twice normal size	2.5	-	-	-
Kidney - unilateral hydronephrosis	2.5	-	-	-
Kidney - bilateral hydronephrosis	-	-	-	2.5
Mammary tissue - pale and/or inactive	2.5	2.5	-	5.0
Mammary tissue - swollen region (30 x 15 mm): cut surface shows pale-green amorphous material	-	-	-	2.5
Thymus - areas of congestion (4 x 7 mm)	2.5	-	-	-
Uterus - unilateral implantation sites	10.0	7.5	12.5	7.5
Uterus - no implantation sites	7.5	7.5	2.5	7.5
Uterus - clotted blood in gravid horn of uterus	-	-	2.5	-

TABLE 64

Group mean absolute weights (g) of male reproductive organs (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Body weight (g)	Prostate	Seminal Vesicles	Testes	Epididymides
1M	569	0.58	2.54	3.64	1.25
S.D.	55	0.17	0.38	0.44	0.12
n	40	40	36	40	40
2M	551	0.56	2.64	3.67	1.29
S.D.	52	0.16	0.30	0.45	0.14
n	40	40	36	40	39
3M	555	0.59	2.54	3.62	1.28
S.D.	50	0.19	0.37	0.41	0.13
n	40	40	40	40	39
4M	529**	0.55	2.61	3.69	1.25
S.D.	63	0.19	0.42	0.60	0.11
n	40	40	36	39	40

S.D. Standard deviation.

n Number of animals.

** Significantly different from Control P<0.01
(Analysis of variance and Student's t-test).

TABLE 65

Group mean relative weights^Δ of male reproductive organs (F₁)

Group		:	1	2	3	4
Compound		:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)		:	0	250	500	750
Group / sex	Body weight (g)	Prostate	Seminal Vesicles	Testes	Epididymides	
1M	569	0.10	0.45	0.64	0.22	
S.D.	55	0.03	0.08	0.09	0.02	
n	40	40	36	40	40	
2M	551	0.10	0.48	0.67	0.23*	
S.D.	52	0.03	0.08	0.09	0.03	
n	40	40	36	40	39	
3M	555	0.11	0.46	0.66	0.23	
S.D.	50	0.04	0.07	0.08	0.03	
n	40	40	40	40	39	
4M	529**	0.11	0.50*	0.71**	0.24**	
S.D.	63	0.04	0.10	0.13	0.03	
n	40	40	36	39	40	

S.D. Standard deviation.

n Number of animals.

* Significantly different from Control: P<0.05
(Analysis of variance and Student's t-test).** Significantly different from Control: P<0.01
(Analysis of variance and Student's t-test).

Δ Expressed as a percentage of bodyweight.

TABLE 66

Group mean absolute weights (g) of female
reproductive organs at Day 20 of gestation (F_1 - F_2)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex		Body weight (g)	Gravid Uterus	Uterus	Ovaries
1F	Mean	397	63	4.02	0.126
	S.D.	30	16	0.61	0.038
	n	17	14	17	17
2F	Mean	391	69	4.40	0.117
	S.D.	36	15	0.70	0.019
	n	18	18	18	18
3F	Mean	393	60	3.86	0.115
	S.D.	35	17	0.83	0.030
	n	18	19	19	19
4F	Mean	395	62	3.95	0.112
	S.D.	30	16	0.80	0.019
	n	17	17	18	17

S.D. Standard deviation.
n Number of animals.

TABLE 67

Group mean relative weights^Δ of female
reproductive organs at Day 20 of gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex		Body weight (g)	Gravid Uterus	Uterus	Ovaries ⁺
1F	Mean	397	15.71	1.02	31.8
	S.D.	30	4.00	0.17	10.0
	n	17	14	17	17
2F	Mean	391	17.45	1.12	30.4
	S.D.	36	3.10	0.12	7.1
	n	18	18	18	18
3F	Mean	393	15.10	0.98	29.5
	S.D.	35	4.17	0.20	7.2
	n	18	18	18	18
4F	Mean	395	15.11	0.99	28.9
	S.D.	30	3.76	0.20	5.3
	n	17	16	17	16

S.D. Standard deviation.

n Number of animals.

Δ Expressed as a percentage of bodyweight unless
otherwise indicated.

+ Ovaries : percentage value multiplied by 1000.

APPENDIX 1

Individual bodyweights (g) of males (F₀)

Group	: 1 2 3 4														
Compound	: Control ----- SC-19129 -----														
Intended dosage (mg/kg/day)	: 0 250 500 750														
Group Animal	Week of treatment														
/ Sex number	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1M 1001	161	222	277	319	360	381	405	437	457	477	494	489	510	524	542
1002	172	240	298	348	387	415	431	451	470	487	504	523	534	540	560
1003	164	223	270	318	354	382	403	430	446	469	480	478	481	492	518
1004	168	227	273	314	349	373	391	409	429	443	459	469	486	494	502
1005	159	226	276	314	345	373	397	412	430	447	465	470	482	496	513
1006	168	231	284	330	368	396	417	439	455	456	475	474	476	485	487
1007	159	209	250	281	305	330	349	366	377	395	410	420	436	445	456
1008	163	222	281	328	373	404	432	455	475	474	494	509	518	522	536
1009	165	221	268	299	331	353	376	395	407	414	427	438	450	472	482
1010	175	244	308	364	415	446	476	500	525	535	552	562	575	590	609
1011	167	223	273	307	337	362	385	404	415	430	449	454	467	477	486
1012	167	238	294	343	375	402	437	455	475	495	523	521	538	550	573
1013	153	220	276	317	355	384	417	435	457	473	490	499	503	516	528
1014	152	227	295	351	394	429	463	493	526	541	571	583	593	605	626
1015	160	233	291	337	378	417	446	470	493	512	527	524	547	570	580
1016	167	227	283	322	361	394	419	440	455	470	485	489	497	510	529
1017	167	219	267	303	334	362	388	401	420	431	447	453	457	470	475

APPENDIX 1 - continued

Individual bodyweights (g) of males (F₀)

Group	: 1 2 3 4														
Compound	: Control ----- SC-19129 -----														
Intended dosage (mg/kg/day)	: 0 250 500 750														
Group Animal / Sex number	Week of treatment														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1M	171	241	306	364	418	458	495	517	535	552	573	581	588	605	631
1018	158	224	283	335	379	412	443	466	493	505	521	532	546	560	585
1019	171	230	284	321	353	374	403	425	440	454	467	474	481	496	513
1020	172	233	286	328	368	399	416	438	465	481	499	517	530	546	563
1021	174	247	313	368	412	453	482	509	535	552	573	590	615	628	642
1022	161	223	284	330	379	413	443	472	505	523	552	561	572	586	601
1023	162	222	271	311	342	372	398	417	435	439	441	457	463	475	485
1024	171	227	280	318	361	392	418	445	465	487	503	504	523	542	563
1025	171	226	272	309	343	375	394	416	435	447	462	474	484	490	505
1026	170	238	301	352	396	428	452	471	500	515	526	540	561	573	586
1027	166	240	304	348	391	420	452	477	492	505	529	529	536	557	576
1028	167	231	298	353	394	430	460	491	510	529	555	569	586	600	626
1029	176	234	282	318	347	375	391	405	420	427	441	447	455	466	477
1030	163	220	273	317	353	384	405	425	438	439	452	466	478	490	496
1031	168	237	300	354	400	437	469	499	522	549	570	580	596	616	617
1032	156	206	258	296	327	352	373	387	395	405	416	423	432	445	445
1033	175	242	302	353	393	422	444	458	480	492	517	535	550	565	580
1034															

APPENDIX 1 - continued

Individual bodyweights (g) of males (F₀)

Group	: 1 2 3 4														
Compound	: Control ----- SC-19129 -----														
Intended dosage (mg/kg/day)	: 0 250 500 750														
Group Animal / Sex number	Week of treatment														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2M	157	213	255	284	309	336	354	367	382	399	408	417	425	440	445
1035	150	219	269	317	363	395	415	436	460	475	487	493	503	517	527
1036	145	211	272	315	352	392	417	440	461	476	495	506	514	530	546
1037	153	215	271	319	358	393	422	442	465	485	513	520	527	550	556
1038	168	240	302	354	403	442	475	496	520	545	565	568	579	595	609
1039	164	229	282	328	368	389	414	430	441	457	472	476	475	485	504
1040	162	235	292	338	372	404	428	448	459	472	490	501	511	526	525
1041	159	230	293	342	375	405	432	457	477	494	512	524	531	543	558
1042	157	216	258	293	320	346	371	384	398	407	420	429	435	450	459
1043	159	222	266	310	345	367	392	404	417	427	434	445	453	460	469
1044	161	224	283	324	362	393	424	448	472	477	491	505	533	550	566
1045	154	229	287	338	387	409	431	452	475	487	500	507	518	532	537
1046	173	234	293	339	372	400	422	444	458	470	485	492	516	531	542
1047	176	231	274	309	338	368	383	404	414	425	440	446	461	470	474
1048	165	236	305	367	416	459	491	523	550	562	580	590	604	620	631
1049	166	229	291	337	383	417	439	462	512	492	500	511	530	535	552
1050	174	236	292	336	374	409	433	454	475	481	490	501	506	525	536
1051															

APPENDIX 1 - continued

Individual bodyweights (g) of males (F₀)

Group : 1 2 3 4
Compound : Control ----- SC-19129 -----
Intended dosage (mg/kg/day) : 0 250 500 750

Group Animal / Sex number	Week of treatment															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
2M	1052	165	227	289	336	382	411	442	472	498	524	542	543	567	582	600
	1053	174	244	310	358	402	437	466	490	513	526	544	550	578	599	625
	1054	168	223	267	308	346	368	391	410	430	442	459	471	477	487	505
	1055	168	223	263	295	322	349	374	393	407	419	429	439	446	462	469
	1056	167	224	274	316	347	384	404	423	440	452	465	479	487	497	506
	1057	154	219	271	317	354	389	417	442	460	475	496	500	509	524	528
	1058	179	250	314	358	396	418	449	473	492	510	525	532	542	554	564
	1059	166	226	278	322	361	398	419	443	458	470	486	494	499	510	519
	1060	163	235	302	357	401	437	461	496	520	542	566	572	596	613	630
	1061	171	223	261	299	325	354	374	391	400	411	430	438	444	454	470
	1062	178	244	304	358	402	439	473	510	531	551	573	585	605	625	644
	1063	181	253	315	370	411	446	473	502	523	544	567	566	591	614	635
	1064	161	218	262	304	337	366	382	394	410	421	438	454	465	477	486
	1065	171	227	272	310	342	365	392	405	425	435	454	469	480	487	497
	1066	156	225	276	315	356	384	410	428	447	462	474	496	506	522	525
	1067	163	231	283	327	367	400	431	455	472	487	496	514	531	546	564
1068	163	234	286	336	374	402	425	436	464	479	506	506	524	540	538	

APPENDIX 1 - continued

Individual bodyweights (g) of males (F₀)

Group	:	1	2	3	4											
Compound	:	Control	-----	SC-19129	-----											
Intended dosage (mg/kg/day)	:	0	250	500	750											
Group Animal		Week of treatment														
/ Sex number		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
3M	1069	173	230	276	310	334	357	371	387	400	409	418	424	431	445	448
	1070	178	243	300	350	395	429	449	472	485	497	515	528	546	559	573
	1071	167	235	291	335	374	408	435	456	479	495	520	520	537	549	571
	1072	158	223	285	333	380	414	438	465	480	499	519	524	539	549	562
	1073	165	221	266	307	340	368	392	410	420	435	452	463	471	485	496
	1074	158	211	263	302	337	370	399	421	440	452	469	474	480	495	501
	1075	160	221	263	305	339	368	388	404	421	427	441	448	449	456	465
	1076	168	228	273	304	337	362	385	400	415	424	432	438	434	445	452
	1077	178	247	308	357	399	428	461	487	510	523	536	532	545	565	582
	1078	161	227	285	322	365	398	422	440	466	482	492	498	503	517	527
	1079	168	230	285	332	373	403	427	452	462	478	497	510	521	500	542
	1080	164	231	282	320	354	373	399	418	436	452	466	480	489	501	524
	1081	163	227	277	317	353	384	407	431	440	453	464	465	466	483	496
	1082	158	221	278	327	369	397	418	450	468	481	501	511	521	537	556
	1083	161	223	274	318	353	382	408	428	436	449	467	467	479	499	522
1084	166	218	262	300	336	367	389	409	424	437	449	447	462	476	485	
1085	153	209	260	305	342	372	400	416	442	449	459	467	474	486	495	

APPENDIX 1 - continued

Individual bodyweights (g) of males (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group Animal / Sex number	Week of treatment															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
3M	1086	166	231	288	338	389	422	448	472	500	498	517	529	548	567	584
	1087	171	225	274	311	347	377	400	418	435	445	464	474	488	502	510
	1088	176	232	274	317	355	383	401	420	436	436	449	462	469	477	486
	1089	179	246	308	369	413	451	478	501	525	537	549	554	563	570	587
	1090	168	226	278	326	363	393	416	434	450	459	476	487	499	515	527
	1091	160	205	250	293	324	347	370	387	403	411	430	436	449	460	476
	1092	181	247	305	352	392	423	451	474	492	505	524	530	538	550	567
	1093	168	229	291	338	370	407	443	463	477	494	514	516	528	544	560
	1094	156	210	258	295	328	361	393	411	435	454	463	473	477	490	506
	1095	173	236	293	343	382	413	443	476	500	516	535	540	546	570	586
	1096	156	216	266	316	355	389	421	451	470	497	521	534	551	562	587
	1097	164	220	261	296	319	344	368	385	395	406	425	428	436	445	460
	1098	174	239	295	343	382	415	434	455	478	498	512	523	535	550	561
	1099	165	217	261	294	324	344	366	380	400	403	415	422	436	440	454
1100	175	236	282	330	367	399	428	453	463	475	495	514	523	538	546	
1101	160	220	272	317	352	389	413	436	456	476	496	508	522	538	561	
1102	156	216	259	295	324	347	366	386	396	411	418	433	444	455	466	

Individual bodyweights (g) of males (F_0)

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APPENDIX 1 - continued

Individual bodyweights (g) of males (F₀)

Group : 1 2 3 4
 Compound : Control ----- SC-19129 -----
 Intended dosage (mg/kg/day) : 0 250 500 750

Group Animal / Sex number	Week of treatment															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
4M	1120	177	241	294	342	378	412	432	451	470	482	495	504	507	520	532
	1121	176	240	293	346	386	418	447	473	500	522	542	552	558	574	597
	1122	169	224	281	326	361	399	414	443	460	483	500	504	517	535	548
	1123	167	229	285	331	359	391	409	424	435	434	445	462	473	480	486
	1124	169	227	281	326	356	390	419	441	460	463	474	483	499	520	531
	1125	163	221	278	323	348	377	398	417	435	429	445	472	491	505	520
	1126	170	230	282	332	367	399	419	438	459	463	470	491	508	525	530
	1127	173	226	275	316	346	375	396	411	427	434	446	461	472	486	507
	1128	156	212	265	317	354	381	406	427	455	473	496	504	511	520	529
	1129	179	239	294	337	372	404	431	459	480	494	516	526	531	545	563
	1130	164	223	270	312	353	385	408	434	450	469	485	495	506	517	533
	1131	173	229	281	321	352	379	400	419	437	447	461	463	471	522	499
	1132	172	237	294	335	362	389	408	440	455	467	482	486	490	505	512
	1133	178	243	294	330	357	388	412	428	453	462	473	495	507	525	535
	1134	168	228	281	328	367	391	414	428	442	459	477	476	480	501	511
	1135	167	228	281	326	358	388	411	430	451	467	472	480	493	516	525
1136	140	207	262	306	343	370	394	406	426	439	450	462	475	488	491	

APPENDIX 2

Individual bodyweights (g) of females before pairing (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group Animal	Week of treatment
/ Sex number	0 1 2

1F	1137	216	226	239
	1138	198	209	237
	1139	203	222	242
	1140	212	227	245
	1141	197	216	224
	1142	210	224	235
	1143	188	212	235
	1144	209	232	257
	1145	199	222	238
	1146	189	205	214
	1147	196	218	236
	1148	193	207	223
	1149	216	243	259
	1150	190	215	224
	1151	196	212	229
	1152	200	213	240
	1153	209	242	269
	1154	201	223	237
	1155	215	236	255
	1156	204	226	246
	1157	201	214	224
	1158	214	237	246
	1159	194	218	233
	1160	205	224	243
	1161	195	222	230
	1162	187	213	227
	1163	206	233	243
	1164	204	220	224
	1165	196	215	220
	1166	196	210	231
	1167	214	229	247
	1168	196	206	219
	1169	207	232	255
	1170	199	224	246

APPENDIX 2 - continued

Individual bodyweights (g) of females before pairing (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group Animal	Week of treatment			
/ Sex number	0	1	2	

2F	1171	202	215	233
	1172	212	236	246
	1173	197	211	222
	1174	198	209	213
	1175	192	219	237
	1176	207	225	240
	1177	189	213	238
	1178	197	214	227
	1179	190	214	231
	1180	212	236	256
	1181	203	211	228
	1182	202	208	228
	1183	206	245	254
	1184	210	249	267
	1185	198	206	223
	1186	197	229	250
	1187	204	229	240
	1188	199	217	229
	1189	210	246	269
	1190	220	239	249
	1191	220	237	243
	1192	197	208	218
	1193	210	216	232
	1194	199	224	241
	1195	202	211	234
	1196	211	223	246
	1197	206	215	228
	1198	197	222	229
	1199	190	208	218
	1200	204	212	224
	1201	205	216	247
	1202	216	224	240
	1203	206	224	235
	1204	190	210	233

APPENDIX 2 - continued

Individual bodyweights (g) of females before pairing (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Animal	Week of treatment		
/ Sex	number	0	1	2

3F	1205	200	235	250
	1206	185	216	229
	1207	200	218	236
	1208	194	207	220
	1209	197	222	245
	1210	202	233	252
	1211	201	235	241
	1212	202	222	231
	1213	194	209	230
	1214	212	234	246
	1215	213	230	261
	1216	186	214	232
	1217	195	214	217
	1218	201	216	235
	1219	200	223	247
	1220	198	234	248
	1221	190	219	243
	1222	194	205	214
	1223	208	234	241
	1224	195	222	233
	1225	197	221	230
	1226	193	218	238
	1227	209	231	243
	1228	216	200	214
	1229	197	221	242
	1230	212	234	235
	1231	188	214	231
	1232	205	226	243
	1233	196	215	235
	1234	206	228	248
	1235	197	220	231
	1236	203	227	249
	1237	189	206	220
	1238	202	219	228

APPENDIX 2 - continued

Individual bodyweights (g) of females before pairing (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group Animal	Week of treatment		
/ Sex number	0	1	2

4F	1239	210	217	228
	1240	197	213	222
	1241	204	220	232
	1242	197	213	226
	1243	193	217	239
	1244	198	220	237
	1245	219	239	254
	1246	192	197	227
	1247	199	224	250
	1248	200	218	228
	1249	204	218	240
	1250	211	236	248
	1251	202	213	227
	1252	195	214	228
	1253	190	209	229
	1254	198	212	246
	1255	215	242	262
	1256	192	215	230
	1257	204	236	262
	1258	204	233	251
	1259	198	211	211
	1260	194	214	228
	1261	211	233	247
	1262	202	223	229
	1263	208	222	249
	1264	211	236	258
	1265	216	218	237
	1266	198	216	240
	1267	217	225	238
	1268	194	215	224
	1269	204	225	244
	1270	186	208	227
	1271	213	234	252
	1272	206	216	233

APPENDIX 3

Food intake (g/rat/week) - individual cage values for males (F₀)

Group : 1 2 3 4
Compound : Control --- SC-19129 ---
Intended dosage (mg/kg/day) : 0 250 500 750

Group	Cage number	Number of animals	Week of treatment													
			1	2	3	4	5	6	7	8	9	10	11 ^A	12	13	14
1	1	5	156	172	184	188	194	185	185	196	188	185	-	179	189	199
	2	5	164	172	186	180	190	185	181	184	175	185	-	173	189	188
	3	5	166	181	191	181	195	197	191	191	184	186	-	183	190	189
	4	5	149	170	194	184	189	189	186	192	180	179	-	173	184	192
	5	5	162	173	185	187	193	193	191	189	188	186	-	185	195	189
	6	5	165	190	197	198	198	202	198	191	189	181	-	181	192	194
	7	4	155	176	188	185	186	196	187	181	186	187	-	184	190	185
2	8	5	159	174	185	182	188	187	183	191	191	189	-	177	196	193
	9	5	169	176	194	186	179	188	192	191	184	184	-	172	180	181
	10	5	162	186	198	187	186	189	189	188	185	185	-	186	192	192
	11	5	167	190	195	194	194	194	193	196	188	190	-	182	198	205
	12	5	163	176	182	176	186	186	185	181	181	183	-	178	185	187
	13	5	162	178	188	184	188	189	191	186	181	181	-	178	192	192
	14	4	171	184	197	192	186	194	189	173	192	181	-	183	184	193

A Animals in mating.

APPENDIX 3 - continued

Food intake (g/rat/week) - individual cage values for males (F_0)

Group : 1 2 3 4
Compound : Control --- SC-19129 ---
Intended dosage (mg/kg/day) : 0 250 500 750

Group	Cage number	Number of animals	Week of treatment													
			1	2	3	4	5	6	7	8	9	10	11 ^A	12	13	14
3	15	5	171	179	190	182	193	184	186	184	181	186	-	177	185	185
	16	5	154	172	183	177	185	183	179	181	173	175	-	161	179	178
	17	5	159	173	184	185	192	198	196	193	196	198	-	180	193	193
	18	5	150	165	178	190	180	174	173	177	171	165	-	170	176	181
	19	5	156	181	192	188	189	191	187	187	185	186	-	171	184	189
	20	5	154	174	179	179	181	186	186	187	181	181	-	174	179	188
	21	4	149	167	177	179	177	177	182	172	169	175	-	172	172	182
	22	5	163	172	181	180	184	185	186	190	191	184	-	179	186	191
	23	5	163	178	185	177	184	181	184	184	174	181	-	168	169	186
	24	5	162	169	184	179	180	186	187	185	174	182	-	174	182	186
4	25	5	167	184	204	205	196	198	198	193	180	185	-	182	197	195
	26	5	156	176	195	180	186	183	191	190	174	176	-	176	188	189
	27	5	159	175	178	179	183	187	183	179	177	181	-	164	181	182
	28	4	166	175	181	187	180	183	181	165	179	177	-	164	177	178

A Animals in mating.

APPENDIX 4

Food intake (g/rat/week) -
individual cage values for females before pairing (F₀)

Group : 1 2 3 4
Compound : Control --- SC-19129 ---
Intended dosage (mg/kg/day) : 0 250 500 750

Group	Cage number	Number of animals	Week of treatment	
			1	2
1	29	5	139	134
	30	5	133	136
	31	5	133	126
	32	5	142	138
	33	5	137	129
	34	5	139	131
	35	4	145	141
2	36	5	138	129
	37	5	143	140
	38	5	137	139
	39	5	139	135
	40	5	130	122
	41	5	133	126
	42	4	147	146
3	43	5	133	126
	44	5	143	131
	45	5	141	140
	46	5	142	128
	47	5	132	126
	48	5	138	128
	49	4	128	130
4	50	5	129	124
	51	5	137	128
	52	5	130	126
	53	5	145	141
	54	5	142	133
	55	5	136	131
	56	4	137	137

APPENDIX 5

Individual oestrous cycle length, mating performance, fertility and gestation length (F₀-F₁)

Group 1: Control

Female number	Oestrous cycle length (days)	Male number	Pre-coital interval (days)	Pregnancy	Gestation length (days)
1137	4/5	1001	4	+	22½
1138	4	1002	1	+	22
1139	4	1003	2	+	22
1140	4/5	1004	2	+	T
1141	4	1005	4	+	T
1142	4	1006	3	+	T
1143	4	1007	2	+	22½
1144	5	1008	2	+	22½
1145	4	1009	2	+	T
1146	4	1010	3	+	T
1147	I.C.	1011	2	+	22½
1148	4	1012	2	+	T
1149	4	1013	3	+	22½
1150	4	1014	2	+	22½
1151	4	1015	3	+	23
1152	5	1016	3	+	T
1153	5	1017	1	+	T
1154	4	1018	3	+	23
1155	4	1019	3	+	22½
1156	4	1020	4	+	22
1157	I.C.	1021	1	+	A
1158	4	1022	2	+	22½
1159	4	1023	3	+	22½
1160	4/5	1024	1	+	T
1161	4	1025	3	+	T
1162	4	1026	2	+	T
1163	4	1027	2	+	22½
1164	4	1028	4	+	23
1165	4	1029	3	+	22
1166	4	1030	1	+	22
1167	4/5	1031	1	+	23
1168	4	1032	1	+	22
1169	4	1033	2	+	T
1170	4	1034	1	+	23

I.C. Irregular cycle.

A Dead foetus found in utero at post mortem examination at Day 25 post coitum

T Killed Day 20 post coitum for teratological examination.

APPENDIX 5 - continued

Individual oestrous cycle length, mating performance, fertility and gestation length (F₀-F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Female number	Oestrous cycle length (days)	Male number	Pre-coital interval (days)	Pregnancy	Gestation length (days)
1171	4	1035	1	+	22½
1172	4	1036	2	+	22
1173	4	1037	2	+	T
1174	4	1038	4	+	22
1175	4	1039	3	+	T
1176	4	1040	4	+	T
1177	4	1041	2	+	T
1178	4	1042	2	+	T
1179	4/5	1043	3	+	23
1180	4	1044	3	+	T
1181	I.C.	1045	2	+	22½
1182	4	1046	1	+	22
1183	A.C.	1047	9	+	T
1184	I.C.	1048	1	+	22
1185	4/5	1049	1	+	23
1186	4	1050	2	+	T
1187	4/5	1051	4	+	22½
1188	4	1052	3	+	22½
1189	4	1053	2	+	22
1190	4	1054	4	+	22½
1191	4/5	1055	3	+	22½
1192	4/5	1056	1	+	22½
1193	4	1057	1	+	22
1194	4	1058	3	+	22½
1195	4	1059	1	+	T
1196	4/5	1060	2	+	22
1197	4	1061	3	+	22½
1198	4	1062	2	+	22½
1199	4	1063	3	+	T
1200	4	1064	1	+	T
1201	4/5	1065	2	+	22½
1202	5	1066	2	+	23
1203	4	1067	3	+	22
1204	4	1068	2	+	T

I.C. Irregular cycle.

A.C. Acyclic and/or pseudopregnant.

T Killed Day 20 post coitum for teratological examination.

APPENDIX 5 - continued

Individual oestrous cycle length, mating performance, fertility and gestation length (F₀-F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Female number	Oestrous cycle length (days)	Male number	Pre-coital interval (days)	Pregnancy	Gestation length (days)
1205	4	1069	3	+	22½
1206	5	1070	1	+	22½
1207	4	1071	2	+	22
1208	4/5	1072	2	+	23½
1209	4	1073	2	+	T
1210	4	1074	2	+	T
1211	4/5	1075	4	+	22
1212	4	1076	3	+	23
1213	4/5	1077	3	+	22½
1214	4/5	1078	5	+	T
1215	5	1079	3	+	T
1216	4	1080	2	+	T
1217	4/5	1081	4	+	22
1218	4	1082	1	+	22½
1219	I.C.	1083	3	+	23
1220	4	1084	2	+	T
1221	4	1085	2	+	T
1222	4	1086	2	+	T
1223	4	1087	2	+	22½
1224	4/5	1088	4	+	T
1225	4/5	1089	1	+	22
1226	4	1090	2	+	22½
1227	4	1091	3	+	22½
1228	4	1092	1	+	22
1229	4	1093	3	+	T
1230	4/5	1094	4	+	22½
1231	4	1095	3	+	T
1232	4/5	1096	2	+	22
1233	4	1097	3	+	22½
1234	4	1098	2	+	22
1235	4	1099	4	+	23
1236	4	1100	2	+	22½
1237	4	1101	2	+	22½
1238	4/5	1102	1	+	T

I.C. Irregular cycle.

T Killed Day 20 post coitum for teratological examination.

APPENDIX 5 - continued

Individual oestrous cycle length, mating performance, fertility and gestation length (F₀-F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Female number	Oestrous cycle length (days)	Male number	Pre-coital interval (days)	Pregnancy	Gestation length (days)
1239	4	1103	4	+	22½
1240	4	1104	4	+	T
1241	4	1105	3	+	22½
1242	4	1106	2	+	22
1243	4	1107	2	+	T
1244	4	1108	3	+	T
1245	4	1109	2	+	22½
1246	4	1110	1	+	22½
1247	4	1111	10	+	T
1248	4	1112	3	+	22
1249	4	1113	1	+	23
1250	4	1114	3	+	T
1251	4/5	1115	1	+	22½
1252	4	1116	2	+	T
1253	4	1117	2	+	22½
1254	4	1118	1	+	22½
1255	4	1119	4	+	22
1256	4/5	1120	4	+	22
1257	I.C.	1121	3	+	23
1258	4	1122	2	+	22
1259	4	1123	4	+	22½
1260	4	1124	2	+	T
1261	4	1125	2	+	T
1262	4	1126	1	+	22½
1263	4/5	1127	2	+	T
1264	4	1128	2	+	T
1265	4	1129	2	+	22½
1266	4	1130	1	+	T
1267	4	1131	4	+	22½
1268	4	1132	3	+	22½
1269	4	1133	3	+	T
1270	5	1134	1	+	22½
1271	4	1135	3	+	22
1272	4	1136	1	+	22½

I.C. Irregular cycle.

T Killed Day 20 post coitum for teratological examination.

APPENDIX 6

Individual bodyweights (g) of females after mating (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Animal number	Day post coitum			
		0	6	13	20

1F	1137	246	275	310	406
	1138	262	272	304	382
	1139	242	271	302	375
	1140	247	288	333	419
	1141	238	284	317	399
	1142	242	275	298	348
	1143	238	276	307	390
	1144	259	299	334	404
	1145	234	264	287	368
	1146	222	259	294	376
	1147	232	262	292	370
	1148	224	261	291	378
	1149	262	293	326	410
	1150	226	267	290	376
	1151	231	268	304	389
	1152	244	287	328	404
	1153	290	313	349	431
	1154	245	281	318	402
	1155	261	300	333	378
	1156	261	293	325	411
	1158	247	273	302	374
	1159	240	278	313	399
	1160	272	279	315	386
	1161	237	272	304	399
	1162	233	278	325	416
	1163	249	288	321	402
	1164	248	291	330	404
	1165	224	254	273	373
	1166	256	264	300	380
	1167	265	270	300	363
	1168	238	251	277	356
	1169	251	289	319	400
	1170	272	285	312	384

1157NL	247	256	280	306
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NL No live litter, excluded from group mean values.

APPENDIX 6 - continued

Individual bodyweights (g) of females after mating (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Animal number	Day post coitum			
		0	6	13	20
2F	1171	252	269	292	380
	1172	247	278	314	384
	1173	222	254	281	361
	1174	231	269	301	373
	1175	240	283	324	406
	1176	256	297	326	377
	1177	238	273	312	391
	1178	227	259	283	362
	1179	237	263	298	376
	1180	264	309	346	418
	1181	228	259	286	368
	1182	254	268	292	378
	1183	285	314	343	417
	1184	285	301	340	431
	1185	242	260	290	364
	1186	250	302	348	437
	1187	254	273	297	382
	1188	234	266	294	365
	1189	260	312	353	423
	1190	266	310	346	440
	1191	251	297	336	428
	1192	238	250	275	350
	1193	256	263	292	384
	1194	248	286	324	411
	1195	255	280	315	401
	1196	244	285	328	407
	1197	239	273	310	405
	1198	231	264	298	356
	1199	217	252	276	354
	1200	242	256	282	366
	1201	237	278	314	400
	1202	240	276	302	402
	1203	238	264	279	362
	1204	233	272	306	407

APPENDIX 6 - continued

Individual bodyweights (g) of females after mating (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Animal number	Day post coitum 0	6	13	20
3F	1205	260	303	334	419
	1206	253	278	320	410
	1207	242	276	306	365
	1208	220	253	271	403
	1209	248	284	312	399
	1210	247	293	325	406
	1211	261	301	341	393
	1212	239	278	321	412
	1213	235	272	305	383
	1214	267	303	341	435
	1215	269	314	354	453
	1216	232	271	303	379
	1217	230	261	292	376
	1218	255	281	317	406
	1219	250	297	341	420
	1220	249	297	333	423
	1221	242	282	318	399
	1222	214	256	290	376
	1223	243	271	296	373
	1224	249	292	320	411
	1225	247	253	281	357
	1226	241	272	311	396
	1227	253	296	327	422
	1228	237	242	277	370
	1229	247	278	311	375
	1230	247	295	325	408
	1231	234	267	299	394
	1232	239	278	314	386
	1233	239	265	297	374
	1234	246	286	325	403
	1235	242	281	307	367
	1236	248	282	298	374
	1237	216	256	281	355
	1238	245	261	298	377

APPENDIX 6 - continued

Individual bodyweights (g) of females after mating (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Animal number	Day post coitum			
		0	6	13	20
4F	1239	243	277	311	398
	1240	232	266	293	385
	1241	241	273	308	386
	1242	234	288	318	391
	1243	237	271	307	377
	1244	244	271	296	374
	1245	258	303	343	436
	1246	240	267	302	374
	1247	275	308	346	410
	1248	234	260	288	364
	1249	262	286	315	374
	1250	250	284	333	391
	1251	252	254	280	344
	1252	228	252	271	346
	1253	237	283	323	412
	1254	262	279	311	394
	1255	279	316	360	453
	1256	235	274	305	387
	1257	274	298	334	436
	1258	250	285	321	421
	1259	222	257	287	356
	1260	210	252	276	347
	1261	246	288	321	412
	1262	255	281	317	395
	1263	242	281	313	401
	1264	252	295	330	417
	1265	240	265	279	366
	1266	262	266	290	360
	1267	252	291	325	429
	1268	231	273	303	400
	1269	245	272	301	351
	1270	247	267	297	382
	1271	251	279	303	388
	1272	252	268	306	374

APPENDIX 7

Food intake (g/rat/day) -
individual values for females after mating (F_0 - F_1)

Group 1 : Control

Animal number	Days <u>post coitum</u>		
	0-5	6-12	13-19
1137	25	26	29
1138	24	24	27
1139	24	26	26
1140	23	33	34
1141	26	30	31
1142	25	27	23
1143	24	28	31
1144	26	28	27
1145	21	24	27
1146	22	28	30
1147	19	21	26
1148	21	25	28
1149	28	29	28
1150	21	22	28
1151	25	26	29
1152	25	29	32
1153	27	29	32
1154	30	30	31
1155	25	27	25
1156	24	26	32
1158	20	23	28
1159	26	31	33
1160	22	23	24
1161	23	23	28
1162	25	29	33
1163	24	27	29
1164	26	26	28
1165	22	27	23
1166	22	21	26
1167	22	23	24
1168	22	23	24
1169	26	26	29
1170	24	24	24
1157NL	20	22	25

NL No live litter - excluded from group mean values.

APPENDIX 7 - continued

Food intake (g/rat/day) -
individual values for females after mating (F_0 - F_1)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Days <u>post coitum</u>		
	0-5	6-12	13-19
1171	25	26	23
1172	24	24	29
1173	22	24	29
1174	25	28	27
1175	24	28	32
1176	27	31	32
1177	23	25	28
1178	25	25	33
1179	24	31	26
1180	27	30	33
1181	24	24	28
1182	24	23	26
1183	25	29	28
1184	25	28	27
1185	22	22	25
1186	25	29	34
1187	22	23	24
1188	22	23	26
1189	27	28	30
1190	29	33	31
1191	24	27	29
1192	23	21	23
1193	20	22	23
1194	25	27	27
1195	25	26	26
1196	25	28	33
1197	22	25	27
1198	24	28	30
1199	23	22	28
1200	23	22	27
1201	23	26	30
1202	24	25	30
1203	20	19	23
1204	24	27	33

APPENDIX 7 - continued

Food intake (g/rat/day) -
individual values for females after mating (F₀-F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Days <u>post coitum</u>		
	0-5	6-12	13-19
1205	26	27	27
1206	25	25	27
1207	24	25	31
1208	20	24	29
1209	22	28	31
1210	25	27	29
1211	25	26	29
1212	29	33	33
1213	23	25	26
1214	30	33	35
1215	27	30	33
1216	23	26	31
1217	22	23	27
1218	27	26	27
1219	26	29	29
1220	27	29	37
1221	25	28	33
1222	23	26	30
1223	22	25	27
1224	26	27	29
1225	21	24	25
1226	23	27	30
1227	24	24	27
1228	20	21	22
1229	24	27	27
1230	28	29	33
1231	23	26	28
1232	23	26	31
1233	23	25	27
1234	25	29	31
1235	25	26	28
1236	24	26	31
1237	23	26	29
1238	22	24	26

APPENDIX 7 - continued

Food intake (g/rat/day) -
individual values for females after mating (F₀-F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Days <u>post coitum</u>		
	0-5	6-12	13-19
1239	25	28	31
1240	23	25	28
1241	27	26	27
1242	25	27	28
1243	20	24	28
1244	23	22	27
1245	28	32	35
1246	22	23	24
1247	25	29	30
1248	22	25	26
1249	25	24	25
1250	24	28	30
1251	20	21	22
1252	20	21	26
1253	28	30	33
1254	28	27	28
1255	26	28	29
1256	21	25	28
1257	29	29	27
1258	24	29	32
1259	29	24	27
1260	21	23	30
1261	25	27	31
1262	27	26	27
1263	26	27	36
1264	25	26	31
1265	21	24	31
1266	21	24	29
1267	24	26	30
1268	26	25	26
1269	22	24	29
1270	26	25	25
1271	24	21	24
1272	22	21	23

APPENDIX 8

Achieved dosage (mg/kg/day) -
individual values for females after mating (F₀-F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Days <u>post coitum</u>		
	0-5	6-12	13-19
1171	263	264	223
1172	251	231	271
1173	254	256	294
1174	275	280	261
1175	252	263	286
1176	268	284	297
1177	247	244	260
1178	282	263	333
1179	264	315	251
1180	259	261	281
1181	271	251	279
1182	252	234	253
1183	238	288	281
1184	234	249	228
1185	241	228	249
1186	249	254	282
1187	229	230	230
1188	242	234	257
1189	259	240	252
1190	276	287	257
1191	240	243	247
1192	259	228	240
1193	212	226	222
1194	257	252	239
1195	257	249	237
1196	259	260	293
1197	236	244	246
1198	266	284	299
1199	269	238	290
1200	254	233	272
1201	245	250	274
1202	255	247	278
1203	219	199	234
1204	261	266	302

APPENDIX 8 - continued

Achieved dosage (mg/kg/day) -
individual values for females after mating (F₀-F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Days <u>post coitum</u>		
	0-5	6-12	13-19
1205	507	483	467
1206	517	477	482
1207	509	490	602
1208	464	522	561
1209	454	536	568
1210	508	498	517
1211	488	462	515
1212	616	628	587
1213	498	494	492
1214	578	584	588
1215	509	512	533
1216	502	516	592
1217	492	474	527
1218	553	496	487
1219	522	518	497
1220	543	525	638
1221	524	532	600
1222	537	543	587
1223	470	503	526
1224	528	503	517
1225	461	512	511
1226	492	528	553
1227	480	439	470
1228	458	461	443
1229	502	523	513
1230	567	533	587
1231	504	524	526
1232	488	501	577
1233	501	507	524
1234	516	541	555
1235	525	504	541
1236	497	511	601
1237	535	552	594
1238	477	489	502

APPENDIX 8 - continued

Achieved dosage (mg/kg/day) -
individual values for females after mating (F₀-F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Days <u>post coitum</u>		
	0-5	6-12	13-19
1239	792	814	855
1240	761	765	807
1241	865	765	761
1242	789	762	772
1243	648	710	800
1244	735	663	788
1245	822	847	878
1246	715	691	694
1247	733	867	827
1248	733	780	780
1249	751	683	709
1250	740	776	810
1251	651	672	689
1252	686	687	824
1253	887	847	878
1254	852	783	776
1255	720	708	697
1256	679	738	791
1257	835	785	685
1258	739	818	843
1259	997	754	821
1260	749	745	941
1261	771	758	827
1262	830	743	741
1263	819	777	986
1264	753	711	811
1265	685	754	940
1266	655	738	872
1267	728	722	778
1268	850	742	723
1269	701	716	869
1270	833	758	720
1271	746	617	679
1272	697	626	661

APPENDIX 9

Individual litter data - females killed on Day 20 of gestation (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a) Small foetus (less than 2.70 g).
- b) Large foetus (more than 4.00 g).
- c) Shiny skin.
- d) Subcutaneous haemorrhage on head.
- e) Subcutaneous haemorrhage on body.
- f) Pale-green area on placenta.
- g) Large placenta (more than 0.70 g).
- h) Thyroid glands dark/haemorrhagic.
- j) Haemorrhagic area on wall of innominate artery.
- k) Free blood in abdominal cavity.
- m) Adrenal glands increased in size.
- n) Adrenal glands dark.
- p) Unilateral hydronephrosis.
- q) Bilateral hydronephrosis.
- r) Unilateral hydroureter.
- s) Bilateral hydroureter.
- t) Right horn of uterus thread-like.
- u) Grossly abnormal foetus : Face cleft; vertebral column exposed; ears displaced caudally; amniotic fluid red.

APPENDIX 9

Individual litter data - females killed on Day 20 of gestation (F_0-F_1)

Group 1 : Control

Animal number	Corpora lutea count	Implantations	Viable young		Resorptions		Implantation loss (%)		Foetal weight (g)		Placental weight (g)		Observations
			M	F	Total	Early	Late	Total	Pre-	Post-	Mean	S.D.	
1140	16	16	7	8	15	0	1	1	0.0	6.3	2.98	0.12	-
1141	19	15	8	6	14	1	0	1	21.1	6.7	3.25	0.08	-
1142	16	12	6	6	12	0	0	0	25.0	0.0	3.26	0.18	3g
1145	16	15	10	5	15	0	0	0	6.3	0.0	3.03	0.35	1a,1ac,1hm,1m,1mn
1146	15	14	5	8	13	1	0	1	6.7	7.1	3.33	0.28	1a,lr
1148	17	17	9	6	15	1	1	2	0.0	11.8	3.34	0.43	1aqs,1g
1152	15	14	5	7	12	1	1	2	6.7	14.3	3.20	0.42	2a
1153	17	13	3	8	11	2	0	2	23.5	15.4	3.23	0.25	1g,1r
1160	14	13	5	8	13	0	0	0	7.1	0.0	3.36	0.24	-
1161	17	17	7	9	16	1	0	1	0.0	5.9	3.49	0.16	1s
1162	17	17	8	7	15	1	1	2	0.0	11.8	3.20	0.23	-
1169	16	15	7	7	14	1	0	1	6.3	6.7	3.39	0.20	-

APPENDIX 9 - continued

Individual litter data - females killed on Day 20 of gestation (F₀-F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Corpora lutea count	Implantations	Viable young		Resorptions		Implantation loss (%)		Foetal weight (g)		Placental weight (g)		Observations
			M	F	Total	Early	Late	Total	Pre-	Post-	Mean	S.D.	
1173	14	14	5	8	13	1	0	1	0.0	7.1	3.10	0.30	0.53 0.08 2a,1p
1175	22	11	4	7	11	0	0	0	50.0	0.0	3.16	0.16	0.49 0.05 -
1176	19	18	10	6	16	1	1	2	5.3	11.1	3.21	0.21	0.49 0.05 -
1177	17	14	5	9	14	0	0	0	17.6	0.0	3.30	0.15	0.47 0.05 1s
1178	19	17	5	10	15	1	1	2	10.5	11.8	3.24	0.23	0.43 0.07 -
1180	14	14	4	8	12	1	1	2	0.0	14.3	3.35	0.11	0.51 0.07 1r
1183	17	17	4	13	17	0	0	0	0.0	0.0	3.55	0.19	0.54 0.08 1g
1186	17	15	5	10	15	0	0	0	11.8	0.0	3.56	0.24	0.57 0.07 -
1195	20	15	7	7	14	0	1	1	25.0	6.7	3.60	0.31	0.54 0.11 1g
1199	15	12	8	3	11	1	0	1	20.0	8.3	3.65	0.29	0.51 0.06 -
1200	17	15	7	8	15	0	0	0	11.8	0.0	3.39	0.29	0.47 0.03 1k,1p
1204	17	17	7	10	17	0	0	0	0.0	0.0	3.51	0.20	0.50 0.05 1pr

APPENDIX 9 - continued

Individual litter data - females killed on Day 20 of gestation (F₀-F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Corpora lutea count	Implantations	Viable young		Resorptions		Implantation loss (%)		Foetal weight (g)		Placental weight (g)		Observations
			M	F	Total	Early	Late	Total	Pre-	Post-	Mean	S.D.	
1209	17	15	6	9	15	0	0	0	11.8	0.0	3.16	0.26	1a
1210	17	16	9	7	16	0	0	0	5.9	0.0	3.13	0.30	1a
1214	20 ^Δ	21	11	9	20	0	1	1	0.0	4.8	3.03	0.34	3a,1h
1215	21	18	6	11	17	1	0	1	14.3	5.6	3.28	0.25	1r,1s
1216	16	13	6	7	13	0	0	0	18.8	0.0	3.00	0.29	2a,1f
1220	18	17	11	6	17	0	0	0	5.6	0.0	3.14	0.35	1a,1ade,1g
1221	17	16	8	8	16	0	0	0	5.9	0.0	3.51	0.19	-
1222	17	15	8	6	14	1	0	1	11.8	6.7	3.20	0.28	1a
1224	15	15	8	7	15	0	0	0	0.0	0.0	3.16	0.17	-
1229	15 ^Δ	16	6	8	14	2	0	2	0.0	12.5	3.06	0.33	3a
1231	18	17	11	6	17	0	0	0	5.6	0.0	3.51	0.22	1d,1g,1j,1r
1238	16	15	7	8	15	0	0	0	6.3	0.0	3.27	0.23	1a

Δ Number of implantations substituted in calculation of pre-implantation loss.

APPENDIX 9 - continued

Individual litter data - females killed on Day 20 of gestation (F₀-F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Corpora lutea count	Implantations	Viable young		Resorptions		Implantation loss (%)		Foetal weight (g)		Placental weight (g)		Observations
			M	F	Total	Early	Late	Total	Pre-	Post-	Mean	S.D.	
1240	17	15	9	6	15	0	0	0	11.8	0.0	3.35	0.20	1r
1243	16	15	6	7	13	1	1	2	6.3	13.3	3.37	0.22	1r,1s
1244	15	15	7	5	12	1	2	3	0.0	20.0	3.62	0.21	1r,1s
1247	16	16	8	8	16	0	0	0	0.0	0.0	2.78	0.30	4a,1t
1250	12	11	6	4	10	1	0	1	8.3	9.1	3.37	0.35	1g
1252	14	14	5	8	13	1	0	1	0.0	7.1	3.37	0.18	-
1260	11	11	4	6	10	0	1	1	0.0	9.1	3.65	0.17	-
1261	16	15	7	8	15	0	0	0	6.3	0.0	3.60	0.24	1g
1263	18	15	11	3	14	1	0	1	16.7	6.7	3.72	0.17	-
1264	17	16	5	10	15	0	1	1	5.9	6.3	3.76	0.16	1bps,2s
1266	17	16	10	5	15	1	0	1	5.9	6.3	3.14	0.23	-
1269 ^a	19	5	2	3	5	0	0	0	73.7	0.0	3.46	0.61	1au,1g

^a Unilateral implantation

APPENDIX 10

Individual foetal observations at free-hand serial sectioning (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a) Haemorrhagic peritoneal fluid.
- b) Subcutaneous oedema - trunk.
- c) Subcutaneous scapular haemorrhage.
- d) Hepatic haemorrhage.
- e) Space between bodywall and organs.
- f) Unilateral hydronephrosis.
- g) Bilateral hydronephrosis.
- h) Unilateral hydroureter.
- j) Bilateral hydroureter.
- k) Haemorrhagic abdomen.
- m) Subcutaneous cranial haemorrhage.
- n) Subcutaneous nasal haemorrhage.
- p) Testis displaced toward midline/cranially.
- q) Subcutaneous haemorrhage(s) - fore/hind limb(s).
- r) Localised internal abdominal haemorrhage.
- s) Subcutaneous haemorrhage - tail.
- t) Intra-muscular nasal haemorrhage.
- u) Intra-muscular haemorrhage - lower jaw.
- v) Slight unilateral microphthalmia.
- w) Subcutaneous dorsal cervical haemorrhage.
- x) Subcutaneous lateral/ventral thoracic haemorrhage.
- y) Blood in mouth.
- z) Subcutaneous lateral/dorsal/ventral abdominal haemorrhage.
- A) Subcutaneous submandibular haemorrhage.
- B) Slight dilatation of lateral ventricles.
- C) Pulmonary haemorrhage.
- D) Haemorrhages on surface of lung lobes.
- E) Slightly kinked tip of tail.
- F) Genital tubercle slightly elongated.
- G) Slightly increased quantity of flocculent pleural fluid.
- H) Cleft face; unilateral ablepharon; unilateral anophthalmia; craniorrachischisis with subsequent displacement and distortion of cranial, thoracic and abdominal tissues.

APPENDIX 10 - continued

Individual foetal observations at free-hand serial sectioning (F₁)

Group 1 : Control

Animal number	Number of foetuses examined	Sex		Observations
		M	F	
1140	7	2	5	1aqtu; 1c; 1cms; 1cq; 1cu; 1dkq; 1rs
1141	7	5	2	1cd
1142	6	3	3	2c; 1k;
1145	7	3	4	1c; 1cdeqvwz; 1q; 1x;
1146	6	1	5	1u;
1148	8	7	1	1b;
1152	6	3	3	1eqs; 2q; 1u;
1153	5	-	5	1cdkq; 1dy; 1u;
1160	6	2	4	-
1161	8	3	5	1cdmq; 1dk; 1h;
1162	7	3	4	1c;
1169	7	3	4	2c; 1d;

APPENDIX 10 - continued

Individual foetal observations at free-hand serial sectioning (F₁)

Group 2 : SC-19129: 250 mg/kg/day (intended)

Animal number	Number of foetuses examined	Sex		Observations
		M	F	
1173	6	2	4	3c; 1dq;
1175	5	1	4	1cd; 1t;
1176	8	4	4	1c; 1d; 1dq;
1177	7	2	5	-
1178	8	3	5	1g; 1h;
1180	6	3	3	1q; 1u;
1183	8	3	5	2a; 4d; 1k; 1u;
1186	7	3	4	1au; 1cn; 2d; 2u;
1195	7	4	3	1d; 1mq; 1u;
1199	5	5	-	1u;
1200	7	2	5	2c; 1qu;
1204	9	4	5	1cdq; 1d; 1dk;

APPENDIX 10 - continued

Individual foetal observations at free-hand serial sectioning (F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Number of fetuses examined	Sex		Observations
		M	F	
1209	7	2	5	1c; 1cd; 1equA; 1x; 1A;
1210	8	5	3	1cd; 2d; 1eB;
1214	10	5	5	2c; 1cequ; 1cu; 1d; 1du; 1e; 1mq;
1215	8	2	6	1d;
1216	7	4	3	1h;
1220	9	6	3	1cdq; 1cdqtu; 1cemqwzDE; 1d; 1dsC; 1q; 1qs;
1221	8	4	4	2c; 2d; 1cdp;
1222	7	4	3	1c; 1cd; 1cf; 1d; 1eq;
1224	8	5	3	1c; 1d; 1e; 1q;
1229	7	3	4	1c; 1eqBF; 1f;
1231	8	7	1	2c; 1d;
1238	7	3	4	1a; 1d;

APPENDIX 10 - continued

Individual foetal observations at free-hand serial sectioning (F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Number of foetuses examined	Sex		Observations
		M	F	
1240	7	3	4	-
1243	6	2	4	2c; 1cd; 2d;
1244	6	4	2	1c; 1p; 1A;
1247	8	5	3	1c; 1cquw; 1d; 2q; 1qt; 1su;
1250	5	2	3	-
1252	6	2	4	2c; 1cq;
1260	5	2	3	1h;
1261	7	5	2	1c; 1d; 2du; 1dG; 1ku; 1q;
1263	7	6	1	1cdfq; 1d; 1u;
1264	7	1	6	1a; 1d;
1266	7	6	1	2b; 1cq;
1269	2	1	1	1egjpquzH; 1h;

APPENDIX 11

Individual foetal observations at skeletal examination (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a) Incomplete ossification of supraoccipital bone.
- b) Incomplete ossification of interparietal bone.
- c) Incomplete ossification of one or both parietal bones.
- d) Small additional plaque of bone in parietal suture.
- e) Incomplete ossification of squamosal bones.
- g) Incomplete ossification of hyoid bone.
- h) Absence of hyoid bone.
- i) 1st sternebra cleft.
- n) 13th rib(s) reduced in length.
- p) Incomplete ossification or absence of one or both pubic bones.
- q) Inner corners absent from one or both scapulae.
- r) Ossification of all cervical vertebral centra.
- s) Incomplete ossification of caudal vertebrae, less than 5 vertebrae ossified.
- t) Incomplete ossification of one or more thoracic vertebral centra.
- u) Incomplete ossification of one or more lumbar vertebral centra.
- v) Incomplete ossification of one or more sacral and/or lumbar vertebral arches.
- w) Incomplete ossification or absence of metacarpals/metatarsals.
- x) Ossification of one or more phalangeal bones.
- y) Incomplete ossification of ischial bones.
- z) Ossification of ventral arch of 1st cervical vertebra.
- A) Asymmetric pelvis, ilia associated with different sacral vertebrae.
- B) 25 presacral vertebrae.
- D) Incomplete ossification of one or more cervical vertebral arches.
- E) Small discrete unossified area in frontal bone.

APPENDIX 11 - continued

Individual foetal observations at skeletal examination (F₁)

Group 1 : Control

Animal number	Number of foetuses examined	Incomplete ossification of sternbrae: number of bones affected						Number of ribs				Number of meta carpals/tarsals		Size of anterior fontanelle			Observations
		1	2	3	4	5	6	13	13/14	14	14	3/4	4/4	Small	Medium	Large	
1140	8	-	2	3	3	-	-	8	-	-	-	8	-	-	7	1	1abgps, lbp, lbpt, lp, lpt
1141	7	1	6	-	-	-	-	7	-	-	-	3	4	1	6	-	1b, lg, lr8, lz
1142	6	-	5	1	-	-	-	6	-	-	-	2	4	-	6	-	lg, 2t
1145	8	-	2	6	-	-	-	8	-	-	-	7	1	-	8	-	labip, lb, lg, 2hit
1146	7	-	7	-	-	-	-	6	-	1	-	6	1	-	7	-	lab, lbh, lh, lz
1148	7	-	6	-	1	-	-	7	-	-	-	1	5	-	6	1	labipstw, lb, lt, lz
1152	6	-	6	-	-	-	-	6	-	-	-	5	1	-	6	-	ltz
1153	6	-	6	-	-	-	-	6	-	-	-	3	3	-	6	-	lt
1160	7	-	6	1	-	-	-	7	-	-	-	7	-	-	7	-	lb, 3t
1161	8	2	5	1	-	-	-	8	-	-	-	3	5	1	7	-	lhp, lhtz, 3z
1162	8	-	7	1	-	-	-	8	-	-	-	6	2	1	7	-	3t
1169	7	2	5	-	-	-	-	7	-	-	-	-	-	-	7	-	2t, ltz

APPENDIX 11 - continued

Individual foetal observations at skeletal examination (F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Number of foetuses examined	Incomplete ossification of sternebrae: number of bones affected						Number of ribs			Number of meta carpal/s/ tarsals		Size of anterior fontanelle			Observations	
		1	2	3	4	5	6	13	13/14	14	3/4	4/4	Small	Medium	Large		
1173	7	1	6	-	-	-	-	7	-	-	6	1	-	-	6	1	lab, lp, lq, lr, 2z
1175	6	-	4	1	1	-	-	6	-	-	6	-	-	-	6	-	labgpyw0, lbcegyz, lbp, lptv, lt
1176	8	-	5	3	-	-	-	8	-	-	8	-	-	-	8	-	labgpty, labpv, lgpt, lpt, lt, lte
1177	7	-	7	-	-	-	-	7	-	-	3	4	-	-	7	-	-
1178	7	1	5	1	-	-	-	7	-	-	5	2	-	-	7	-	li, lr, lt
1180	6	-	5	1	-	-	-	6	-	-	5	1	-	-	6	-	lb, lg
1183	9	1	7	1	-	-	-	9	-	-	3	6	-	-	8	1	2b, lbqz, lbx, 2bz, lqz, lt, lxz
1186	8	6	1	-	-	-	-	8	-	-	3	5	-	-	8	-	lq, lt, ltx
1195	7	-	6	-	1	-	-	7	-	-	2	5	-	-	7	-	lah, lb, lq, 2z
1199	6	-	6	-	-	-	-	6	-	-	3	3	-	-	6	-	lgt, 3t
1200	8	-	7	1	-	-	-	8	-	-	4	4	-	-	8	-	lr, lt, lz
1204	8	-	7	1	-	-	-	8	-	-	4	4	-	-	8	-	labgt, lbh, lbt, lt

APPENDIX 11 - continued

Individual foetal observations at skeletal examination (F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Number of foetuses examined	Incomplete ossification of sternebrae: number of bones affected										Number of ribs of ribs	Number of meta carpals/tarsals		Size of anterior fontanelle			Observations
		1	2	3	4	5	6	13	13	14	14		3/4	4/4	Small	Medium	Large	
1209	8	-	8	-	-	-	-	8	-	-	-	-	8	-	-	8	-	1agt, 1ah, 1ahD, 2b, 1bn
1210	8	-	6	-	2	-	-	8	-	-	-	-	5	3	-	8	-	1b, 1bp, 2t
1214	10	-	10	-	-	-	-	10	-	-	-	-	9	1	-	10	-	1abp, 2b, 2h, 1ht, 1tz
1215	9	1	8	-	-	-	-	9	-	-	-	-	7	2	-	9	-	1t, 1tz, 1z
1216	6	-	2	1	3	-	-	6	-	-	-	-	5	1	-	5	1	1abstD, 1bt, 1bD
1220	8	-	6	2	-	-	-	7	1	-	-	-	8	-	-	8	-	1hq, 2t, 1tz
1221	8	-	6	2	-	-	-	7	1	-	-	-	-	8	1	7	-	1b, 2t, 1x
1222	7	1	6	-	-	-	-	7	-	-	-	-	5	2	-	7	-	1b, 1bt, 1q, 2t
1224	7	-	2	4	-	-	1	7	-	-	-	-	7	-	-	7	-	1abpwtD, 1bgt, 1gpy
1229	7	-	4	2	1	-	-	7	-	-	-	-	7	-	-	7	-	3g, 1h
1231	9	1	7	-	1	-	-	9	-	-	-	-	3	6	-	9	-	1i, 1it, 4t
1238	8	2	6	-	-	-	-	8	-	-	-	-	1	7	1	7	-	1dq, 1n, 1mtAB, 1t

APPENDIX 11 - continued

Individual foetal observations at skeletal examination (F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Number of foetuses examined	Incomplete ossification of sternebrae: number of bones affected										Number of ribs of ribs	Number of meta carpals/tarsals		Size of anterior fontanelle			Observations
													3/4	4/4				
		1	2	3	4	5	6	13	13/14	14		Small			Medium	Large		
1240	8	3	3	2	-	-	-	8	-	-	4	4	-	8	-	1brtAB, 3i, 1tB		
1243	7	-	6	1	-	-	-	7	-	-	4	3	-	7	-	1q, 2t		
1244	6	1	5	-	-	-	-	6	-	-	2	4	-	6	-	1x		
1247	8	1	6	-	-	1	-	8	-	-	7	-	-	8	-	1abehpw, 1b, 1bet, 3t, 1z		
1250	5	-	5	-	-	-	-	5	-	-	3	1	-	5	-	1abchD, 1abgtwD, 1abhpw, 1bhqt		
1252	7	-	6	-	1	-	-	7	-	-	2	5	-	7	-	1ab, 1abh, 2b		
1260	5	2	3	-	-	-	-	5	-	-	1	4	-	5	-	1t, 1xz		
1261	8	1	7	-	-	-	-	8	-	-	4	4	-	8	-	1q, 2t		
1263	7	2	4	-	-	-	-	7	-	-	2	5	-	6	1	1b, 1bcegz, 1bz, 1t		
1264	8	3	2	-	-	-	-	8	-	-	2	6	-	8	-	1dx, 1t, 3tz, 1z		
1266	8	-	7	-	1	-	-	8	-	-	7	-	-	8	-	1a, 1abcegpw, 1abcehpwD, 1tu		
1269	3	-	3	-	-	-	-	3	-	-	-	3	-	3	-	1g		

APPENDIX 12

Individual bodyweights (g) of females during lactation (F₀ - F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group Animal / Sex number	1	Day post partum				
		4	7	14	21	
1F 1137	300	299	306	326	322	
1138	314	322	337	355	349	
1139	282	293	275	332	326	
1143	308	321	323	332	319	
1144	328	339	347	347	314	
1147	293	300	303	282	306	
1149	316	337	336	345	323	
1150	243	280	293	314	321	
1151	297	311	316	334	313	
1154	292	308	305	313	315	
1155	302	318	331	318	339	
1156	329	325	327	348	351	
1158	279	279	295	320	332	
1159	308	310	320	335	329	
1163	326	311	310	317	309	
1164	277	314	332	351	319	
1165	267	278	295	279	312	
1166	270	290	309	331	321	
1167	299	314	324	348	318	
1168	275	279	294	310	300	
1170	279	293	298	320	307	

1157NL

NL No live litter

APPENDIX 12 - continued

Individual bodyweights (g) of females during lactation (F₀ - F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group Animal / Sex number	Day post partum				
	1	4	7	14	21
2F 1171	260	279	287	314	307
1172	312	306	314	333	339
1174	288	302	302	325	305
1179	293	309	313	318	306
1181	277	283	295	312	294
1182	261	297	300	338	317
1184	330	329	330	339	328
1185	258	282	300	307	309
1187	260	300	306	329	317
1188	285	291	305	324	317
1189	336	356	362	374	349
1190	332	325	324	344	360
1191	315	329	341	361	351
1192	269	279	298	312	274
1193	284	301	303	326	323
1194	325	327	336	354	341
1196	324	336	349	364	379
1197	290	313	333	342	330
1198	294	305	316	283	303
1201	311	315	321	340	359
1202	272	300	304	295	299
1203	278	286	292	309	299

APPENDIX 12 - continued

Individual bodyweights (g) of females during lactation (F₀ - F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / Sex	Animal number	Day post partum				
		1	4	7	14	21
3F	1205	323	334	349	362	369
	1206	288	320	337	360	316
	1207	294	310	326	340	330
	1208	263	261	270	283	305
	1211	326	318	Litter died		
	1212	324	321	318	328	311
	1213	296	305	320	338	311
	1217	274	282	Litter died		
	1218	303	316	326	354	346
	1219	326	343	351	364	376
	1223	290	294	295	282	293
	1225	262	292	291	305	318
	1226	312	322	336	365	321
	1227	333	338	353	354	363
	1228	245	265	278	308	284
	1230	312	323	322	346	338
	1232	324	333	347	373	370
	1233	293	303	312	292	313
	1234	300	315	303	347	355
1235	268	303	314	341	318	
1236	283	313	317	293	340	
1237	278	288	301	323	316	

APPENDIX 12 - continued

Individual bodyweights (g) of females during lactation (F₀ - F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Animal / Sex number	Day post partum				
		1	4	7	14	21
4F	1239	266	289	307	321	303
	1241	306	312	315	332	307
	1242	313	318	331	356	350
	1245	333	340	351	350	355
	1246	268	285	296	329	332
	1248	283	289	290	308	296
	1249	308	315	330	349	330
	1251	269	274	280	298	287
	1253	319	326	320	297	322
	1254	307	316	311	331	334
	1255	334	340	343	358	368
	1256	301	307	316	348	333
	1257	296	309	321	338	336
	1258	312	323	337	360	338
	1259	292	295	292	307	278
	1262	312	314	327	358	343
	1265	260	274	293	317	315
	1267	297	326	335	350	339
	1268	281	298	310	305	325
	1270	266	277	291	324	327
	1271	294	302	308	309	317
	1272	281	287	301	320	308

APPENDIX 13

Food intake (g/rat/day) -
individual values for females during lactation (F_0 - F_1)

Group 1 : Control

Animal number	Days <u>post partum</u>		
	1-6	7-13	14-20 ^A
1137	42	50	65
1138	48	55	72
1139	30	45	56
1143	32	52	65
1144	41	58	70
1147	37	43	76
1149	37	50	67
1150	34	50	73
1151	49	53	71
1154	47	58	75
1155	33	45	71
1156	31	46	68
1158	36	54	79
1159	29	58	74
1163	28	50	66
1164	47	63	68
1165	33	42	67
1166	34	52	63
1167	41	59	73
1168	34	52	60
1170	32	46	64
1157 NL			

A Includes food eaten by offspring.
NL No live litter.

APPENDIX 13 - continued

Food intake (g/rat/day) -
individual values for females during lactation (F₀-F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Days <u>post partum</u>		
	1-6	7-13	14-20 ^A
1171	46	56	67
1172	28	54	62
1174	38	53	68
1179	38	47	71
1181	35	52	65
1182	46	66	65
1184	43	57	62
1185	40	55	76
1187	43	57	68
1188	31	49	75
1189	35	55	65
1190	33	46	64
1191	42	58	81
1192	37	53	69
1193	34	56	65
1194	39	53	73
1196	28	53	70
1197	38	52	66
1198	36	44	77
1201	34	53	80
1202	37	46	75
1203	29	45	63

A Includes food eaten by offspring.

APPENDIX 13 - continued

Food intake (g/rat/day) -
individual values for females during lactation (F₀-F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Days <u>post partum</u>		
	1-6	7-13	14-20 ^A
1205	35	48	67
1206	40	61	72
1207	31	52	62
1208	18	23	36
1212	42	52	71
1213	42	50	72
1218	38	53	67
1219	40	54	74
1223	37	46	73
1225	37	57	70
1226	38	65	74
1227	31	48	69
1228	37	53	66
1230	43	64	81
1232	40	59	73
1233	37	45	74
1234	34	50	72
1235	47	57	71
1236	40	47	85
1237	34	51	62
1211	LD		
1217	LD		

A Includes food eaten by offspring.
LD Litter died.

APPENDIX 13 - continued

Food intake (g/rat/day) -
individual values for females during lactation (F₀-F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Days <u>post partum</u>		
	1-6	7-13	14-20 ^A
1239	51	58	72
1241	46	57	76
1242	38	52	75
1245	35	52	70
1246	28	50	71
1248	33	46	65
1249	40	52	67
1251	29	48	58
1253	40	43	78
1254	39	57	84
1255	31	47	63
1256	38	54	70
1257	36	57	64
1258	38	54	69
1259	40	52	65
1262	40	58	83
1265	34	54	76
1267	40	54	64
1268	35	45	70
1270	32	51	66
1271	35	43	59
1272	30	54	63

A Includes food eaten by offspring.

APPENDIX 14

Achieved dosage (mg/kg/day) -
individual values for females during lactation (F₀-F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Days post partum		
	1-6	7-13	14-20 ^A
1171	321	283	
1172	171	254	
1174	246	257	
1179	239	226	
1181	233	260	
1182	313	314	
1184	248	259	
1185	273	275	
1187	290	273	
1188	200	237	
1189	191	227	
1190	192	209	
1191	244	251	
1192	249	264	
1193	221	271	
1194	225	234	
1196	159	226	
1197	233	234	
1198	225	223	
1201	205	244	
1202	245	233	
1203	194	228	

A Offspring consuming diet; concentration of chemical in
diet maintained at levels set for Days 7-13 post partum.

APPENDIX 14 - continued

Achieved dosage (mg/kg/day) -
individual values for females during lactation (F₀-F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Days post partum		
	1-6	7-13	14-20 ^A
1205	397	410	
1206	488	532	
1207	382	475	
1208	258	253	
1212	499	489	
1213	520	462	
1218	461	474	
1219	451	459	
1223	483	485	
1225	511	581	
1226	447	564	
1227	345	413	
1228	540	550	
1230	517	583	
1232	455	498	
1233	467	453	
1234	430	468	
1235	616	529	
1236	509	468	
1237	448	497	
1211	LD		
1217	LD		

A Offspring consuming diet; concentration of chemical
in diet maintained at levels set for Days 7-13 post partum.
LD Litter died.

APPENDIX 14 - continued

Achieved dosage (mg/kg/day) -
individual values for females during lactation (F₀-F₁)

Group 4 : SC-19129 :750 mg/kg/day (intended)

Animal number	Days post partum		
	1-6	7-13	14-20 ^A
1239	1019	843	
1241	848	804	
1242	676	691	
1245	586	677	
1246	568	730	
1248	659	702	
1249	718	699	
1251	605	758	
1253	717	636	
1254	722	810	
1255	524	612	
1256	705	742	
1257	668	789	
1258	670	707	
1259	784	792	
1262	717	773	
1265	704	808	
1267	725	719	
1268	678	668	
1270	658	757	
1271	666	636	
1272	590	793	

A Offspring consuming diet; concentration of chemical
in diet maintained at levels set for Days 7-13 post partum.

APPENDIX 15

Individual litter sizes (F₁)

Group 1 : Control

Animal number	Implan- tation sites	Total at Day 1 post partum	Number alive on Day post partum					
			1	4	4 ⁺	7	14	21
1137	18	17	17	14	8	8	8	8
1138	12	11	11	11	8	8	8	8
1139	15	15	15	15	8	8	8	8
1143	16	14	13	13	8	8	8	8
1144	16	14	14	14	8	8	8	8
1147	13	11	11	11	8	8	8	8
1149	15	13	13	13	8	8	8	8
1150	16	16	15	12	8	8	8	8
1151	14	13	13	13	8	8	8	8
1154	16	16	15	14	8	8	8	8
1155	19	17	16	14	8	8	8	8
1156	12	12	12	9	8	8	8	8
1158	15	14	11	10	8	8	8	8
1159	13	12	11	11	8	8	8	8
1163	13	13	13	13	8	8	8	8
1164	15	15	15	15	8	8	8	8
1165	15	14	14	13	8	8	8	8
1166	15	15	14	11	8	8	8	8
1167	14	10	10	10	8	8	8	8
1168	13	13	13	13	8	8	8	8
1170	18	15	14	14	8	8	8	8
1157	NL	1						

+ Following litter size adjustment.

NL No live litter, single foetus present in utero
at necropsy Day 25 post coitum; excluded from group mean values.

APPENDIX 15 - continued

Individual litter sizes (F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Implan- tation sites	Total at Day 1 post partum	Number alive on Day post partum					
			1	4	4 ⁺	7	14	21
1171	17	17	17	12	8	8	8	8
1172	15	14	14	8	8	7	7	7
1174	13	13	13	13	8	8	8	8
1179	15	13	13	13	8	8	8	8
1181	15 [#]	16	16	16	8	8	8	8
1182	15	15	15	15	8	8	8	8
1184	16	16	16	16	8	8	8	8
1185	14	14	13	13	8	8	8	8
1187	17	14	14	13	8	8	8	8
1188	13	12	12	12	8	8	8	8
1189 ^{\$}	10	10	10	10	8	8	8	8
1190	15 [#]	16	16	14	8	8	8	8
1191	16	14	14	14	8	8	8	8
1192	14	12	12	12	8	8	8	8
1193	17	16	14	14	8	8	8	8
1194	15	14	13	13	8	8	8	8
1196	14	13	13	13	8	8	8	8
1197	18	16	16	15	8	8	8	8
1198	15	10	10	10	8	8	8	8
1201	15	15	15	15	8	8	8	8
1202	17	16	16	16	8	8	8	8
1203	14	14	14	12	8	8	8	8

+ Following litter size adjustment.

^{\$} Unilateral implantations.

[#] Total at Day 1 substituted in calculation of post-implantation survival index.

APPENDIX 15 - continued

Individual litter sizes (F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Implan- tation sites	Total at Day 1 post partum	Number alive on Day post partum					
			1	4	4 ⁺	7	14	21
1205	16	16	16	9	8	8	8	8
1206	15	14	14	13	8	8	8	8
1207	14	11	11	10	8	8	8	8
1208 ^{\$}	4	3	3	2	2	2	2	2
1211	16	15	15	1	1	Litter died		
1212	16	13	13	13	8	8	8	8
1213	15	13	13	13	8	8	8	8
1217	15	14	14	3	3	Litter died		
1218	18	15	14	9	8	8	7	7
1219	13	12	12	9	8	8	8	8
1223	16	15	15	15	8	8	8	8
1225	15	12	12	12	8	8	8	8
1226	15	14	14	13	8	8	8	8
1227	16	14	14	12	8	8	8	8
1228	15	14	14	14	8	8	8	8
1230	16	15	15	15	8	8	8	8
1232	13	12	12	11	8	8	8	8
1233	11	11	11	11	8	8	8	8
1234	17	17	16	9	8	8	8	8
1235	16	10	10	10	8	8	8	8
1236	16	14	14	14	8	8	8	8
1237	14	12	12	12	8	8	8	8

^{\$} Unilateral implantations.

⁺ Following litter size adjustment.

APPENDIX 15 - continued

Individual litter sizes (F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Implan- tation sites	Total at Day 1 post partum	Number alive on Day post partum					
			1	4	4 ⁺	7	14	21
1239	19	17	17	13	8	8	7	7
1241	15	13	13	12	8	8	8	8
1242	14	13	13	13	8	8	8	8
1245	16	15	15	13	8	8	8	8
1246	14	14	13	13	8	8	8	8
1248	12	12	12	12	8	8	8	8
1249	11	9	7	7	7	7	6	6
1251	13	11	11	11	8	8	8	8
1253	16	14	13	12	8	8	8	8
1254	15	14	14	14	8	8	8	8
1255	20	18	17	14	8	8	7	7
1256	17	15	15	15	8	8	8	7
1257	20	19	16	13	8	8	8	8
1258	19	18	18	14	8	8	8	8
1259	15	13	13	13	8	8	8	8
1262	13	13	12	12	8	8	8	8
1265	17	15	15	15	8	8	8	8
1267	16	16	15	15	8	8	8	8
1268	17	16	16	16	8	8	8	8
1270	17	16	15	14	8	8	8	8
1271	17	15	15	15	8	8	8	8
1272	14	14	14	9	8	8	8	8

+ Following litter size adjustment.

APPENDIX 16

Individual litter mean bodyweights (g) of offspring (F₁)

Group 1 : Control

Animal number		Day post partum				
		1	4	7	14	21
1137	Mean	5.5	6.9	10.0	25.6	41.7
	S.D.	0.4	0.9	2.3	4.6	7.5
1138	Mean	6.3	8.7	14.1	31.5	51.1
	S.D.	0.6	0.5	1.1	1.6	3.6
1139	Mean	5.2	6.8	9.6	22.5	36.1
	S.D.	0.3	0.8	0.7	1.7	2.5
1143	Mean	5.9	8.2	13.5	30.5	49.6
	S.D.	0.4	0.9	2.2	3.5	6.5
1144	Mean	6.7	9.5	15.8	34.5	55.6
	S.D.	0.5	1.1	1.6	2.2	4.3
1147	Mean	7.1	9.8	16.4	31.5	53.6
	S.D.	0.3	0.6	0.7	0.7	2.3
1149	Mean	5.8	8.2	13.8	32.0	51.9
	S.D.	0.5	0.8	1.2	1.6	2.3
1150	Mean	5.8	8.2	14.3	33.4	53.8
	S.D.	0.5	1.8	3.9	5.9	9.5
1151	Mean	7.0	9.7	14.9	32.4	55.2
	S.D.	0.4	0.5	1.5	2.7	3.6
1154	Mean	6.4	8.5	15.4	33.0	53.4
	S.D.	0.5	1.3	2.3	2.7	4.8
1155	Mean	5.8	6.8	11.4	27.8	48.1
	S.D.	0.4	0.9	1.3	2.5	4.2
1156	Mean	5.4	6.6	11.6	27.7	44.8
	S.D.	0.5	1.0	1.2	2.4	3.6
1158	Mean	5.6	8.4	13.2	28.3	47.9
	S.D.	0.3	0.6	1.0	1.4	2.0
1159	Mean	6.8	9.9	16.1	36.4	56.3
	S.D.	0.5	0.6	1.0	1.7	2.8
1163	Mean	6.6	8.3	13.9	30.2	49.1
	S.D.	0.4	0.8	1.4	2.2	4.1
1164	Mean	6.1	9.2	15.7	35.2	56.3
	S.D.	0.4	0.7	1.3	1.9	4.2
1165	Mean	5.7	7.9	13.8	29.7	49.3
	S.D.	0.5	1.0	1.4	1.8	3.5
1166	Mean	5.3	6.9	11.0	27.8	47.0
	S.D.	0.4	0.5	1.0	1.8	2.7
1167	Mean	7.4	10.9	16.7	33.9	56.5
	S.D.	0.4	0.7	1.2	1.6	2.3
1168	Mean	5.9	7.7	13.4	29.1	48.3
	S.D.	0.3	0.6	0.6	1.3	2.6
1170	Mean	6.2	8.3	14.3	27.7	46.6
	S.D.	0.6	1.1	2.3	2.6	4.9
1157	NL					

NL No live litter.

S.D. Standard deviation.

APPENDIX 16 - continued

Individual litter mean bodyweights (g) of offspring (F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number		Day post partum				
		1	4	7	14	21
1171	Mean	5.1	6.4	11.0	26.2	43.4
	S.D.	0.3	1.0	1.9	3.7	5.1
1172	Mean	4.9	5.6	9.3	26.9	44.7
	S.D.	0.4	0.5	0.8	2.1	3.6
1174	Mean	5.7	7.5	14.0	32.3	49.8
	S.D.	0.4	1.3	0.9	1.2	2.4
1179	Mean	6.8	9.8	15.5	32.5	52.8
	S.D.	0.4	0.5	0.7	0.9	2.0
1181	Mean	6.2	7.7	12.6	29.7	46.6
	S.D.	0.4	0.8	1.8	2.7	4.0
1182	Mean	5.5	7.9	13.2	31.1	52.6
	S.D.	0.3	0.6	1.4	2.0	3.5
1184	Mean	5.8	8.3	15.0	32.7	50.2
	S.D.	0.3	0.6	0.7	1.6	1.7
1185	Mean	6.9	9.8	15.9	35.2	57.3
	S.D.	0.4	0.7	1.6	2.3	3.9
1187	Mean	5.9	8.9	16.1	36.2	57.5
	S.D.	0.6	1.2	0.9	1.7	4.1
1188	Mean	6.5	8.3	13.3	30.9	51.7
	S.D.	0.4	0.7	1.3	2.1	5.0
1189	Mean	6.0	8.7	13.6	31.6	48.5
	S.D.	0.7	1.4	2.8	5.0	7.0
1190	Mean	5.6	6.5	10.8	26.8	42.8
	S.D.	0.5	0.8	1.3	2.2	3.2
1191	Mean	6.8	9.8	16.3	36.7	59.2
	S.D.	0.6	1.2	1.0	1.9	4.0
1192	Mean	6.8	9.8	15.5	31.5	53.1
	S.D.	0.6	0.9	1.5	2.2	4.7
1193	Mean	5.5	7.4	13.3	31.3	48.3
	S.D.	0.5	1.0	1.6	2.5	3.2
1194	Mean	6.7	9.2	15.0	31.9	53.9
	S.D.	0.3	0.7	1.5	2.0	4.3
1196	Mean	5.1	5.7	10.0	24.7	41.7
	S.D.	0.3	0.9	1.6	1.8	2.6
1197	Mean	6.1	8.1	14.0	31.6	51.5
	S.D.	0.4	0.6	1.1	2.0	3.5
1198	Mean	7.2	11.1	17.8	31.9	54.5
	S.D.	0.4	0.6	1.2	1.8	4.0
1201	Mean	6.5	8.1	13.7	31.3	51.4
	S.D.	0.4	0.7	1.1	1.5	2.4
1202	Mean	6.7	9.2	14.5	30.2	51.9
	S.D.	0.4	0.8	1.1	1.4	2.8
1203	Mean	5.0	6.6	10.5	26.4	42.4
	S.D.	0.5	0.8	1.6	3.8	5.5

S.D. Standard deviation.

APPENDIX 16 - continued

Individual litter mean bodyweights (g) of offspring (F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number		Day post partum				
		1	4	7	14	21
1205	Mean	5.5	6.5	9.1	24.3	40.6
	S.D.	0.3	1.1	2.4	6.8	10.1
1206	Mean	6.4	7.7	11.1	29.8	49.2
	S.D.	0.6	0.9	2.2	4.3	5.9
1207	Mean	5.5	7.7	12.3	26.7	42.7
	S.D.	0.3	0.3	0.6	1.1	2.2
1208	Mean	8.0	8.7	10.1	19.8	36.6
	S.D.	0.4	0.6	1.1	1.9	1.7
1211	Mean	4.8 ^a	3.7			
	S.D.	0.4	-	Litter died		
1212	Mean	6.6	9.1	15.6	33.0	54.9
	S.D.	0.5	0.9	1.0	2.1	3.6
1213	Mean	6.7	9.5	15.1	32.6	53.2
	S.D.	0.4	0.9	1.8	2.7	5.0
1217	Mean	4.8 ^b	4.3			
	S.D.	0.4	0.6	Litter died		
1218	Mean	5.8	7.4	11.9	28.3	47.6
	S.D.	0.6	1.3	3.4	3.0	5.7
1219	Mean	6.1	8.1	13.1	31.2	50.8
	S.D.	0.5	1.5	2.8	4.5	7.2
1223	Mean	6.8	9.5	15.8	31.3	52.8
	S.D.	0.3	0.5	0.8	1.0	1.9
1225	Mean	6.2	9.0	14.7	33.6	55.9
	S.D.	0.5	0.6	1.1	1.5	3.1
1226	Mean	5.9	8.6	15.0	33.4	54.4
	S.D.	0.3	0.5	0.8	1.5	1.8
1227	Mean	5.6	7.3	12.2	28.1	46.1
	S.D.	0.5	1.2	1.8	3.3	6.2
1228	Mean	5.7	7.7	13.1	28.5	46.5
	S.D.	0.4	0.6	1.9	2.8	4.6
1230	Mean	6.8	10.1	16.8	35.8	60.0
	S.D.	0.4	0.9	1.3	2.4	3.1
1232	Mean	5.4	7.2	13.0	31.3	50.0
	S.D.	0.3	0.6	1.4	1.8	2.2
1233	Mean	6.3	8.8	14.1	29.2	47.9
	S.D.	0.4	0.9	1.3	2.2	4.0
1234	Mean	5.2	6.9	10.0	27.0	45.2
	S.D.	0.7	0.6	1.5	3.9	5.6
1235	Mean	6.3	8.7	14.2	30.7	51.8
	S.D.	0.2	0.7	1.1	1.3	2.4
1236	Mean	6.4	9.4	16.0	30.0	52.5
	S.D.	0.5	0.8	1.5	2.3	3.6
1237	Mean	5.8	7.9	11.8	26.4	42.6
	S.D.	0.2	0.8	1.4	2.6	3.7

S.D. Standard deviation.

a Mean of 14 offspring only.

b Mean of 13 offspring only.

APPENDIX 16 - continued

Individual litter mean bodyweights (g) of offspring (F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number		Day post partum				
		1	4	7	14	21
1239	Mean	5.6	7.3	12.5	34.2	54.4
	S.D.	0.4	1.5	2.8	2.9	4.2
1241	Mean	6.6	10.3	16.8	36.9	60.1
	S.D.	0.9	1.5	3.0	4.5	7.6
1242	Mean	5.8	7.2	12.7	30.9	49.8
	S.D.	0.4	1.1	0.8	1.4	1.7
1245	Mean	5.9	7.1	12.3	29.5	47.0
	S.D.	0.5	1.3	1.7	3.5	4.2
1246	Mean	5.5	7.2	12.0	28.2	52.0
	S.D.	0.3	0.6	1.0	1.4	6.2
1248	Mean	5.7	8.3	13.1	29.7	45.1
	S.D.	0.6	1.2	2.8	5.8	9.5
1249	Mean	7.5	11.5	16.6	36.6	59.8
	S.D.	0.3	0.5	1.6	1.3	2.6
1251	Mean	5.8	8.1	13.5	28.7	47.5
	S.D.	0.3	0.4	0.8	1.3	2.6
1253	Mean	6.9	9.8	15.7	29.6	52.3
	S.D.	0.5	1.0	2.5	4.5	7.0
1254	Mean	7.0	9.7	16.3	35.5	61.4
	S.D.	0.6	1.1	1.8	2.3	5.1
1255	Mean	5.5	6.5	10.7	28.9	47.6
	S.D.	0.4	1.0	2.1	2.3	3.7
1256	Mean	5.7	7.6	13.1	31.1	53.1
	S.D.	0.5	0.8	1.5	2.8	4.7
1257	Mean	4.9	8.2	13.9	31.8	48.2
	S.D.	0.4	0.8	0.9	1.3	3.4
1258	Mean	5.4	7.4	13.0	31.1	51.3
	S.D.	0.4	0.8	1.1	1.7	2.3
1259	Mean	6.4	9.4	15.3	30.5	49.7
	S.D.	0.4	0.6	0.9	0.9	1.6
1262	Mean	7.2	9.8	16.3	33.9	56.4
	S.D.	0.5	0.8	1.3	2.3	4.8
1265	Mean	6.0	7.9	13.1	31.2	51.2
	S.D.	0.3	0.7	1.8	2.5	3.1
1267	Mean	6.1	7.6	13.4	33.6	51.2
	S.D.	0.4	1.0	1.9	3.9	5.3
1268	Mean	6.1	7.6	12.0	28.0	46.5
	S.D.	0.5	0.7	1.7	3.1	3.8
1270	Mean	5.5	6.8	11.1	26.7	44.7
	S.D.	0.4	0.8	1.7	3.0	5.3
1271	Mean	5.6	7.1	11.4	27.6	43.0
	S.D.	0.4	0.7	1.8	2.7	3.9
1272	Mean	5.5	6.6	11.9	27.9	44.8
	S.D.	0.3	1.3	1.9	2.8	3.9

S.D. Standard deviation.

APPENDIX 17

Individual litter sex ratios (F_1)

Group 1 : Control

Animal number	Total at Day 1		Number alive at Day 1		Number alive Day 4 (pre-cull)		Number alive Day 4 (post-cull)		Number alive Day 21	
	M	F	M	F	M	F	M	F	M	F
1137	12	5	12	5	10	4	4	4	4	4
1138	5	6	5	6	5	6	4	4	4	4
1139	6	9	6	9	6	9	4	4	4	4
1143	6	8	6	7	6	7	3	5	3	5
1144	9	5	9	5	9	5	4	4	4	4
1147	4	7	4	7	4	7	4	4	4	4
1149	6	7	6	7	6	7	4	4	4	4
1150	10	6	10	5	7	5	4	4	4	4
1151	4	9	4	9	4	9	4	4	4	4
1154	11	5	10	5	9	5	4	4	4	4
1155	10	7	9	7	7	7	4	4	4	4
1156	4	8	4	8	3	6	3	5	3	5
1158	7	7	6	5	6	4	4	4	4	4
1159	6	6	5	6	5	6	4	4	4	4
1163	5	8	5	8	5	8	4	4	4	4
1164	8	7	8	7	8	7	4	4	4	4
1165	8	6	8	6	8	5	4	4	4	4
1166	7	8	7	7	6	5	4	4	4	4
1167	5	5	5	5	5	5	4	4	4	4
1168	4	9	4	9	4	9	4	4	4	4
1170	5	10	5	9	5	9	4	4	4	4
1157	NL									

NL No live litter.

APPENDIX 17 - continued

Individual litter sex ratios (F_1)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Total at Day 1		Number alive at Day 1		Number alive Day 4 (pre-cull)		Number alive Day 4 (post-cull)		Number alive Day 21	
	M	F	M	F	M	F	M	F	M	F
1171	7	10	7	10	6	6	4	4	4	4
1172	6	8	6	8	3	5	3	5	3	4
1174	8	5	8	5	8	5	4	4	4	4
1179	7	6	7	6	7	6	4	4	4	4
1181	6	10	6	10	6	10	4	4	4	4
1182	5	10	5	10	5	10	4	4	4	4
1184	8	8	8	8	8	8	4	4	4	4
1185	11	3	11	2	11	2	6	2	6	2
1187	6	8	6	8	5	8	4	4	4	4
1188	6	6	6	6	6	6	4	4	4	4
1189	4	6	4	6	4	6	4	4	4	4
1190	6	10	6	10	6	8	4	4	4	4
1191	7	7	7	7	7	7	4	4	4	4
1192	6	6	6	6	6	6	4	4	4	4
1193	5	11	3	11	3	11	3	5	3	5
1194	4	10	4	9	4	9	4	4	4	4
1196	7	6	7	6	7	6	4	4	4	4
1197	4	12	4	12	3	12	3	5	3	5
1198	7	3	7	3	7	3	5	3	5	3
1201	8	7	8	7	8	7	4	4	4	4
1202	12	4	12	4	12	4	4	4	4	4
1203	7	7	7	7	6	6	4	4	4	4

APPENDIX 17 - continued

Individual litter sex ratios (F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Total at Day 1		Number alive at Day 1		Number alive Day 4 (pre-cull)		Number alive Day 4 (post-cull)		Number alive Day 21	
	M	F	M	F	M	F	M	F	M	F
1205	9	7	9	7	7	2	6	2	6	2
1206	7	7	7	7	6	7	4	4	4	4
1207	7	4	7	4	6	4	4	4	4	4
1208	0	3	0	3	0	2	0	2	0	2
1211	7	8	7	8	0	1	0	1	Litter died	
1212	3	10	3	10	3	10	3	5	3	5
1213	6	7	6	7	6	7	4	4	4	4
1217	6	8	6	8	0	3	0	3	Litter died	
1218	12	3	11	3	7	2	6	2	6	1
1219	6	6	6	6	5	4	4	4	4	4
1223	8	7	8	7	8	7	4	4	4	4
1225	8	4	8	4	8	4	4	4	4	4
1226	5	9	5	9	5	8	4	4	4	4
1227	7	7	7	7	6	6	4	4	4	4
1228	5	9	5	9	5	9	4	4	4	4
1230	12	3	12	3	12	3	5	3	5	3
1232	5	7	5	7	5	6	4	4	4	4
1233	6	5	6	5	6	5	4	4	4	4
1234	10	7	9	7	5	4	4	4	4	4
1235	7	3	7	3	7	3	5	3	5	3
1236	6	8	6	8	6	8	4	4	4	4
1237	3	9	3	9	3	9	3	5	3	5

APPENDIX 17 - continued

Individual litter sex ratios (F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Total at Day 1		Number alive at Day 1		Number alive Day 4 (pre-cull)		Number alive Day 4 (post-cull)		Number alive Day 21	
	M	F	M	F	M	F	M	F	M	F
1239	11	6	11	6	8	5	4	4	4	3
1241	3	10	3	10	3	9	3	5	3	5
1242	5	8	5	8	5	8	4	4	4	4
1245	5	10	5	10	5	8	4	4	4	4
1246	6	8	6	7	6	7	4	4	4	4
1248	5	7	5	7	5	7	4	4	4	4
1249	6	3	5	2	5	2	5	2	4	2
1251	6	5	6	5	6	5	4	4	4	4
1253	7	7	6	7	5	7	4	4	4	4
1254	6	8	6	8	6	8	4	4	4	4
1255	10	8	10	7	7	7	4	4	4	4
1256	6	9	6	9	6	9	4	4	4	3
1257	10	9	7	9	5	8	4	4	4	3
1258	6	12	6	12	3	11	3	5	3	5
1259	6	7	6	7	6	7	4	4	4	4
1262	6	7	6	6	6	6	4	4	4	4
1265	8	7	8	7	8	7	4	4	4	4
1267	8	8	8	7	8	7	4	4	4	4
1268	8	8	8	8	8	8	4	4	4	4
1270	7	9	7	8	6	8	4	4	4	4
1271	9	6	9	6	9	6	4	4	4	4
1272	6	8	6	8	4	5	4	4	4	4

APPENDIX 18

Offspring development within individual litters (F₁)

Group 1 : Control

Animal number	Time of onset and completion (Days post partum)					
	Pinna unfolding	Hair growth	Testes descent	Tooth eruption	Eye opening	Vaginal opening
1137	3½-4½	3½-4½	3½-4½	10½-11½	13½-14½	31½-37½
1138	4	4-5	4-6	10-12	13-15	32-33
1139	4-5	4	4-5	9-11	15-16	34-35
1143	2½-3½	2½-3½	4½	9½-11½	13½-14½	31½-32½
1144	2-3	3	4	8-10	13-14	31
1147	2-3	2-3	4	8-11	13-14	31-32
1149	2½-3½	3½	3½-4½	9½-10½	13½-14½	30½-32½
1150	3-4	3	4-5	8-13	14-15	32
1151	3	3	4	9-10	14-15	31-35
1154	3-4	3-4	4	10-11	14-17	32-33
1155	3½	3½	3½	10½-11½	13½-14½	30½-31½
1156	3½	3½	3½	11½	11½-13½	30½-33½
1158	2½-3½	3½	4½	10½-11½	13½-14½	32½-35½
1159	2½-3½	2½-3½	3½-4½	9½-10½	13½-14½	30½-32½
1163	2½-3½	3½	4½	8½-10½	13½	31½-34½
1164	3	3	4	9-10	14	29-32
1165	4	4	4-5	10-11	14-15	31-34
1166	3½-4½	3½-4½	3½-5½	9½-12½	13½-14½	32½-35½
1167	2	2-3	5	9	13-14	32-33
1168	3-4	3-4	4-5	10-12	14-15	32-34
1170	2-3	2-4	5	9-10	13-14	32-33
1157	NL					

NL No live litter.

Offspring development within individual litters (F_1)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

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APPENDIX 18 - continued

Offspring development within individual litters (F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Time of onset and completion (Days post partum)					
	Pinna unfolding	Hair growth	Testes descent	Tooth eruption	Eye opening	Vaginal opening
1205	3½-4½	2½	3½-4½	10½-11½	13½-15½	32½
1206	3½	3½-4½	3½-5½	9½-11½	13½-14½	31½-33½
1207	2½-3½	3½	4½	11½	14½	32½
1208	1½	2½	a	9½	11½-12½	32½-33½
1212	2-3	3	4	9-10	14	30-32
1213	2-3	3	4-5	9-10	14	31-34
1218	3-5	3-4	5	9-10	14-15	34
1219	2½	2½	3½	9½-10½	13½-14½	29½-36½
1223	2-3	3	4	8-10	14	32-33
1225	3-4	3-4	4-5	9-11	14-15	32-34
1226	2½-4½	3½	4½	8½-11½	13½-14½	32½-34½
1227	3½	3½	3½-4½	10½	14½-15½	31½-39½
1228	3-4	4	4-5	9-11	14-15	32-35
1230	2-3	3	4	10-11	14-15	30-34
1232	3½	3½	4½	8½-9½	13½	31½-33½
1233	3½	3½	3½-4½	9½-10½	14½-15½	30½-32½
1234	3½-4½	3½	4½	10½-12½	13½-14½	32½-33½
1235	2½-3½	2½	3½-4½	9½	13½-14½	28½-30½
1236	2-3	3	4	8-11	13-14	31-33
1237	3½	3½	4½	10½-12½	14½-15½	31½-34½
1211	LD					
1217	LD					

a No males in litter.

LD Litter died.

APPENDIX 18 - continued

Offspring development within individual litters (F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Time of onset and completion (Days post partum)					
	Pinna unfolding	Hair growth	Testes descent	Tooth eruption	Eye opening	Vaginal opening
1239	3-4	3	4	9-11	14-15	34-35
1241	2-4	2	3-4	10-11	14	30-35
1242	3½	3½	4½	11½-12½	13½	32½-33½
1245	2½-4½	3½	4½-6½	8½-11½	14½	31½-33½
1246	2½-3½	2½-4½	3½-5½	9½-11½	14½	33½-35½
1248	3-4	4	4-5	9-13	14-15	32-33
1249	2	2	5	9-10	13-14	33
1251	2½-3½	2½-4½	3½-5½	8½-10½	13½-14½	30½-33½
1253	2-3	2-3	4	8-10	14	32-34
1254	2-4	3-4	5	9-11	14-15	32-33
1255	3½	3½-4½	3½-4½	10½-11½	13½-15½	31½-36½
1256	2½-3½	3½	3½	10½-11½	13½-15½	32½-36½
1257	3	3	4	9-10	14	31-34
1258	2½-3½	3½	4½	11½	13½-14½	31½-32½
1259	2-3	3	4	10-11	14-15	31-33
1262	2-3	2-3	4-5	9	13-14	32-33
1265	3½	3½	4½	8½-10½	13½-14½	31½-35½
1267	2½-3½	2½-3½	3½-4½	9½-10½	13½-14½	30½-31½
1268	3½	2½-3½	3½	9½-11½	13½-14½	30½-31½
1270	3-4	4	5	9-12	13-15	32-33
1271	3½	2½	3½-4½	10½-11½	13½-14½	32½-34½
1272	3½-4½	3½-4½	4½-5½	8½-10½	13½-14½	31½-34½

APPENDIX 19

Individual auditory and visual function responses (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations#

- a) Pupils failed to dilate : failed pupil closure test.
- b) Small cloudy area over both pupils : failed pupil closure test.
- c) Small pale area in centre of one or both pupils :
passed pupil closure test.
- d) Small pup, unable to assess in pupil closure test :
classed as failure.

Key to maternal/litter status

NL No live litter.
LD Litter died.

All animals tested showed normal responses unless indicated otherwise.

APPENDIX 19 - continued

Individual auditory and visual function responses (F₁)

Group : 1 2 3 4
 Compound : Control --- SC-19129 ---
 Intended dosage (mg/kg/day) : 0 250 500 750

Group 1			Group 2			Group 3			Group 4		
Animal number	Number of offspring examined	Observations	Animal number	Number of offspring examined	Observations	Animal number	Number of offspring examined	Observations	Animal number	Number of offspring examined	Observations
1137	8	-	1171	8	-	1205	8	1d	1239	7	-
1138	8	-	1172	7	-	1206	8	-	1241	8	-
1139	8	-	1174	8	-	1207	8	-	1242	8	-
1143	8	lab, 1c	1179	8	-	1208	2	-	1245	8	-
1144	8	-	1181	8	-	1212	8	-	1246	8	-
1147	8	-	1182	8	-	1213	8	-	1248	8	-
1149	8	-	1184	8	-	1218	7	-	1249	6	-
1150	8	-	1185	8	-	1219	8	-	1251	8	-
1151	8	-	1187	8	-	1223	8	-	1253	8	-
1154	8	-	1188	8	-	1225	8	-	1254	8	-
1155	8	-	1189	8	1c	1226	8	-	1255	7	-
1156	8	-	1190	8	-	1227	8	-	1256	7	-
1158	8	-	1191	8	-	1228	8	-	1257	8	-
1159	8	-	1192	8	-	1230	8	-	1258	8	-
1163	8	-	1193	8	-	1232	8	-	1259	8	-
1164	8	-	1194	8	-	1233	8	-	1262	8	-
1165	8	-	1196	8	-	1234	8	-	1265	8	-
1166	8	-	1197	8	-	1235	8	-	1267	8	-
1167	8	-	1198	8	-	1236	8	-	1268	8	1c
1168	8	-	1201	8	-	1237	8	-	1270	8	-
1170	8	-	1202	8	-	-	-	-	1271	8	-
			1203	8	-	1211	10	-	1272	8	-
1157	NL					1217	10				

APPENDIX 20

Individual litter mean activity scores (F₁)

Group 1 : Control

Animal number	Male offspring		Female offspring	
	Number of offspring	Mean activity score	Number of offspring	Mean activity score
1137	4	1820	4	1377
1138	4	1523	4	1192
1139	4	806	4	856
1143	4	1451 ^a	4	1891
1144	4	1586	4	1710
1147	4	2212	4	2252
1149	4	1483	4	1875
1150	4	1737	4	1452
1151	4	1686	4	1918
1154	4	2217	4	1796
1155	4	1612	4	1147
1156	3	1803	5	1628
1158	4	1878	4	1775
1159	4	1691	4	1813
1163	4	2020	4	1692
1164	4	1446	4	1554
1165	4	1793	4	1606
1166	4	1361	4	1278
1167	4	1680	4	1810
1168	4	1612	4	2043
1170	4	1681	4	1376
1157	NL			

a Excluded from calculations - one animal found to be female at post mortem examination.

NL No live litter.

APPENDIX 20 - continued

Individual litter mean activity scores (F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Male offspring		Female offspring	
	Number of offspring	Mean activity score	Number of offspring	Mean activity score
1171	4	1799	4	1144
1172	3	1334	4	1529
1174	4	1776	4	1955
1179	4	1925	4	1858
1181	4	1627	4	1362
1182	4	1438	4	1598
1184	4	1677	4	1525
1185	6	1780	2	1998
1187	4	1468	4	2167
1188	4	1752	4	1451
1189	4	1901	4	1774
1190	4	1225	4	1375
1191	4	1869	4	2167
1192	4	1719	4	1679
1193	3	1165	5	1499
1194	4	1956	4	2101
1196	4	1767	4	1342
1197	3	1662	5	1899
1198	5	2052	3	1839
1201	4	1602	4	1564
1202	4	1949	4	1819
1203	4	1517	4	1742

APPENDIX 20 - continued

Individual litter mean activity scores (F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Male offspring		Female offspring	
	Number of offspring	Mean activity score	Number of offspring	Mean activity score
1205 ^a	6	1130	1	1277
1206	4	1428	4	1140
1207	4	1370	4	927
1208	0	-	2	1824
1212	3	2116	5	2260
1213	4	2027	4	2241
1218	6	1556	1	1846
1219	4	1730	4	1865
1223	4	1811	4	2080
1225	4	1675	4	1670
1226	4	1828	4	990
1227	4	1606	4	1632
1228	4	1397	4	1363
1230	5	1500	3	1901
1232	4	1931	4	1932
1233	4	1672	4	1445
1234	4	1674	4	1672
1235	5	2030	3	2133
1236	4	1957	4	1997
1237	3	1585	5	1526
1211	LD			
1217	LD			

a One female offspring died Day 23 post partum.
LD Litter died.

APPENDIX 20 - continued

Individual litter mean activity scores (F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Male offspring		Female offspring	
	Number of offspring	Mean activity score	Number of offspring	Mean activity score
1239	4	1667	3	1648
1241	3	1936	5	2012
1242	4	1757	4	1991
1245	4	1297	4	1804
1246	4	1548	4	1114
1248	4	2093	4	1942
1249	4	1611	2	1950
1251	4	1425	4	1649
1253	4	1962	4	2105
1254	4	2274	4	2140
1255	4	1881	3	1858
1256	4	1721	3	1173
1257	4	1422	4	1279
1258	3	1916	5	1916
1259	4	1589	4	2020
1262	4	1602	4	1874
1265	4	1152	4	1890
1267	4	1653	4	1488
1268	4	1728	4	1691
1270	4	1538	4	1321
1271	4	1715	4	1762
1272	4	1253	4	1512

APPENDIX 21

Water maze - individual litter mean swimming times (seconds) (F_1)

Group 1 : Control

Animal number	Number passing	Male offspring						Female offspring						Number failing
		Trial						Trial						
		1	2	3	4	5	6	1	2	3	4	5	6	
1137	4	25.6	5.5	5.5	3.9	3.4	5.9	15.8	9.5	13.0	8.8	3.6	3.9	0
1138	4	13.4	8.4	3.9	3.3	3.1	3.3	20.8	9.6	16.9	7.5	6.0	6.1	0
1139	3	25.8	6.8	6.2	15.0	4.8	10.3	18.5	8.0	8.3	9.0	8.5	11.1	0
1143	3	22.3	6.3	3.3	4.8	5.2	5.8	19.7	9.2	4.0	4.2	4.0	7.9	0
1144	4	15.8	18.4	5.5	3.5	4.5	4.3	30.4	7.3	5.1	5.4	5.3	6.5	0
1147	4	21.0	9.5	6.0	5.1	3.6	4.3	17.8	7.5	5.4	6.5	4.3	3.5	0
1149	4	17.4	6.5	3.8	4.5	3.6	4.5	13.3	5.1	3.9	3.0	3.0	2.4	0
1150	4	17.5	6.3	3.8	3.0	3.0	2.8	13.3 ^a	4.0	3.0	3.0	3.0	2.6	0
1151	4	19.3	6.5	4.1	3.0	2.9	4.4	17.8	6.6	4.0	3.4	2.9	2.5	0
1154	4	16.0	10.0	4.9	6.8	3.6	13.6	12.0	5.5	4.8	3.6	6.6	4.9	0
1155	4	16.1	8.0	7.6	7.5	5.4	4.9	14.0	8.9	5.1	5.4	4.1	3.1	0
1156	3	14.7	2.8	6.2	3.8	2.7	4.0	15.7	6.7	3.6	3.2	3.3	4.0	0
1158	4	28.4	9.4	5.6	4.5	4.5	3.9	22.0	8.6	8.9	9.6	11.4	7.1	0
1159	4	24.8	4.1	3.4	2.8	2.9	3.1	13.8	4.8	3.1	5.4	2.8	2.8	0
1163	4	19.9	7.3	4.8	3.9	3.5	3.4	15.0	6.6	4.0	3.1	3.0	3.6	0
1164	4	19.8	3.8	3.5	2.5	2.6	3.3	18.8	6.5	2.9	5.1	4.5	4.8	0
1165	4	12.9	6.6	4.3	4.5	2.6	3.0	16.6	9.8	6.1	5.5	3.4	4.6	0
1166	4	12.5	7.9	4.8	4.3	3.6	4.1	12.5	5.3	5.6	3.4	3.1	4.5	0
1167	4	21.5	6.1	4.6	4.9	4.1	6.5	15.4	5.3	3.6	3.0	3.0	6.8	0
1168	4	15.1	6.0	4.1	4.1	4.4	3.3	20.6	7.1	4.5	7.1	3.9	4.3	0
1170	4	18.8	7.1	4.5	4.8	5.3	4.0	16.5	9.0	5.3	6.1	3.8	4.4	0
1157	NL													

^a Calculated from 3 animals - data not recorded for one offspring.
 NL No live litter.

APPENDIX 21 - continued

Water maze - individual litter mean swimming times (seconds) (F_1)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Number passing	Male offspring						Female offspring						Number failing
		Trial						Trial						
		1	2	3	4	5	6	1	2	3	4	5	6	
1171	4	12.6	13.3	6.9	11.8	7.4	8.4	14.5	5.8	3.6	5.9	8.3	8.8	0
1172	3	17.0	7.2	5.8	4.5	5.2	8.8	27.3	5.4	3.3	3.6	3.3	3.5	0
1174	4	12.9	6.8	5.6	2.9	3.9	3.6	10.6	4.6	3.9	2.9	2.8	3.1	0
1179	4	22.3	4.5	3.0	2.8	2.6	3.0	15.5	4.6	4.4	3.6	3.6	3.5	0
1181	4	19.3	13.8	7.1	7.4	5.5	6.1	21.6	6.1	4.3	3.3	6.5	5.0	0
1182	4	17.3	8.6	5.4	6.5	4.6	6.4	10.0	8.6	6.3	3.8	2.9	4.9	0
1184	4	18.4	6.2 ^a	4.8	8.6	5.3	4.0	16.3	6.6	5.0	4.1	4.4	5.9	0
1185	6	19.7	6.4	4.5	3.8	3.1	2.8	11.0	14.8	6.8	2.5	4.0	2.5	0
1187	4	22.4	5.4	4.5	3.9	2.9	3.3	16.6	5.0	3.1	3.1	3.0	3.0	0
1188	3	28.2	9.0	10.0	8.5	13.2	5.7	16.6	7.3	2.4	7.4	4.6	3.4	0
1189	4	18.5	7.8	3.8	3.9	2.8	3.3	16.0	8.4	6.1	3.5	5.8	6.0	0
1190	4	21.5	7.3	6.4	4.6	6.5	10.6	21.3	7.9	8.9	8.8	8.3	6.6	0
1191	4	20.6	5.5	4.6	3.1	3.4	2.9	18.9	5.9	5.1	7.8	4.1	5.8	0
1192	4	12.4	3.9	4.0	5.3	2.8	3.4	19.3	7.5	5.0	4.4	3.4	4.0	0
1193	3	18.7	6.0	3.2	4.2	3.5	5.7	22.5	6.5	8.2	6.7	5.6	3.8	0
1194	4	9.9	3.5	3.3	3.5	2.4	3.3	15.5	6.3	3.6	4.4	3.6	3.9	0
1196	4	14.1	8.0	7.1	4.8	3.1	3.1	15.8	8.8	5.1	4.0	4.1	3.6	0
1197	3	20.3	4.8	3.8	3.5	3.0	2.8	15.5	6.6	4.4	3.3	4.1	4.2	0
1198	5	13.4	7.4	5.2	5.0	4.6	3.6	19.5	9.0	7.2	7.0	5.7	5.8	0
1201	4	25.9	8.0	6.1	5.5	4.3	5.0	9.4	7.0	9.0	9.8	9.6	13.5	0
1202	4	23.3	8.0	4.4	3.3	5.1	6.3	25.0	8.6	5.1	4.6	3.3	2.9	0
1203	4	13.0	7.9	5.3	3.0	2.6	3.8	13.8	6.1	4.5	2.9	3.8	3.0	0

^a Calculated from 3 animals - data not recorded for one offspring.

APPENDIX 21 - continued

Water maze - individual litter mean swimming times (seconds) (F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Number passing	Male offspring						Number failing	Number passing	Female offspring						Number failing
		Trial								Trial						
		1	2	3	4	5	6			1	2	3	4	5	6	
1205	6	13.8	6.0	5.0	3.9	3.8	3.2	0	1b	14.5	4.0	3.0	3.0	13.0	3.0	0
1206	4	19.5	7.0	6.1	12.6	8.1	7.5	0	4	14.5	25.8	10.4	9.4	14.0	12.4	0
1207	4	15.4	10.6	6.5	5.6	3.8	3.9	0	4	14.0	8.4	4.5	6.9	3.8	5.4	0
1208	0	-	-	-	-	-	-	0	2	18.8	9.5	8.5	5.8	4.8	4.3	0
1212	3	20.8	5.7	3.7	5.7	2.7	3.2	0	5	9.8	7.8	3.1	4.0	3.7	3.1	0
1213	4	25.9	11.8	10.0	4.3	6.3	3.5	0	4	20.6	5.8	8.9	4.5	4.3	3.5	0
1218	6	19.8	10.8	8.8	6.5	4.7	5.8	0	1	4.5	7.5	4.0	5.0	3.0	3.5	0
1219	4	13.6	4.3	5.1	7.4	3.9	3.3	0	4	17.5	6.0	3.3	5.6	4.6	3.9	0
1223	4	16.9	9.9	4.1	3.1	2.6	2.8	0	4	22.4	5.1	3.8	2.5	2.5	3.9	0
1225	4	22.9	6.9	4.1	3.1	4.0	3.1	0	4	16.4	6.0	4.4	3.9	5.6	3.5	0
1226	4	21.0	6.4	5.6	5.9	8.8	5.8	0	4	16.6	3.8	7.3	4.5	6.0	6.9	0
1227	4	15.0	5.3	4.4	3.1	5.4	4.6	0	4	17.4	3.4	5.3	3.0	5.3	5.3	0
1228	4	14.6	5.8	4.4	7.0 ^a	3.6	4.0	0	4	14.4	4.7 ^a	7.0	3.8	4.3	3.3	0
1230	5	12.8	5.6	3.2	4.7	3.3	3.2	0	3	13.3	6.8	4.5	5.7	8.3	9.7	0
1232	4	19.1	7.3	3.6	3.3	6.1	3.3	0	4	20.5	5.0	5.4	3.8	4.8	7.5	0
1233	4	21.8	13.5	9.1	9.1	13.8	7.9	0	3	23.3	10.2	3.8	3.5	3.2	3.8	1
1234	4	12.8	6.1	4.3	6.3	3.9	5.3	0	4	8.3	4.3	3.5	3.6	3.3	3.3	0
1235	5	27.9	10.8	5.0	3.6	3.4	3.7	0	3	15.7	3.3	4.7	4.5	6.2	3.3	0
1236	4	26.5	8.6	4.9	4.6	4.9	5.9	0	4	19.8	6.0	3.8	5.9	4.0	14.8	0
1237	3	18.7	5.3	5.5	6.0	3.3	3.3	0	5	25.1	7.4	4.2	3.9	3.9	4.4	0
1211	LD															
1217	LD															

^a Calculated from 3 animals - data not recorded for one offspring.

^b One female offspring died Day 23 post partum.
LD Litter died.

APPENDIX 21 - continued

Water maze - individual litter mean swimming times (seconds) (F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Number passing	Male offspring						Female offspring						Number failing
		Trial						Trial						
		1	2	3	4	5	6	1	2	3	4	5	6	
1239	4	12.0	6.0	4.3	3.6	3.3	3.1	19.8	5.2	3.8	3.2	3.0	3.0	0
1241	3	20.0	4.3	10.2	6.3	6.2	5.0	20.1	4.5	5.7	5.0	4.3	4.0	0
1242	4	22.3	9.4	4.5	3.5	3.8	6.3	20.3	3.6	2.9	3.8	3.3	3.6	0
1245	4	22.1	9.3	4.6	3.5	3.4	3.4	19.3	4.3	3.4	5.3	3.3	4.4	0
1246	4	20.9	7.8	5.1	5.5	5.0	5.4	18.8	5.5	4.9	4.3	4.0	4.1	0
1248	4	16.6	4.4	3.4	3.1	2.8	3.0	21.8	7.1	5.6	3.9	3.9	3.5	0
1249	4	29.3	7.3	6.6	6.8	3.8	3.9	19.5	9.0	6.8	3.5	3.5	4.8	0
1251	3	29.0	12.0	5.0	7.2	7.0	7.2	19.8	8.8	5.8	8.3	10.3	8.0	0
1253	4	16.1	5.0	4.0	4.6	5.0	3.0	15.5	7.5	4.0	4.8	4.6	3.4	0
1254	4	23.4	7.3	3.5	4.8	4.3	3.3	34.6	10.5	6.4	8.5	7.3	8.0	0
1255	4	16.6	5.4	4.0	3.8	3.0	3.6	18.2	4.3	3.0	3.0	2.7	4.7	0
1256	4	14.8	4.4	3.4	3.1	3.4	3.1	26.7	8.8	7.0	4.7	3.7	6.5	0
1257	4	19.4	9.3	4.0	3.6	2.9	2.9	27.6	7.6	4.4	3.4	6.5	6.3	0
1258	3	13.5	7.2	5.3	4.8	4.0	3.3	15.9	6.9	5.3	3.2	4.0	3.5	0
1259	4	14.8	5.5	9.3	4.3	3.6	4.5	15.1	6.1	10.9	6.3	3.8	8.0	0
1262	4	23.9	4.8	3.3	4.0	3.1	3.1	16.8	7.0	6.5	5.0	6.1	4.8	0
1265	4	18.1	5.9	3.1	3.0	3.0	3.1	21.1	6.8	3.3	2.8	3.4	4.3	0
1267	3	31.0	6.7	5.0	4.3	5.7	12.7	28.6	18.5	7.1	5.0	7.6	4.1	0
1268	4	25.9	7.6	4.5	3.3	3.1	2.9	20.0	3.6	5.3	2.8	4.9	3.3	0
1270	4	23.3	17.8	7.3	6.0	4.8	5.0	14.6	11.4	5.4	6.8	3.5	4.4	0
1271	4	16.1	8.3	7.4	4.1	4.5	4.1	17.4	6.3	4.9	5.6	3.9	3.5	0
1272	4	16.9	4.3	4.1	6.1	4.3	5.9	22.9	6.3	5.9	4.4	5.3	6.0	0

APPENDIX 22

Individual observations at necropsy of offspring (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a) Appearance - small pup for age.
- b) Brain - one or both lateral ventricles dilated.
- c) Eye - one pupil constricted, partially red-rimmed.
- C) Eye - Opaque area in centre of left eye, haemorrhage on retina.
- d) Head - haemorrhage/wound on head.
- e) Jaw - apparent agenesis of lower jaw; no mouth.
- f) Kidney - unilateral hydronephrosis.
- g) Kidney - bilateral hydronephrosis.
- h) Kidney - several punctate cysts on surface of one kidney.
- j) Kidney - single large kidney.
- k) Limb - right hind limb misshapen.
- m) Limb - loss of use of hind limbs, haemorrhaging on left hind limb.
- n) Palate - dark area(s) on palate.
- p) Stomach - no milk or reduced amounts of food in stomach.
- q) Tail - damaged, reddened, loss of part or all of tail.
- r) Ureter - unilateral hydroureter.
- s) Ureter - bilateral hydroureter.
- t) Urinary bladder - full.
- u) Urinary bladder - distended.
- v) Urinary bladder - contents cloudy.
- x) Died after weaning - small; no food in stomach.
- y) Died after weaning - red stain on snout; one eye misshapen; wound on abdomen; lungs congested; haemorrhagic area on one kidney

APPENDIX 22 - continued

Individual observations at necropsy of offspring (F_1)

Group 1 : Control

Animal number	Offspring dying before weaning ^A		Offspring killed Day 4		Offspring killed after weaning	
	Number examined	Observations	Number examined	Observations	Number examined	Observations
1137	2	2p	6	5t	4	1b
1138	0	-	3	2r, 1rt	4	1f
1139	0	-	7	-	4	-
1143	1	1q	5	1u	4	-
1144	0	-	6	1k	4	-
1147	0	-	3	3t	4	-
1149	0	-	5	1t	4	-
1150	4	1fp, 3p	4	-	4	-
1151	0	-	5	1p	4	-
1154	2	2p	6	4t	4	-
1155	3	3p	6	2t	4	-
1156	3	1fp, 2p	1	1at	4	-
1158	4	1fp, 1gp, 1p	2	-	5	1b
1159	1	-	3	-	5	1c
1163	0	-	5	-	4	-
1164	0	-	7	5t	4	-
1165	0	-	5	5t	4	-
1166	3	3p	3	1rt	4	-
1167	0	-	2	1u	6	-
1168	0	-	5	2p	4	-
1170	1	1p	6	1p, 1t	4	-
1157	NL					

A Excludes missing, autolysed and grossly cannibalised offspring.
 NL No litter.

APPENDIX 22 - continued

Individual observations at necropsy of offspring (F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Offspring dying before weaning [#]		Offspring killed Day 4		Offspring killed after weaning	
	Number examined	Observations	Number examined	Observations	Number examined	Observations
1171	5	5p	4	1u	5	-
1172	7	7p	0	-	4	-
1174	0	-	5	2a	4	-
1179	0	-	5	4t	4	-
1181	0	-	8	-	4	1h
1182	0	-	7	1frt	5	-
1184	0	-	8	-	5	-
1185	0	-	5	3t	4	-
1187	0	-	5	-	5	-
1188	0	-	4	4t	4	-
1189	0	-	2	-	5	1f
1190	1	1p	6	1t	4	-
1191	0	-	6	-	5	-
1192	0	-	4	1u	4	-
1193	2	1fr	6	-	4	-
1194	0	-	5	-	5	-
1196	0	-	5	-	4	-
1197	1	1p	7	-	4	-
1198	0	-	2	2t	4	1f
1201	0	-	7	6t	4	-
1202	0	-	8	4t	4	-
1203	1	1p	4	1t	4	-

Excludes missing, autolysed and grossly cannibalised offspring.

APPENDIX 22 - continued

Individual observations at necropsy of offspring (F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Offspring dying before weaning [#]		Offspring killed Day 4		Offspring killed after weaning	
	Number examined	Observations	Number examined	Observations	Number examined	Observations
1205	6*	1djp, 4p, 1x	1	1t	4	-
1206	1*	1y	5	-	3	-
1207	0	-	2	-	3	-
1208	1	-	0	-	0	-
1211	13	1dp, 1n, 1lp	Litter died			
1212	0	-	5	1q	4	-
1213	0	-	5	3t	4	-
1217	12	12p	Litter died			
1218	5	5p	1	-	4	1b
1219	3	3p	1	1fst	4	1q
1223	0	-	7	1gst, 6t	4	-
1225	0	-	4	4t	4	-
1226	1	1p	5	1t	4	-
1227	0	-	4	1a, 3t	3	-
1228	0	-	6	3t	4	-
1230	0	-	7	-	4	-
1232	1	1p	3	-	4	-
1233	0	-	3	3t	4	-
1234	7	1np, 4p	1	-	3	-
1235	0	-	2	-	4	-
1236	0	-	6	2t	3	-
1237	0	-	4	-	4	-

Excludes missing, autolysed and grossly cannibalised offspring.

* Includes one offspring dying after weaning but before scheduled necropsy.

APPENDIX 22 - continued

Individual observations at necropsy of offspring (F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Offspring dying before weaning [#]		Offspring killed Day 4		Offspring killed after weaning	
	Number examined	Observations	Number examined	Observations	Number examined	Observations
1239	5	1gp,4p	5	1a	4	-
1241	1	1p	4	2t	5	-
1242	0	-	5	1a	4	-
1245	2	1fp, 1p	5	1at, 3t	4	1c
1246	1	1p	5	1p,1r	6	-
1248	0	-	4	4t	4	1a, 1g
1249	3	2p	0	-	3	-
1251	0	-	3	-	4	-
1253	2	1fp, 1p	4	1t	4	-
1254	0	-	6	-	4	-
1255	4	1fp, 3gp	6	1m	3	1f
1256	0	-	7	1fr, 1gt, 5t	4	-
1257	4	4p	5	1agst, 2ftr, 2gst	4	-
1258	2	1p	6	3t, 1u	4	-
1259	0	-	5	1f	4	-
1262	1	1e	4	-	4	-
1265	0	-	7	5t	5	-
1267	1	1p	7	-	4	-
1268	0	-	8	-	5	-
1270	2	2p	6	4t, 1v	4	-
1271	0	-	7	-	4	1b
1272	4	4p	1	-	4	-

[#] Excludes missing, autolysed and grossly cannibalised offspring.

APPENDIX 23

Individual observations at necropsy of males (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a Caecum - contents - yellow mucoid material.
- b Epididymis - small raised yellow body (1 mm diameter) attached to caput epididymis, unilateral.
- c Epididymis - several small pale firm areas between head and tail of organ; cut surface - pale firm tissue, unilateral.
- d Eye - red-rimmed.
- e Intestine - section of wall near caecum reddened.
- f Intestine - entire tract contents pale-green fluid.
- g Intestine - generally devoid of contents.
- h Jejunum - section of wall dark and haemorrhagic, contents red mucus.
- j Lung - one or more lobes congested and/or consolidated.
- k Rectum - devoid of pellets.
- m Rectum - contents soft faecal material.
- n Skin - red stain on face/around nares.
- p Skin - encrustations on cheeks/nose.
- q Skin - firm swelling on left ear, cut surface pale amorphous tissue.
- r Skin - scabs at base of tail.
- s Skull - subcutaneous haemorrhage overlying skull.
- t Spleen - split into two parts.
- u Stomach - devoid of contents.
- v Thymus - firm and enlarged (8.5 g; 35 x 25 mm).

APPENDIX 23 - continued

Individual observations at necropsy of males (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group 1		Group 2		Group 3		Group 4	
Animal number	Observations	Animal number	Observations	Animal number	Observations	Animal number	Observations
1001	e	1035	-	1069	-	1103	-
1002	-	1036	b	1070	-	1104	-
1003	q	1037	-	1071	-	1105	-
1004	-	1038	-	1072	-	1106	-
1005	-	1039	-	1073	-	1107	-
1006	-	1040	-	1074	-	1108	-
1007	-	1041	-	1075	-	1109	-
1008	-	1042	-	1076	-	1110	-
1009	-	1043	-	1077	-	1111	r
1010	-	1044	h	1078	-	1112	-
1011	-	1045	v	1079	n	1113	-
1012	-	1046	-	1080	-	1114	-
1013	-	1047	-	1081	-	1115	-
1014	-	1048	-	1082	-	1116	-
1015	-	1049	n	1083	t	1117	-
1016	-	1050	-	1084	-	1118	gu
1017	-	1051	-	1085	-	1119	-
1018	p	1052	-	1086	j	1120	-
1019	-	1053	-	1087	-	1121	-
1020	-	1054	-	1088	-	1122	j
1021	-	1055	cp	1089	ak	1123	-
1022	-	1056	-	1090	-	1124	-
1023	s	1057	-	1091	-	1125	s
1024	s	1058	-	1092	-	1126	-
1025	fm	1059	-	1093	-	1127	-
1026	-	1060	-	1094	-	1128	-
1027	-	1061	-	1095	-	1129	-
1028	-	1062	-	1096	-	1130	-
1029	-	1063	-	1097	-	1131	-
1030	-	1064	-	1098	-	1132	-
1031	-	1065	-	1099	-	1133	-
1032	-	1066	-	1100	-	1134	-
1033	-	1067	d	1101	-	1135	-
1034	-	1068	-	1102	-	1136	-

APPENDIX 24

Individual observations at necropsy of females (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a Caecum - slightly enlarged/enlarged.
- b Caecum - contents gassy.
- c Caecum - contents fluid.
- d Eye - red-rimmed.
- e Eye - pupil oval and constricted.
- f Eye - haemorrhagic.
- g Intestine - contents green/translucent/mucoid.
- h Intestine - areas of reddened walls and/or red mucus contents.
- j Jejunum - swollen with yellow mucoid material.
- k Kidney - unilateral hydronephrosis.
- m Kidney - bilateral hydronephrosis.
- n Kidney - misshapen and/or enlarged.
- p Kidney - contains cloudy material.
- q Lung - pale foci/grey areas on lung tissue.
- r Mammary tissue - pale and inactive.
- s Rectum - contents soft faecal material/pellets.
- t Rectum - devoid of faecal pellets.
- u Skin - hairloss on snout.
- v Skin - encrustations.
- w Skull - subcutaneous haemorrhage overlying skull.
- x Spleen - pale raised areas (<2 mm diameter) over surface.
- y Stomach - contents yellow.
- z Ureter - unilateral hydroureter.
- A Ureter - bilateral hydroureter.
- B Urinary bladder - contains stone(s) with or without purulent fluid.
- C Urinary bladder - walls thickened.
- D Uterus - unilateral implantation sites.
- E Uterus - free blood in one horn.
- F Uterus - fluid-filled cyst (3 mm diameter) in one horn.
- G Uterus - single resorbing foetus retained in utero.
- H Uterine mesentery/fat - small hard white body(ies) present.

APPENDIX 24 - continued

Individual observations at necropsy of females (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group 1			Group 2		
Animal number	Stage of study	Observations	Animal number	Stage of study	Observations
1137	W	q	1171	W	g
1138	W	-	1172	W	-
1139	W	-	1173	T	-
1140	T	-	1174	W	a
1141	T	-	1175	T	df
1142	T	mnABC	1176	T	-
1143	W	-	1177	T	-
1144	W	-	1178	T	-
1145	T	-	1179	W	-
1146	T	n	1180	T	v
1147	W	y	1181	W	F
1148	T	-	1182	W	g
1149	W	-	1183	T	-
1150	W	q	1184	W	zBC
1151	W	-	1185	W	-
1152	T	-	1186	T	-
1153	T	-	1187	W	-
1154	W	abs	1188	W	u
1155	W	-	1189	W	H
1156	W	sw	1190	W	aqs
1157	NL	DG	1191	W	-
1158	W	H	1192	W	-
1159	W	-	1193	W	g
1160	T	-	1194	W	-
1161	T	-	1195	T	-
1162	T	-	1196	W	k
1163	W	-	1197	W	ab
1164	W	q	1198	W	-
1165	W	-	1199	T	-
1166	W	-	1200	T	-
1167	W	-	1201	W	-
1168	W	j	1202	W	-
1169	T	-	1203	W	-
1170	W	-	1204	T	-

T Sacrificed on Day 20 of gestation for teratological examination.
W Sacrificed after litter weaned.
NL Sacrificed when no live litter produced by Day 25 post coitum.

APPENDIX 24 - continued

Individual observations at necropsy of females (F₀)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group 3			Group 4		
Animal number	Stage of study	Observations	Animal number	Stage of study	Observations
1205	W	-	1239	W	-
1206	W	cy	1240	T	-
1207	W	-	1241	W	-
1208	W	-	1242	W	-
1209	T	-	1243	T	-
1210	T	-	1244	T	-
1211	LD	rx	1245	W	-
1212	W	-	1246	W	g
1213	W	-	1247	T	-
1214	T	-	1248	W	k
1215	T	de	1249	W	-
1216	T	-	1250	T	-
1217	LD	r	1251	W	gh
1218	W	-	1252	T	-
1219	W	a	1253	W	q
1220	T	-	1254	W	-
1221	T	-	1255	W	ab
1222	T	E	1256	W	-
1223	W	-	1257	W	as
1224	T	-	1258	W	-
1225	W	-	1259	W	-
1226	W	-	1260	T	-
1227	W	-	1261	T	-
1228	W	gtw	1262	W	-
1229	T	-	1263	T	-
1230	W	-	1264	T	-
1231	T	-	1265	W	-
1232	W	-	1266	T	-
1233	W	-	1267	W	-
1234	W	-	1268	W	-
1235	W	-	1269	T	kABD
1236	W	-	1270	W	-
1237	W	g	1271	W	-
1238	T	-	1272	W	h

T Sacrificed on Day 20 of gestation for teratological examination.
W Sacrificed after litter weaned.
LD Sacrificed after litter died.

APPENDIX 25

Individual absolute weights (g) of male reproductive organs (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Prostate	Testes	Seminal Vesicles	Epididymides
1M	1001	534	0.33	3.67	3.00	1.54
	1002	557	0.71	3.60	2.95	1.37
	1003	512	0.70	3.01	2.38	1.08
	1004	500	0.67	3.60	2.32	1.26
	1005	514	0.73	3.13	2.92	1.16
	1006	478	0.46	3.45	2.24	1.24
	1007	450	0.50	3.21	2.44	1.15
	1008	526	0.60	2.95	2.52	1.17
	1009	478	0.65	3.41	2.56	1.19
	1010	600	0.48	3.61	2.90	1.24
	1011	491	0.61	3.55	3.12	1.10
	1012	571	0.73	3.11	2.20	1.07
	1013	533	0.68	3.50	2.71	1.16
	1014	626	0.27	3.19	2.90	1.14
	1015	585	0.34	3.73	2.33	1.24
	1016	537	0.69	3.74	2.79	1.38
	1017	479	0.36	3.53	2.27	1.21
	1018	630	0.34	3.63	2.97	1.30
	1019	592	0.64	3.39	2.36	1.06
	1020	514	0.53	3.44	2.46	1.18
	1021	563	0.43	3.16	2.64	1.22
	1022	647	0.46	3.11	2.91	1.39
	1023	608	0.48	3.74	3.43	1.25
	1024	479	0.49	3.36	3.01	1.21
	1025	571	0.52	3.26	2.95	1.20
	1026	508	0.63	3.33	2.66	1.23
	1027	589	0.56	3.50	2.91	1.26
	1028	584	0.36	3.74	2.97	1.21
	1029	636	0.76	3.72	2.71	1.29
	1030	479	0.62	3.25	2.10	1.11
	1031	502	0.65	3.52	2.94	1.33
	1032	630	1.05	3.19	3.13	1.27
	1033	453	0.44	2.70	2.18	1.13
	1034	586	0.65	3.28	2.87	1.29

APPENDIX 25 - continued

Individual absolute weights (g) of males reproductive organs (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Prostate	Testes	Seminal Vesicles	Epididymides
2M	1035	440	0.76	3.34	2.57	1.12
	1036	520	0.47	3.77	2.74	1.25
	1037	534	0.62	3.24	2.74	1.22
	1038	555	0.87	3.54	2.43	1.25
	1039	606	0.41	3.44	2.30	1.27
	1040	499	0.72	3.54	3.11	1.34
	1041	522	0.56	3.51	2.79	1.23
	1042	549	0.77	2.40	2.12	0.90
	1043	452	0.42	2.98	2.63	1.06
	1044	461	0.50	2.86	2.51	1.16
	1045	572	0.56	3.64	2.93	1.16
	1046	542	0.58	3.55	2.77	1.21
	1047	544	0.69	2.90	2.62	1.10
	1048	480	0.40	3.39	2.69	1.17
	1049	642	0.58	3.45	2.03	1.22
	1050	549	0.50	3.52	2.86	1.34
	1051	547	0.56	3.20	3.20	1.27
	1052	603	0.38	3.19	2.80	1.18
	1053	640	0.67	3.41	3.14	1.30
	1054	509	0.48	3.56	2.67	1.38
	1055	466	0.74	3.50	2.43	NW
	1056	512	0.52	3.76	2.69	1.22
	1057	518	0.64	3.06	2.63	1.22
	1058	567	0.42	3.94	3.12	1.46
	1059	520	0.65	3.42	2.73	1.29
	1060	635	0.65	3.62	2.91	1.43
	1061	475	0.60	3.20	2.31	1.15
	1062	658	0.72	3.57	3.30	1.27
	1063	642	0.40	3.38	3.36	1.16
	1064	494	0.56	3.89	2.50	1.25
	1065	511	0.51	3.86	2.63	1.43
	1066	535	0.67	3.29	3.17	1.17
	1067	578	0.39	3.27	2.81	1.32
	1068	547	0.95	3.27	2.88	1.28

NW Left epididymis not weighed.

APPENDIX 25 - continued

Individual absolute weights (g) of male reproductive organs (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Prostate	Testes	Seminal Vesicles	Epidid-ymides
3M	1069	438	0.61	3.46	2.83	1.30
	1070	567	0.53	3.32	3.19	1.42
	1071	560	0.74	3.81	2.59	1.38
	1072	560	0.76	2.76	3.22	1.19
	1073	490	0.54	3.27	2.58	1.25
	1074	495	0.56	3.31	2.94	1.29
	1075	462	0.53	3.54	2.36	1.18
	1076	446	1.07	3.18	2.57	1.14
	1077	576	0.88	3.44	3.13	1.25
	1078	522	0.77	3.55	3.17	1.28
	1079	548	0.42	3.01	2.25	1.08
	1080	522	0.30	2.97	2.23	1.12
	1081	495	0.55	3.36	2.78	1.19
	1082	564	0.68	3.24	2.56	1.17
	1083	529	0.38	2.80	2.32	1.00
	1084	490	0.43	3.40	2.14	1.22
	1085	499	0.58	3.41	2.31	1.31
	1086	593	0.66	3.20	2.60	1.20
	1087	520	0.52	3.24	2.60	1.32
	1088	485	0.77	3.46	2.55	1.30
	1089	586	0.49	3.66	2.81	1.27
	1090	523	0.92	3.18	2.63	1.27
	1091	477	0.49	3.31	2.75	1.28
	1092	574	0.31	3.68	2.83	1.42
	1093	566	0.36	3.34	2.46	1.30
	1094	515	0.68	3.16	2.36	1.24
	1095	592	0.91	3.57	2.57	1.35
	1096	596	0.78	2.84	2.17	1.16
	1097	459	0.51	3.44	2.74	1.14
	1098	575	0.71	3.55	2.27	1.27
	1099	462	0.55	3.24	2.45	1.19
	1100	565	0.70	3.82	3.19	1.22
	1101	574	0.57	2.95	2.35	1.07
	1102	465	0.54	3.16	2.27	1.20

APPENDIX 25 - continued

Individual absolute weights (g) of male reproductive organs (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Prostate	Testes	Seminal Vesicles	Epididymides
4M	1103	521	0.51	2.98	2.34	1.07
	1104	468	0.97	3.10	2.36	1.19
	1105	515	0.38	3.56	2.86	1.34
	1106	532	0.51	3.51	2.76	1.34
	1107	560	0.48	3.18	2.35	1.13
	1108	623	0.45	3.52	3.18	1.32
	1109	520	0.65	3.71	2.38*	1.24
	1110	549	0.85	3.24	2.33	1.17
	1111	416	0.25	2.82	2.86	1.03
	1112	498	0.77	3.60	2.61*	1.33
	1113	489	0.46	2.99	1.99	1.03
	1114	617	0.51	3.80	2.83	1.22
	1115	530	0.67	3.19	2.15	1.19
	1116	497	0.35	3.33	2.51	1.18
	1117	545	0.47	3.48	2.16	1.15
	1118	565	0.38	3.36	2.41	1.25
	1119	445	0.83	3.60	2.73	1.30
	1120	535	0.56	3.73	2.19	1.29
	1121	602	0.63	3.26	2.36	1.37
	1122	550	0.38	2.92	2.15	0.99
	1123	489	0.32	3.00	2.32*	1.23
	1124	533	1.05	3.23	2.47	1.24
	1125	524	0.55	3.15	3.00	1.18
	1126	533	0.50	3.60	2.98	1.38
	1127	518	0.43	3.35	2.26	1.16
	1128	538	0.87	3.60	2.83	1.37
	1129	569	0.58	3.69	3.11	1.30
	1130	538	0.57	3.38	2.62	1.08
	1131	505	0.76	3.51	2.94	1.17
	1132	514	0.50	3.85	2.96	1.37
	1133	542	0.71	3.51	2.83	1.21
	1134	515	0.42	3.18	2.09	1.19
	1135	538	0.84	3.26	2.95	1.18
	1136	499	0.56	2.93	2.25	1.14

* Damaged at necropsy, excluded from group mean value.

APPENDIX 26

Individual relative weights^Δ of male reproductive organs (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Prostate	Testes	Seminal Vesicles	Epididymides
1M	1001	534	0.06	0.69	0.56	0.29
	1002	557	0.13	0.65	0.53	0.25
	1003	512	0.14	0.59	0.46	0.21
	1004	500	0.13	0.72	0.46	0.25
	1005	514	0.14	0.61	0.57	0.23
	1006	478	0.10	0.72	0.47	0.26
	1007	450	0.11	0.71	0.54	0.26
	1008	526	0.11	0.56	0.48	0.22
	1009	478	0.14	0.71	0.54	0.25
	1010	600	0.08	0.60	0.48	0.21
	1011	491	0.12	0.72	0.64	0.22
	1012	571	0.13	0.54	0.39	0.19
	1013	533	0.13	0.66	0.51	0.22
	1014	626	0.04	0.51	0.46	0.18
	1015	585	0.06	0.64	0.40	0.21
	1016	537	0.13	0.70	0.52	0.26
	1017	479	0.08	0.74	0.47	0.25
	1018	630	0.05	0.58	0.47	0.21
	1019	592	0.11	0.57	0.40	0.18
	1020	514	0.10	0.67	0.48	0.23
	1021	563	0.08	0.56	0.47	0.22
	1022	647	0.07	0.48	0.45	0.21
	1023	608	0.08	0.62	0.56	0.21
	1024	479	0.10	0.70	0.63	0.25
	1025	571	0.09	0.57	0.52	0.21
	1026	508	0.12	0.66	0.52	0.24
	1027	589	0.10	0.59	0.49	0.21
	1028	584	0.06	0.64	0.51	0.21
	1029	636	0.12	0.58	0.43	0.20
	1030	479	0.13	0.68	0.44	0.23
	1031	502	0.13	0.70	0.59	0.26
	1032	630	0.17	0.51	0.50	0.20
	1033	453	0.10	0.60	0.48	0.25
	1034	586	0.11	0.56	0.49	0.22

Δ Expressed as a percentage of bodyweight.

APPENDIX 26 - continued

Individual relative weights^Δ of male reproductive organs (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Prostate	Testes	Seminal Vesicles	Epididymides
2M	1035	440	0.17	0.76	0.58	0.25
	1036	520	0.09	0.73	0.53	0.24
	1037	534	0.12	0.61	0.51	0.23
	1038	555	0.16	0.64	0.44	0.23
	1039	606	0.07	0.57	0.38	0.21
	1040	499	0.14	0.71	0.62	0.27
	1041	522	0.11	0.67	0.53	0.24
	1042	549	0.14	0.44	0.39	0.16
	1043	452	0.09	0.66	0.58	0.23
	1044	461	0.11	0.62	0.54	0.25
	1045	572	0.10	0.64	0.51	0.20
	1046	542	0.11	0.65	0.51	0.22
	1047	544	0.13	0.53	0.48	0.20
	1048	480	0.08	0.71	0.56	0.24
	1049	642	0.09	0.54	0.32	0.19
	1050	549	0.09	0.64	0.52	0.24
	1051	547	0.10	0.59	0.59	0.23
	1052	603	0.06	0.53	0.46	0.20
	1053	640	0.10	0.53	0.49	0.20
	1054	509	0.09	0.70	0.52	0.27
	1055	466	0.16	0.75	0.52	NW
	1056	512	0.10	0.73	0.53	0.24
	1057	518	0.12	0.59	0.51	0.24
	1058	567	0.07	0.69	0.55	0.26
	1059	520	0.13	0.66	0.53	0.25
	1060	635	0.10	0.57	0.46	0.23
	1061	475	0.13	0.67	0.49	0.24
	1062	658	0.11	0.54	0.50	0.19
	1063	642	0.06	0.53	0.52	0.18
	1064	494	0.11	0.79	0.51	0.25
	1065	511	0.10	0.76	0.51	0.28
	1066	535	0.13	0.61	0.59	0.22
	1067	578	0.07	0.57	0.49	0.23
	1068	547	0.17	0.60	0.53	0.23

NW Left epididymis not weighed.

Δ Expressed as a percentage of bodyweight.

APPENDIX 26 - continued

Individual relative weights^Δ of male reproductive organs (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Prostate	Testes	Seminal Vesicles	Epididymides
3M	1069	438	0.14	0.79	0.65	0.30
	1070	567	0.09	0.59	0.56	0.25
	1071	560	0.13	0.68	0.46	0.25
	1072	560	0.14	0.49	0.58	0.21
	1073	490	0.11	0.67	0.53	0.26
	1074	495	0.11	0.67	0.59	0.26
	1075	462	0.11	0.77	0.51	0.26
	1076	446	0.24	0.71	0.58	0.26
	1077	576	0.15	0.60	0.54	0.22
	1078	522	0.15	0.68	0.61	0.25
	1079	548	0.08	0.55	0.41	0.20
	1080	522	0.06	0.57	0.43	0.21
	1081	495	0.11	0.68	0.56	0.24
	1082	564	0.12	0.57	0.45	0.21
	1083	529	0.07	0.53	0.44	0.19
	1084	490	0.09	0.69	0.44	0.25
	1085	499	0.12	0.68	0.46	0.26
	1086	593	0.11	0.54	0.44	0.20
	1087	520	0.10	0.62	0.50	0.25
	1088	485	0.16	0.71	0.53	0.27
	1089	586	0.08	0.62	0.48	0.22
	1090	523	0.18	0.61	0.50	0.24
	1091	477	0.10	0.69	0.58	0.27
	1092	574	0.05	0.64	0.49	0.25
	1093	566	0.06	0.59	0.43	0.23
	1094	515	0.13	0.61	0.46	0.24
	1095	592	0.15	0.60	0.43	0.23
	1096	596	0.13	0.48	0.36	0.19
	1097	459	0.11	0.75	0.60	0.25
	1098	575	0.12	0.62	0.39	0.22
	1099	462	0.12	0.70	0.53	0.26
	1100	565	0.12	0.68	0.56	0.22
	1101	574	0.10	0.51	0.41	0.19
	1102	465	0.12	0.68	0.49	0.26

Δ Expressed as a percentage of bodyweight.

APPENDIX 26 - continued

Individual relative weights^Δ of male reproductive organs (F₀)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Prostate	Testes	Seminal Vesicles	Epididymides
-------------	---------------	-----------------	----------	--------	------------------	--------------

4M	1103	521	0.10	0.57	0.45	0.21
	1104	468	0.21	0.66	0.50	0.25
	1105	515	0.07	0.69	0.56	0.26
	1106	532	0.10	0.66	0.52	0.25
	1107	560	0.09	0.57	0.42	0.20
	1108	623	0.07	0.57	0.51	0.21
	1109	520	0.13	0.71	0.46*	0.24
	1110	549	0.15	0.59	0.42	0.21
	1111	416	0.06	0.68	0.69	0.25
	1112	498	0.15	0.72	0.52*	0.27
	1113	489	0.09	0.61	0.41	0.21
	1114	617	0.08	0.62	0.46	0.20
	1115	530	0.13	0.60	0.41	0.22
	1116	497	0.07	0.67	0.51	0.24
	1117	545	0.09	0.64	0.40	0.21
	1118	565	0.07	0.59	0.43	0.22
	1119	445	0.19	0.81	0.61	0.29
	1120	535	0.10	0.70	0.41	0.24
	1121	602	0.10	0.54	0.39	0.23
	1122	550	0.07	0.53	0.39	0.18
	1123	489	0.07	0.61	0.47*	0.25
	1124	533	0.20	0.61	0.46	0.23
	1125	524	0.10	0.60	0.57	0.23
	1126	533	0.09	0.68	0.56	0.26
	1127	518	0.08	0.65	0.44	0.22
	1128	538	0.16	0.67	0.53	0.25
	1129	569	0.10	0.65	0.55	0.23
	1130	538	0.11	0.63	0.49	0.20
	1131	505	0.15	0.70	0.58	0.23
	1132	514	0.10	0.75	0.58	0.27
	1133	542	0.13	0.65	0.52	0.22
	1134	515	0.08	0.62	0.41	0.23
	1135	538	0.16	0.61	0.55	0.22
	1136	499	0.11	0.59	0.45	0.23

* Damaged at necropsy, excluded from group mean value.

Δ Expressed as a percentage of bodyweight.

APPENDIX 27

Individual absolute weights (g) of female reproductive organs at Day 20 of gestation (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Gravid Uterus	Uterus	Ovaries
1F	1140	409	NW	4.40	0.130
	1141	395	74	4.62	0.145
	1142	345	66	3.49	0.108
	1145	361	71	4.70	0.095
	1146	367	71	4.38	0.114
	1148	370	80	4.47	0.119
	1152	397	61	4.07	0.161
	1153	423	60	3.89	0.150
	1160	380	68	4.55	0.090
	1161	390	88	4.72	0.166
	1162	411	76	5.05	0.119
	1169	395	75	4.37	0.130
2F	1173	353	66	3.91	0.094
	1175	396	56	3.85	0.152
	1176	376	80	4.66	0.122
	1177	383	72	4.84	0.120
	1178	357	77	4.84	0.118
	1180	410	64	3.94	0.132
	1183	415	99	4.90	0.132
	1186	430	86	4.97	0.077
	1195	395	78	4.12	0.120
	1199	345	64	3.47	0.151
	1200	361	77	4.54	0.110
	1204	395	89	4.78	0.110

NW Not weighed.

APPENDIX 27 - continued

Individual absolute weights (g) of female reproductive organs at Day 20 of gestation (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Gravid Uterus	Uterus	Ovaries
3F	1209	395	74	4.34	0.110
	1210	400	81	4.56	0.142
	1214	427	102	5.34	0.131
	1215	347	88	4.42	0.131
	1216	375	65	4.25	0.112
	1220	414	84	4.65	0.150
	1221	392	83	4.77	0.112
	1222	368	70	4.13	0.122
	1224	401	80	5.80	0.118
	1229	370	68	4.27	0.122
	1231	387	94	5.69	0.108
	1238	371	76	4.60	0.113
4F	1240	375	79	4.40	0.108
	1243	373	71	3.99	0.130
	1244	368	68	4.03	0.108
	1247	405	90	5.07	0.121
	1250	386	58	3.91	0.106
	1252	339	68	3.93	0.106
	1260	338	59	3.70	0.105
	1261	400	84	5.49	0.135
	1263	395	80	4.48	0.111
	1264	409	84	4.90	0.130
	1266	356	74	4.63	0.130
	1269	345	31	2.56	0.124

APPENDIX 28

Individual relative weights^Δ of female reproductive organs at Day 20 of gestation (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Gravid Uterus	Uterus	Ovaries ⁺
1F	1140	409	NW	1.08	31.8
	1141	395	18.73	1.17	36.7
	1142	345	19.13	1.01	31.3
	1145	361	19.67	1.30	26.3
	1146	367	19.35	1.19	31.1
	1148	370	21.62	1.21	32.2
	1152	397	15.37	1.03	40.6
	1153	423	14.18	0.92	35.5
	1160	380	17.89	1.20	23.7
	1161	390	22.56	1.21	42.6
	1162	411	18.49	1.23	29.0
	1169	395	18.99	1.11	32.9
2F	1173	353	18.70	1.11	26.6
	1175	396	14.14	0.97	38.4
	1176	376	21.28	1.24	32.4
	1177	383	18.80	1.26	31.3
	1178	357	21.57	1.36	33.1
	1180	410	15.61	0.96	32.2
	1183	415	23.86	1.18	31.8
	1186	430	20.00	1.16	17.9
	1195	395	19.75	1.04	30.4
	1199	345	18.55	1.01	43.8
	1200	361	21.33	1.26	30.5
	1204	395	22.53	1.21	27.8

NW Not weighed.

Δ Expressed as a percentage of bodyweight unless otherwise indicated.

+ Ovaries : percentage value multiplied by 1000.

APPENDIX 28 - continued

Individual relative weights^Δ of female
reproductive organs at Day 20 of gestation (F₀-F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Gravid Uterus	Uterus	Ovaries
-------------	---------------	-----------------	---------------	--------	---------

3F	1209	395	18.73	1.10	27.8
	1210	400	20.25	1.14	35.5
	1214	427	23.89	1.25	30.7
	1215	347	25.36	1.27	37.8
	1216	375	17.33	1.13	29.9
	1220	414	20.29	1.12	36.2
	1221	392	21.17	1.22	28.6
	1222	368	19.02	1.12	33.2
	1224	401	19.95	1.45	29.4
	1229	370	18.38	1.15	33.0
	1231	387	24.29	1.47	27.9
	1238	371	20.49	1.24	30.5

4F	1240	375	21.07	1.17	28.8
	1243	373	19.03	1.07	34.9
	1244	368	18.48	1.10	29.3
	1247	405	22.22	1.25	29.9
	1250	386	15.03	1.01	27.5
	1252	339	20.06	1.16	31.3
	1260	338	17.46	1.09	31.1
	1261	400	21.00	1.37	33.8
	1263	395	20.25	1.13	28.1
	1264	409	20.54	1.20	31.8
	1266	356	20.79	1.30	36.5
	1269	345	8.99	0.74	35.9

Δ Expressed as a percentage of bodyweight
unless otherwise indicated.

+ Ovaries : percentage value multiplied by 1000.

APPENDIX 29

F₁ generation inter-relationships

Group 1 : Control

Maternal animal number	Paternal animal number	Selected animals			
		F ₁ male numbers		F ₁ female numbers	
1137	1001	2035	2036	2195	2196
1138	1002	2001	2002	2161	2162
1139	1003	2010	2011	2170	2171
1143	1007	2012	2013	2172	2173
1144	1008	2018	2019	2177	2178
1147	1011	2020	2021	2179	2180
1149	1013	2026	2027	2185	2186
1150	1014	2022	2023	2181	2182
1151	1015	2031	2032	2191	2192
1154	1018	2033	2034	2193	2194
1155	1019	2028	2029	2187	2188
1156	1020	2037	2038	2197	2198
1158	1022	2014	2015	2174	
1159	1023	2030		2189	2190
1163	1027	2016	2017	2175	2176
1164	1028	2039	2040	2199	2200
1165	1029	2024	2025	2183	2184
1166	1030	2005	2006	2165	2166
1167	1031	2007		2167	
1168	1032	2003	2004	2163	2164
1170	1034	2008	2009	2168	2169
1157	NL				

NL No live litter.

APPENDIX 29 - continued

F₁ generation inter-relationships

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Maternal animal number	Paternal animal number	Selected animals			
		F ₁ male numbers		F ₁ female numbers	
1171	1035	2043		2205	2206
1172	1036	2050	2051	2213	
1174	1038	2075	2076	2236	2237
1179	1043	2073	2074	2234	2235
1181	1045	2052	2053	2214	2215
1182	1046	2041		2201	2202
1184	1048	2042		2203	2204
1185	1049	2048	2049	2211	2212
1187	1051	2079	2080	2240	
1188	1052	2065	2066	2228	2229
1189	1053	2054		2216	2217
1190	1054	2077	2078	2238	2239
1191	1055	2067	2068	2230	
1192	1056	2046	2047	2209	2210
1193	1057	2044	2045	2207	2208
1194	1058	2069	2070	2231	
1196	1060	2055	2056	2218	2219
1197	1061	2071	2072	2232	2233
1198	1062	2059	2060	2222	2223
1201	1065	2057	2058	2220	2221
1202	1066	2061	2062	2224	2225
1203	1067	2063	2064	2226	2227

APPENDIX 29 - continued

F₁ generation inter-relationships

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Maternal animal number	Paternal animal number	Selected animals				
		F ₁ male numbers		F ₁ female numbers		
1205	1069	2105	2106	2265		
1206	1070	2085	2086	2245	2246	
1207	1071	2089	2090	2248	2249	2250
1208	1072	-	-	2263	2264	
1212	1076	2111	2112	2271	2272	
1213	1077	2113	2114	2273	2274	
1218	1082	2087	2088	2247		
1219	1083	2115	2116	2275	2276	
1223	1087	2100	2101	2259	2260	
1225	1089	2081	2082	2241	2242	
1226	1090	2091	2092	2251	2252	
1227	1091	2107	2108	2266	2267	2268
1228	1092	2083	2084	2243	2244	
1230	1094	2117	2118	2277	2278	
1232	1096	2093	2094	2253	2254	
1233	1097	2109	2110	2269	2270	
1234	1098	2095	2096 2097	2255	2256	
1235	1099	2119	2120	2279	2280	
1236	1100	2102	2103 2104	2261	2262	
1237	1101	2098	2099	2257	2258	
1211	LD					
1217	LD					

LD Litter died.

APPENDIX 29 - continued

F₁ generation inter-relationships

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Maternal animal number	Paternal animal number	Selected animals			
		F ₁ male numbers		F ₁ female numbers	
1239	1103	2155	2156	2316	
1241	1105	2148		2309	2310
1242	1106	2133	2134	2294	2295
1245	1109	2135	2136	2296	2297
1246	1110	2121		2281	
1248	1112	2142	2143	2304	2305
1249	1113	2128		2288	2289
1251	1115	2122	2123	2282	2283
1253	1117	2140	2141	2302	2303
1254	1118	2126	2127	2286	2287
1255	1119	2151	2152	2313	2314
1256	1120	2153	2154	2315	
1257	1121	2149	2150	2311	2312
1258	1122	2137	2138	2298	2299
1259	1123	2156	2158	2317	2318
1262	1126	2129	2130	2290	2291
1265	1129	2139		2300	2301
1267	1131	2159	2160	2319	2320
1268	1132	2144	2145	2306	
1270	1134	2131	2132	2292	2293
1271	1135	2146	2147	2307	2308
1272	1136	2124	2125	2284	2285

APPENDIX 30

Individual bodyweights (g) of males (F₁)

Group	: 1 2 3 4														
Compound	: Control														
Intended dosage (mg/kg/day)	: 0 250 500 750														
Group Animal / Sex number	Week of treatment														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1M 2001	54	104	167	235	296	359	411	447	480	503	527	530	571	599	620
2002	50	93	146	200	261	320	372	415	443	463	480	492	514	532	544
2003	47	94	151	210	269	319	371	405	436	460	488	495	522	543	556
2004	52	102	156	214	271	326	364	404	442	466	491	509	523	542	558
2005	45	89	145	208	277	344	399	441	472	496	513	518	533	541	552
2006	52	100	153	219	285	343	394	429	458	472	497	506	519	541	549
2007	56	106	162	222	281	333	380	419	445	464	486	490	508	526	535
2008	50	98	151	213	282	332	379	420	449	474	494	498	527	555	589
2009	53	106	166	231	298	351	402	436	463	494	517	522	530	551	563
2010	37	77	126	179	241	295	357	398	433	452	473	475	502	520	546
2011	39	73	116	171	229	284	334	378	413	440	463	483	501	521	536
2012	53	97	154	214	282	341	396	442	476	496	515	514	535	553	566
2013	52	100	154	213	281	341	406	460	502	538	568	584	608	634	666
2014	49	93	146	214	275	337	395	436	468	486	511	513	543	567	584
2015	50	96	148	210	276	338	395	439	465	495	525	537	557	584	600
2016	53	97	152	204	262	310	349	379	411	432	449	465	479	493	512
2017	52	92	147	205	267	317	357	393	421	447	471	480	497	512	533
2018	55	89	147	202	262	314	362	402	435	464	483	491	514	536	554
2019	59	96	153	214	277	330	369	409	434	452	472	484	494	511	519
2020	54	91	138	192	241	293	332	367	400	421	439	443	452	469	500

APPENDIX 30 - continued

Individual bodyweights (g) of males (F₁)

Group		:	1	2	3	4											
Compound		:	Control	----- SC-19129 -----													
Intended dosage (mg/kg/day)		:	0	250	500	750											
Group Animal			Week of treatment														
/ Sex number			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1M	2021		53	92	148	209	265	309	355	390	426	454	478	482	511	531	549
	2022		61	100	158	215	279	336	387	433	457	484	508	524	546	564	581
	2023		65	108	166	226	290	350	396	438	464	490	512	512	523	538	554
	2024		42	75	123	176	231	282	326	371	402	424	443	450	462	471	486
	2025		54	91	151	223	298	364	418	461	496	528	557	562	576	594	613
	2026		50	89	142	205	262	321	371	416	436	458	467	480	489	495	493
	2027		53	96	159	222	283	346	414	472	512	552	578	602	634	667	667
	2028		56	94	155	226	290	360	422	469	504	533	556	572	588	604	617
	2029		44	77	128	194	259	328	398	452	487	521	551	566	590	619	639
	2030		61	97	151	213	274	335	382	421	454	474	493	502	512	525	527
	2031		59	91	145	205	259	316	367	410	452	478	506	532	543	564	584
	2032		56	86	140	203	255	326	384	433	469	506	533	545	552	573	584
	2033		56	87	134	194	255	337	398	454	494	522	549	574	595	622	648
	2034		58	87	145	217	279	352	408	464	498	536	568	577	599	632	655
	2035		49	74	117	169	214	269	307	345	372	402	417	424	438	451	452
	2036		44	70	110	158	210	272	324	363	398	426	457	468	484	507	525
	2037		50	83	140	206	273	333	386	431	464	494	515	529	540	554	567
	2038		50	79	130	194	257	321	385	426	464	502	532	548	573	600	619
	2039		61	87	143	214	286	348	403	456	494	531	557	561	581	597	618
	2040		62	89	137	200	262	326	385	427	463	480	507	519	538	557	570

Individual bodyweights (g) of males (F₁)

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APPENDIX 30 - continued

Individual bodyweights (g) of males (F₁)

Group	:	1	2	3	4											
Compound	:	Control	----- SC-19129 -----													
Intended dosage (mg/kg/day)	:	0	250	500	750											
Group Animal		Week of treatment														
/ Sex number		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2M	2061	50	85	136	194	254	311	348	384	407	424	437	443	452	469	489
	2062	53	93	147	210	274	343	402	447	492	514	535	541	564	581	602
	2063	48	78	128	187	246	300	342	381	412	432	453	462	485	496	510
	2064	48	82	130	185	247	303	341	379	416	440	457	464	483	488	496
	2065	54	87	134	184	238	294	341	381	412	430	439	449	469	497	511
	2066	57	99	153	216	286	344	403	451	494	520	545	556	594	626	661
	2067	62	89	137	193	254	325	373	417	454	478	497	513	528	544	564
	2068	63	90	139	194	261	322	366	413	449	486	511	527	544	573	596
	2069	63	97	158	212	280	332	381	421	454	474	489	501	521	546	562
	2070	57	87	142	203	267	334	388	432	462	480	505	523	528	540	551
	2071	53	78	126	179	236	288	325	361	388	414	428	448	455	471	490
	2072	55	87	138	190	244	300	338	373	400	416	431	444	450	463	478
	2073	51	84	134	194	247	299	333	361	382	394	411	417	421	433	440
	2074	53	85	131	184	229	268	306	340	366	384	398	412	425	438	452
	2075	52	83	132	190	251	312	364	411	446	478	493	511	529	548	568
	2076	51	81	133	194	266	322	368	401	438	472	503	525	551	580	606
	2077	45	72	121	180	245	309	369	410	446	484	506	521	552	573	595
	2078	45	74	131	192	260	321	378	428	461	500	518	524	544	564	576
	2079	61	89	149	221	294	355	413	459	490	519	549	561	566	586	598
	2080	63	91	145	208	274	334	384	426	458	478	504	511	518	536	549

APPENDIX 30 - continued

Individual bodyweights (g) of males (F₁)

Group	:	1	2	3	4										
Compound	:	Control	----- SC-19129 -----												
Intended dosage (mg/kg/day)	:	0	250	500	750										
Group Animal	Week of treatment														
/ Sex number	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
3M 2081	60	114	174	236	304	362	413	455	488	510	535	543	556	571	580
2082	55	113	169	224	301	361	408	453	484	501	517	528	546	559	572
2083	51	100	161	215	286	335	390	419	454	482	507	511	517	530	550
2084	51	103	161	213	283	333	378	417	446	472	488	500	518	533	551
2085	52	99	152	203	276	328	383	424	463	476	490	503	516	526	542
2086	47	90	143	207	273	338	393	439	477	494	510	514	536	555	560
2087	48	87	134	189	244	298	344	377	408	420	441	464	475	491	504
2088	51	91	146	211	279	334	381	413	457	492	516	533	557	581	604
2089	44	86	144	209	279	346	397	438	469	504	525	536	555	572	590
2090	41	81	133	194	261	323	379	424	457	496	507	522	540	562	574
2091	52	93	143	201	258	313	353	393	422	440	462	469	490	500	522
2092	55	98	152	213	274	328	375	414	438	458	472	472	491	501	519
2093	47	88	142	201	263	317	369	416	448	474	500	504	535	562	576
2094	51	93	142	197	254	306	354	396	426	448	471	488	496	517	528
2095	51	92	143	202	267	327	381	425	453	480	509	520	543	567	582
2096	49	89	138	203	268	330	388	440	478	520	543	552	568	584	599
2097	51	93	143	197	255	318	376	426	468	498	518	514	519	532	564
2098	44	85	132	184	240	298	346	395	431	451	476	486	499	519	537
2099	43	82	128	184	242	295	341	375	414	441	462	466	489	499	524
2100	51	89	138	190	240	293	331	366	399	421	443	441	468	470	490

APPENDIX 30 - continued

Individual bodyweights (g) of males (F_1)

Group	:	1	2	3	4											
Compound	:	Control	----- SC-19129 -----													
Intended dosage (mg/kg/day)	:	0	250	500	750											
Group Animal		Week of treatment														
/ Sex number																
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
3M	2101	56	95	144	199	266	326	374	414	448	462	486	486	515	538	556
	2102	57	101	150	204	265	322	372	415	449	476	499	502	524	537	557
	2103	50	83	133	191	254	311	362	402	428	466	496	508	530	546	568
	2104	51	86	131	187	246	301	353	400	439	464	490	496	513	536	552
	2105	46	78	128	181	243	304	349	388	417	435	456	465	483	497	512
	2106	48	80	132	185	241	300	332	367	392	402	414	424	439	447	451
	2107	39	69	110	157	204	254	300	333	361	378	395	404	418	428	444
	2108	55	90	140	198	254	305	334	367	394	414	424	438	452	467	480
	2109	53	93	154	221	291	361	418	456	490	512	538	549	573	592	612
	2110	51	89	152	213	289	346	397	434	466	491	519	530	547	564	586
	2111	59	93	150	214	282	348	411	464	508	546	577	592	611	639	662
	2112	56	88	139	201	261	328	386	432	466	494	518	527	554	567	584
	2113	56	89	144	211	285	344	403	436	466	494	516	531	552	564	582
	2114	54	83	132	192	256	314	356	392	409	422	435	451	471	486	492
	2115	55	89	137	197	258	314	381	421	450	485	505	510	542	563	588
	2116	57	87	144	208	274	341	395	437	468	491	524	528	545	570	596
	2117	63	90	144	204	266	322	373	416	438	462	481	496	502	511	520
	2118	59	91	150	218	293	365	426	478	516	555	581	601	622	643	663
	2119	54	73	117	169	231	286	331	371	398	417	444	453	466	486	503
	2120	51	73	114	169	230	285	338	384	422	445	471	483	501	517	537

APPENDIX 30 - continued

Individual bodyweights (g) of males (F₁)

Group	: 1 2 3 4														
Compound	: Control ----- SC-19129 -----														
Intended dosage (mg/kg/day)	: 0 250 500 750														
Group Animal / Sex number	Week of treatment														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4M 2121	50	97	145	192	254	310	352	388	414	440	460	472	491	510	524
2122	47	99	153	203	262	309	335	363	381	404	416	422	433	444	462
2123	44	95	146	216	284	343	386	420	442	462	478	478	498	515	533
2124	47	98	150	208	267	321	359	392	405	426	447	457	479	496	509
2125	50	106	163	224	288	343	393	423	445	468	492	492	516	533	554
2126	54	96	148	205	272	339	394	437	462	492	510	518	540	567	586
2127	65	117	180	242	309	369	414	445	471	498	511	515	537	554	572
2128	63	105	161	224	279	339	383	416	444	467	481	481	491	501	516
2129	53	100	157	224	296	355	403	444	472	498	518	528	539	551	562
2130	56	98	152	212	276	332	371	407	427	452	457	469	479	493	498
2131	50	93	153	210	286	342	396	441	479	494	532	542	566	591	612
2132	42	82	136	194	259	308	351	383	416	439	454	463	478	488	501
2133	50	97	151	214	281	338	382	411	437	445	453	466	483	501	510
2134	54	103	167	234	307	373	420	454	498	534	561	570	594	608	633
2135	51	100	161	217	284	347	401	448	482	514	544	549	580	602	632
2136	49	93	151	207	270	319	369	411	444	464	481	485	500	518	540
2137	48	87	144	204	270	330	378	417	452	474	496	505	532	546	566
2138	50	96	155	210	277	337	394	438	463	484	500	511	534	546	558
2139	51	92	136	183	234	279	329	356	379	401	425	427	439	454	472
2140	56	97	152	211	277	324	370	410	432	455	472	481	497	504	521

APPENDIX 30 - continued

Individual bodyweights (g) of males (F_1)

Group	:	1	2	3	4										
Compound	:	Control	----- SC-19129 -----												
Intended dosage (mg/kg/day)	:	0	250	500	750										
Group Animal / Sex number		Week of treatment													
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4M 2141	57	96	147	198	258	313	358	396	431	458	481	484	488	494	501
2142	53	97	150	210	278	332	392	426	457	482	503	516	529	543	558
2143	52	87	129	181	236	282	309	334	360	374	395	400	421	433	442
2144	48	85	139	202	261	312	363	396	418	437	461	463	485	493	503
2145	48	79	133	195	265	316	360	398	436	464	489	492	518	531	552
2146	43	77	131	186	249	296	344	377	407	425	445	450	462	476	498
2147	40	73	126	184	240	298	346	384	415	436	459	468	482	504	524
2148	62	94	151	213	271	322	356	389	413	430	443	454	479	492	506
2149	55	76	127	182	245	298	335	372	405	422	439	448	463	486	502
2150	48	78	128	188	251	307	352	384	406	424	434	444	458	478	591*
2151	54	86	142	208	270	331	395	439	473	498	518	531	541	557	572
2152	44	69	118	183	238	298	358	400	432	452	476	484	502	514	526
2153	58	89	143	209	274	333	389	438	475	507	528	539	552	580	588
2154	55	85	138	204	269	331	388	433	466	488	504	514	532	547	568
2155	56	77	122	179	235	282	332	367	392	406	427	426	441	459	467
2156	57	78	119	177	239	297	353	394	423	448	475	482	501	519	538
2157	49	73	121	178	241	288	331	363	392	409	430	438	438	442	450
2158	52	78	130	189	247	292	334	364	388	410	433	445	453	463	472
2159	55	82	132	195	266	340	408	456	499	532	562	580	506	628	643
2160	50	75	126	186	254	321	387	435	483	508	533	554	572	592	603

* Suspected recording error, excluded from group mean value.

APPENDIX 31

Individual bodyweights (g) of females before pairing (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Animal / Sex number	Week of treatment										
		0	1	2	3	4	5	6	7	8	9	10
1F	2161	49	92	127	154	180	197	200	219	231	232	236
	2162	57	104	145	182	212	242	263	277	280	296	311
	2163	47	88	118	144	174	193	208	218	236	252	256
	2164	45	86	120	150	177	207	220	234	248	260	262
	2165	48	94	126	166	191	210	232	246	258	264	279
	2166	45	92	129	165	196	218	232	239	257	270	267
	2167	58	98	137	171	196	225	249	268	274	285	288
	2168	45	90	134	176	210	238	253	280	300	310	316
	2169	39	86	125	164	192	248	266	280	285	309	329
	2170	37	70	103	141	171	201	225	253	271	282	292
	2171	36	73	111	146	181	214	231	242	254	270	274
	2172	52	96	134	170	201	237	257	276	282	298	313
	2173	53	94	129	159	188	215	242	253	271	274	285
	2174	46	84	120	155	185	200	227	242	253	254	268
	2175	45	81	113	138	167	182	201	217	226	230	240
	2176	48	91	130	167	195	221	237	252	261	268	274
	2177	48	78	113	149	174	199	208	230	244	250	251
	2178	52	86	125	154	194	219	249	273	279	298	298
	2179	55	91	127	161	188	202	209	227	239	242	245
	2180	51	86	120	143	169	190	200	208	209	230	230
	2181	42	79	119	151	181	208	237	255	267	270	284
	2182	46	78	108	138	161	182	201	217	229	240	244
	2183	50	86	121	151	185	215	234	248	271	284	285
	2184	52	90	127	171	204	237	253	279	302	316	315
	2185	57	96	144	181	207	234	247	256	272	286	291
	2186	51	82	118	146	189	205	225	242	242	262	258
	2187	45	84	125	156	189	212	236	244	264	258	269
	2188	48	85	124	160	193	219	249	272	290	307	315
	2189	51	92	132	171	204	234	256	271	285	302	307
	2190	54	94	140	176	207	229	246	264	281	284	281
	2191	52	84	117	152	184	210	231	244	263	278	282
	2192	58	80	118	154	186	227	254	278	289	312	324
	2193	54	85	129	169	200	234	262	282	286	304	315
	2194	46	73	109	145	165	193	216	230	234	246	255
	2195	39	61	94	126	152	177	190	207	219	230	231
	2196	36	62	97	133	162	188	208	231	245	252	265
	2197	45	72	110	147	170	206	229	242	252	268	278
	2198	41	67	106	149	182	211	256	266	267	276	284
	2199	50	73	112	147	178	206	224	233	260	270	272
	2200	53	77	109	147	174	201	226	245	250	254	279

APPENDIX 31 - continued

Individual bodyweights (g) of females before pairing (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Animal / Sex number	Week of treatment										
		0	1	2	3	4	5	6	7	8	9	10
2F	2201	51	100	139	169	202	226	248	263	301	300	299
	2202	50	96	136	166	182	201	216	231	246	254	253
	2203	48	88	130	159	184	204	230	247	259	264	276
	2204	50	93	132	160	179	202	215	222	239	248	250
	2205	43	83	122	149	174	195	206	212	228	235	236
	2206	47	87	118	148	165	189	204	212	216	235	240
	2207	44	81	120	153	176	195	215	230	239	240	253
	2208	45	83	122	156	180	203	217	233	243	251	258
	2209	53	94	129	164	182	199	221	226	239	242	253
	2210	45	88	130	163	193	217	234	239	256	266	265
	2211	59	105	146	180	204	237	268	284	294	308	316
	2212	51	93	134	164	192	203	231	239	247	266	274
	2213	44	76	110	144	171	191	213	223	241	254	255
	2214	44	82	119	151	175	196	211	232	248	258	257
	2215	45	82	118	148	168	198	220	231	241	255	263
	2216	53	95	136	167	192	220	243	259	273	286	295
	2217	54	100	148	184	207	223	247	265	268	270	286
	2218	37	68	103	140	166	186	203	222	234	237	236
	2219	41	73	108	143	173	199	238	253	256	266	274
	2220	49	85	120	150	178	207	236	261	265	292	293
	2221	51	91	133	170	203	224	273	272	294	312	342
	2222	49	86	124	157	182	205	217	245	257	266	285
	2223	50	89	129	163	183	224	240	266	272	296	297
	2224	47	81	119	152	175	196	226	241	252	266	272
	2225	50	87	128	167	193	221	240	253	273	270	290
	2226	33	58	90	124	149	168	190	196	217	228	228
	2227	46	73	110	152	177	195	208	230	243	250	248
	2228	44	76	111	144	170	194	213	228	247	249	254
	2229	48	83	121	153	186	214	234	260	269	286	294
	2230	60	86	124	158	178	202	223	232	236	257	260
	2231	52	85	122	160	188	216	246	265	276	280	291
	2232	45	66	100	129	152	174	187	205	220	227	230
	2233	52	81	120	155	178	212	232	262	271	276	281
	2234	52	86	129	165	192	212	238	257	264	271	281
	2235	50	80	116	148	175	202	220	236	245	256	262
	2236	49	76	121	161	193	207	241	263	278	291	295
	2237	48	69	102	143	161	181	203	214	218	232	234
	2238	39	63	101	135	168	197	212	236	256	266	268
	2239	44	73	117	155	188	208	236	258	276	282	297
	2240	54	80	122	159	176	204	233	230	259	262	278

APPENDIX 31 - continued

Individual bodyweights (g) of females before pairing (F₁)

Group	:	1	2	3	4							
Compound	:	Control	-----	SC-19129	-----							
Intended dosage (mg/kg/day)	:	0	250	500	750							
Group Animal / Sex number		0	1	2	3	Week of treatment						
						4	5	6	7	8	9	10
3F 2241	53	100	145	178	212	241	263	270	284	290	291	
2242	54	100	138	176	205	223	238	259	276	282	283	
2243	46	90	123	152	177	203	220	236	245	260	264	
2244	38	72	104	132	153	171	191	206	218	222	229	
2245	48	94	131	164	195	221	238	252	271	286	292	
2246	48	95	133	167	189	223	241	258	264	282	293	
2247	43	78	112	135	164	186	209	229	236	257	255	
2248	41	80	115	144	169	190	205	210	230	242	240	
2249	40	80	118	152	182	206	234	248	272	278	290	
2250	41	79	121	157	185	208	231	250	261	266	281	
2251	54	93	132	168	202	231	257	276	292	296	310	
2252	54	94	132	167	191	209	232	245	257	272	280	
2253	48	82	126	161	190	215	239	257	275	288	288	
2254	50	86	132	170	207	236	263	279	294	298	311	
2255	40	78	112	150	176	198	226	241	255	257	274	
2256	36	67	108	139	167	194	216	233	249	264	272	
2257	37	73	113	146	181	206	217	241	257	266	271	
2258	45	85	131	169	188	227	232	244	256	273	275	
2259	54	84	118	149	173	196	213	232	241	248	248	
2260	53	92	132	172	216	235	271	286	295	306	325	
2261	57	94	131	163	189	216	237	250	264	278	288	
2262	47	82	121	158	189	214	230	252	271	272	278	
2263	35	68	104	131	152	178	201	216	228	238	247	
2264	38	72	108	140	166	186	214	231	237	246	259	
2265	36	65	96	124	145	166	183	196	200	214	221	
2266	49	82	119	152	176	201	225	236	246	249	264	
2267	43	75	116	144	164	184	204	217	232	244	250	
2268	40	71	106	139	168	192	213	229	238	246	256	
2269	42	75	111	143	173	201	223	234	253	266	263	
2270	44	77	120	151	185	216	233	248	264	278	284	
2271	50	77	122	161	182	208	230	239	257	278	287	
2272	54	82	120	154	179	187	215	234	239	243	258	
2273	56	86	131	169	195	224	236	256	264	284	278	
2274	44	67	106	132	160	186	200	216	228	230	227	
2275	39	67	98	132	156	200	205	230	243	250	265	
2276	46	77	117	158	190	220	235	261	287	296	299	
2277	59	87	135	176	207	232	251	261	285	296	304	
2278	54	80	126	164	188	224	252	271	291	292	310	
2279	49	73	104	138	159	177	208	216	230	242	251	
2280	50	72	104	137	160	187	211	230	246	240	256	

APPENDIX 31 - continued

Individual bodyweights (g) of females before pairing (F₁)

Group	:	1	2	3	4								
Compound	:	Control	-----	SC-19129	-----								
Intended dosage (mg/kg/day)	:	0	250	500	750								
Group Animal / Sex number		0	1	2	3	Week of treatment							
		0	1	2	3	4	5	6	7	8	9	10	
4F 2281	47	86	118	154	179	208	227	242	249	261	278		
2282	47	91	127	158	180	200	224	243	250	262	265		
2283	44	87	127	156	180	205	221	234	245	263	262		
2284	43	88	131	161	182	205	215	242	245	248	258		
2285	42	84	120	147	174	195	212	221	237	248	249		
2286	56	96	138	173	199	223	238	256	271	277	275		
2287	59	104	147	188	223	254	272	294	313	324	330		
2288	57	93	127	157	179	206	227	241	246	266	276		
2289	57	87	125	159	182	203	220	238	248	252	256		
2290	57	94	137	167	188	202	221	241	249	249	253		
2291	52	94	137	168	186	214	235	247	253	270	279		
2292	50	91	135	168	186	214	221	253	261	266	282		
2293	38	74	114	152	192	222	239	267	282	294	300		
2294	49	87	136	168	198	218	248	261	277	280	291		
2295	49	87	125	161	180	205	224	241	264	292	292		
2296	51	89	134	171	204	226	242	262	271	271	274		
2297	46	88	130	162	187	204	227	244	252	250	259		
2298	52	90	130	163	192	221	241	255	263	270	274		
2299	51	93	138	175	212	236	262	278	290	301	304		
2300	52	90	126	153	183	205	227	251	260	264	269		
2301	51	85	118	143	167	176	204	208	215	220	225		
2302	57	92	131	161	184	203	230	243	246	252	258		
2303	58	97	139	169	192	213	241	261	269	269	281		
2304	43	78	110	141	156	178	195	200	204	214	212		
2305	45	78	115	142	165	186	206	220	225	231	233		
2306	39	72	113	149	181	208	233	252	268	276	285		
2307	42	76	121	156	163	211	220	240	249	252	253		
2308	45	76	116	148	184	198	222	238	246	256	263		
2309	42	64	106	141	168	183	197	218	227	230	244		
2310	62	91	137	163	188	205	231	247	255	259	271		
2311	45	72	102	143	175	197	228	242	258	268	280		
2312	48	78	119	148	183	212	236	261	271	284	290		
2313	45	73	118	157	191	216	238	251	264	278	280		
2314	48	76	116	150	178	206	226	235	250	260	267		
2315	46	57	109	161	185	219	239	274	287	296	314		
2316	51	68	101	130	156	174	190	200	213	226	229		
2317	47	66	105	138	167	191	206	220	223	241	248		
2318	49	70	105	147	169	193	211	228	233	242	248		
2319	42	63	103	145	180	208	228	234	258	274	273		
2320	56	79	116	153	179	212	239	269	278	295	298		

APPENDIX 32

Food intake (g/rat/week) - individual cage values for males between weaning and selection^A (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Litter number	Number of males	Mean intake (g/rat/week)	Litter number	Number of males	Mean intake (g/rat/week)
Group 1			Group 2		
1137	4	61	1171	4	60
1138	4	72	1172	3	68
1139	4	56	1174	4	80
1143	4	73	1179	4	76
1144	4	78	1181	4	82
1147	4	79	1182	4	82
1149	4	73	1184	4	73
1150	4	83	1185	6	62
1151	4	70	1187	4	72
1154	4	83	1188	4	74
1155	4	70	1189	4	79
1156	3	77	1190	4	65
1158	4	78	1191	4	74
1159	4	80	1192	4	80
1163	4	73	1193	3	87
1164	4	68	1194	4	76
1165	4	71	1196	4	63
1166	4	64	1197	3	73
1167	4	79	1198	5	76
1168	4	68	1201	4	82
1170	4	77	1202	4	79
			1203	4	64

A Animals housed as littermates for 5-9 days after weaning.

APPENDIX 32 - continued

Food intake (g/rat/week) - individual cage
values for males between weaning and selection^A (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Litter number	Number of males	Mean intake (g/rat/week)	Litter number	Number of males	Mean intake (g/rat/week)
Group 3			Group 4		
1205	6	58	1239	4	60
1206	4	70	1241	3	102
1207	4	71	1242	4	72
1212	3	96	1245	4	66
1213	4	81	1246	4	68
1218	6	62	1248	4	77
1219	4	82	1249	4	73
1223	4	72	1251	4	79
1225	4	79	1253	4	78
1226	4	73	1254	4	84
1227	4	72	1255	4	76
1228	4	72	1256	4	68
1230	5	86	1257	4	83
1232	4	71	1258	3	77
1233	4	72	1259	4	63
1234	4	64	1262	4	84
1235	5	60	1265	4	72
1236	4	75	1267	4	60
1237	3	81	1268	4	74
			1270	4	82
			1271	4	62
			1272	4	73
1208	No males.				

A Animals housed as littermates for 5-9 days after weaning.

APPENDIX 33

Food intake (g/rat/week) - individual
cage values for males after selection (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group Cage ^A / sex number		Week of treatment											
		2	3	4	5	6	7	8	9	10 ^B	13	14	
1M	1	135	162	181	203	216	212	213	211	191	202	216	
	2	131	162	181	205	205	206	211	207	201	194	215	
	3	129	159	176	200	213	222	213	213	207	198	214	
	4	130	151	164	185	180	185	193	193	178	167	188	
	5	126	164	174	193	199	213	211	205	197	182	197	
	6	136	160	182	203	222	224	216	214	202	200	200	
	7	121	159	185	205	211	223	219	205	210	204	190	
	8	118	158	182	193	206	210	211	216	204	190	194	
2M	9	134	163	183	204	212	205	197	194	188	183	193	
	10	134	163	185	203	211	214	213	220	204	199	223	
	11	128	158	180	204	208	205	205	206	194	192	200	
	12	125	164	176	201	205	208	206	207	198	198	206	
	13	120	160	170	197	202	204	202	190	184	175	188	
	14	127	160	180	199	210	210	209	208	198	173	204	
	15	123	159	165	190	208	199	193	187	181	167	195	
	16	124	160	176	204	213	215	215	220	209	173	204	
3M	17	135	165	186	204	208	212	210	211	202	184	199	
	18	124	163	181	202	210	210	209	209	205	192	206	
	19	129	161	179	202	204	205	213	202	202	205	210	
	20	124	157	182	201	210	212	220	215	205	185	210	
	21	124	156	169	198	205	209	209	200	197	183	190	
	22	125	156	175	192	195	196	205	192	182	171	183	
	23	130	158	180	203	216	219	210	211	206	207	219	
	24	122	163	181	198	209	214	208	206	200	190	202	
4M	25	134	162	172	196	195	194	206	191	178	177	188	
	26	141	162	185	204	203	205	197	188	186	179	195	
	27	139	164	180	201	206	204	206	205	191	207	217	
	28	133	162	180	207	203	211	203	208	195	185	195	
	29	127	164	181	202	208	202	214	206	197	181	198	
	30	123	155	167	190	190	192	190	182	175	176	184	
	31	118	164	181	190	212	216	208	206	192	188	198	
	32	113	162	182	200	217	216	220	213	198	196	202	

A 5 animals / cage.

B Animals paired for mating weeks 11 and 12.

APPENDIX 34

Food intake (g/rat/week) - individual cage values for females between weaning and selection^A (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Litter number	Number of females	Mean intake (g/rat/week)	Litter number	Number of females	Mean intake (g/rat/week)
Group 1			Group 2		
1137	4	48	1171	4	65
1138	4	82	1172	4	64
1139	4	59	1174	4	69
1143	4	76	1179	4	72
1144	4	72	1181	4	88
1147	4	76	1182	4	80
1149	4	74	1184	4	73
1150	4	77	1185	2	91
1151	4	66	1187	4	67
1154	4	76	1188	4	67
1155	4	66	1189	4	73
1156	5	61	1190	4	63
1158	4	68	1191	4	73
1159	4	72	1192	4	76
1163	4	72	1193	5	66
1164	4	64	1194	4	63
1165	4	69	1196	4	60
1166	4	64	1197	5	65
1167	4	77	1198	3	83
1168	4	72	1201	4	68
1170	4	78	1202	4	72
			1203	4	53

A Animals housed as littermates for 5-9 days after weaning.

APPENDIX 34 - continued

Food intake (g/rat/week) - individual cage values for females between weaning and selection^A (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Litter number	Number of females	Mean intake (g/rat/week)	Litter number	Number of females	Mean intake (g/rat/week)
Group 3			Group 4		
1205	2 ^a	70	1239	3	61
1206	4 ^a	67	1241	5	69
1207	4	68	1242	4	77
1208	2	75	1245	4	70
1212	5	77	1246	4	74
1213	4	80	1248	4	72
1218	1	117	1249	2	90
1219	4	63	1251	4	81
1223	4	82	1253	4	76
1225	4	83	1254	4	95
1226	4	82	1255	3	79
1227	4	60	1256	3	93
1228	4	71	1257	4	70
1230	3	83	1258	5	72
1232	4	70	1259	4	73
1233	4	63	1262	4	85
1234	4	69	1265	4	78
1235	3	74	1267	4	75
1236	4	69	1268	4	72
1237	5	64	1270	4	70
			1271	4	63
			1272	4	71

A Animals housed as littermates for 5-9 days after weaning.

a One pup died during period, data based on number of rat/day units.

APPENDIX 35

Food intake (g/rat/week) - individual cage values for females between selection and pairing (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Cage ^A / sex number	Week of treatment								
		2	3	4	5	6	7	8	9	10
1F	33	116	138	139	138	135	136	149	139	134
	34	116	144	155	165	159	159	159	156	144
	35	103	133	141	149	146	144	145	144	144
	36	114	130	138	136	138	142	133	138	131
	37	115	138	149	150	150	155	156	153	138
	38	111	133	143	145	150	152	145	146	133
	39	104	131	140	157	160	159	190*	161	142
	40	98	125	136	141	145	139	139	137	135
2F	41	121	139	138	144	140	144	151	141	138
	42	118	141	138	150	144	135	146	136	139
	43	115	136	143	151	145	147	150	142	133
	44	112	135	131	142	153	142	136	133	138
	45	115	139	138	154	156	160	156	158	152
	46	99	135	135	141	145	134	147	135	130
	47	109	132	140	147	142	144	138	129	127
	48	105	141	135	150	150	145	154	143	142
3F	49	117	135	139	142	139	141	145	136	129
	50	108	132	129	139	149	146	144	142	131
	51	121	148	158	158	168	153	155	163	149
	52	112	140	137	141	143	149	147	145	141
	53	106	134	132	137	140	139	136	136	136
	54	110	130	129	138	141	135	145	129	129
	55	105	137	136	143	136	142	144	143	139
	56	110	144	131	145	148	149	152	144	137
4F	57	115	131	134	133	135	131	143	140	137
	58	119	137	158	146	150	147	149	145	137
	59	121	139	140	151	151	153	168	154	144
	60	121	146	154	151	155	156	152	141	140
	61	112	133	139	137	141	137	146	133	132
	62	115	139	136	140	144	142	149	141	130
	63	109	139	151	154	153	150	152	145	138
	64	101	136	140	154	145	143	146	139	133

A 5 animals / cage.

* Excluded, suspected recording error.

APPENDIX 36

Individual oestrous cycle length,
mating performance, fertility and gestation length (F₁-F₂)

Group 1 : Control

Female number	Oestrous cycle length (days)	Pre-coital interval (days)	Male number	Pregnancy	Gestation length (days)
2161	4	4	2031	+	22½
2162	4	2	2032	+	22
2163	4	3	2033	+	22
2164	4	3	2034	+	T
2165	4	1	2035	+	22½
2166	4	3	2036	+	22
2167	5	1	2037	+	22
2168	4	4	2038	+	23
2169	4/5 (A.P.)	19	2035	+	T
2170	4	4	2040	+	T
2171	4	3	2001	+	22½
2172	4	2	2002	+	22
2173	4	1	2003	+	T
2174	4	1	2004	+	T
2175	4	1	2005	+	T
2176	4	2	2006	+	22
2177	4	4	2007	+	T
2178	4/5	4	2008	+	23½
2179	4	4	2009	+	23
2180	4	3	2010	+	T
			2039	F.M.	

continued on next page

A.P. Acyclic during pairing.

F.M. Failed to mate.

T Killed Day 20 post coitum for teratological examination.

APPENDIX 36 - continued

Individual oestrous cycle length,
mating performance, fertility and gestation length (F₁-F₂)

Group 1 : Control

continued from previous page

Female number	Oestrous cycle length (days)	Pre-coital interval (days)	Male number	Pregnancy	Gestation length (days)
2181	4	1	2011	+	23
2182	4	4	2012	+	T
2183	4	3	2013	+	T
2184	4	4	2014	+	22½
2185	4	3	2015	+	T
2186	4/5	4	2016	+	T
2187	5	3	2017	+	22½
2188	5	2	2018	+	T
2189	4	2	2019	+	T
2190	4/5	4	2020	+	23
2191	4	3	2021	+	T
2192	4	2	2022	-	T
2193	4	2	2023	+	T
2194	4	2	2024	+	22
2195	4	4	2025	+	T
2196	4	1	2026	+	23
2197	4	2	2027	-	-
2198	4	6	2028	+	23
2199	4	3	2029	-	T
2200	4	1	2030	+	T

T Killed Day 20 post coitum for teratological examination.

APPENDIX 36 - continued

Individual oestrous cycle length,
mating performance, fertility and gestation length (F₁-F₂)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Female number	Oestrous cycle length (days)	Pre-coital interval (days)	Male number	Pregnancy	Gestation length (days)
2201	4	3	2071	+	22
2202	4	4	2072	+	22½
2203	4	1	2073	+	22½
2204	4	3	2074	+	22½
2205	4	3	2075	+	22½
2206	4	2	2076	+	22½
2207	4	1	2077	+	T
2208	4/5	4	2078	+	T
2209	4	1	2079	+	T
2210	4	3	2080	+	T
2211	4	2	2041	+	T
2212	4	2	2042	+	22½
2213	4	4	2043	+	22½
2214	4	4	2044	+	24½
2215	4	2	2045	+	22½
2216	4	2	2046	+	T
2217	4	1	2047	+	23
2218	4	4	2048	+	T
2219	4	2	2049	+	T
2220	4/5	2	2050	+	22

continued on next page

T Killed Day 20 post coitum for teratological examination.

APPENDIX 36 - continued

Individual oestrous cycle length,
mating performance, fertility and gestation length (F₁-F₂)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

continued from previous page

Female number	Oestrous cycle length (days)	Pre-coital interval (days)	Male number	Pregnancy	Gestation length (days)
2221	Ac	4	2051	+	22½
2222	4	1	2052	+	22½
2223	5	1	2053	+	22½
2224	I.C.	1	2054	+	T
2225	4/5	2	2055	+	T
2226	4	3	2056	+	T
2227	4	4	2057	+	T
2228	I.C.	1	2058	+	22½
2229	4/5	2	2059	-	-
2230	4	2	2060	+	T
2231	4	1	2061	-	T
2232	4	4	2062	+	T
2233	4	1	2063	+	23
2234	4	1	2064	+	T
2235	4	1	2065	+	T
2236	4	3	2066	+	T
2237	4	2	2067	+	22½
2238	4	1	2068	-	T
2239	4	1	2069	+	23
2240	Ac	5	2070	+	T

I.C. Irregular cycle.

Ac Acyclic and/or pseudopregnant.

T Killed Day 20 post coitum for teratological examination.

APPENDIX 36 - continued

Individual oestrous cycle length,
mating performance, fertility and gestation length (F₁-F₂)

Group 3 : SC-19129 500 mg/kg/day (intended)

Female number	Oestrous cycle length (days)	Pre-coital interval (days)	Male number	Pregnancy	Gestation length (days)
2241	4	4	2111	+	22½
2242	4	4	2112	+	T
2243	4	2	2113	+	22½
2244	4	1	2114	+	22½
2245	4	3	2115	+	23
2246	4	2	2116	+	23
2247	4/5	1	2117	+	22½
2248	4	3	2118	-	T
2249	4	2	2119	+	T
2250	4	1	2120	+	T
2251	4	4	2081	+	22½
2252	4	2	2082	+	T
2253	4	8	2083	+	T
2254	4	1	2084	+	23
2255	4	1	2085	+	T
2256	4	3	2086	+	22½
2257	4	4	2087	+	T
2258	5	1	2088	+	T
2259	4	4	2089	+	T
2260	Ac	2	2090	+	23

continued on next page

Ac Acyclic and/or pseudopregnant.

T Killed Day 20 post coitum for teratological examination.

APPENDIX 36 - continued

Individual oestrous cycle length,
mating performance, fertility and gestation length (F₁-F₂)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

continued from previous page

Female number	Oestrous cycle length (days)	Pre-coital interval (days)	Male number	Pregnancy	Gestation length (days)
2261	4	3	2091	+	T
2262	4	4	2092	+	22½
2263	4	3	2093	+	T
2264	4	1	2094	+	23
2265	4	2	2095	+	T
2266	4	1	2096	+	22½
2267	4	1	2097	+	23
2268	4	1	2098	+	23
2269	4	3	2099	+	22½
2270	4	3	2100	+	22½
2271	4	3	2101	+	T
2272	5	3	2102	+	23
2273	5	1	2103	+	T
2274	4	4	2104	+	T
2275	4	1	2105	+	T
2276	4	4	2106	+	23
2277	4	3	2107	+	23
2278	4	1	2108	+	T
2279	4	3	2109	+	T
2280	4	1	2110	+	T

T Killed Day 20 post coitum for teratological examination.

APPENDIX 36 - continued

Individual oestrous cycle length,
mating performance, fertility and gestation length (F₁-F₂)

Group 4 : SC-19129 750 mg/kg/day (intended)

Female number	Oestrous cycle length (days)	Pre-coital interval (days)	Male number	Pregnancy	Gestation length (days)
2281	4	2	2151	+	T
2282	4	1	2152	+	22
2283	4	2	2153	+	22
2284	4	1	2154	+	23
2285	4	3	2155	+	22½
2286	4	4	2156	-	-
2287	4	4	2157	+	22½
2288	4	2	2158	+	T
2289	5	1	2159	+	T
2290	4	1	2160	+	T
2291	4	2	2121	+	T
2292	4	1	2122	+	22½
2293	4	4	2123	+	23
2294	4	1	2124	+	22½
2295	4	2	2125	+	22
2296	4	4	2126	-	T
2297	4	1	2127	+	T
2298	4	2	2128	+	T
2299	4	3	2129	+	23
2300	4	4	2130	+	22½

continued on next page

T Killed Day 20 post coitum for teratological examination.

APPENDIX 36 - continued

Individual oestrous cycle length,
mating performance, fertility and gestation length (F₁-F₂)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

continued from previous page

Female number	Oestrous cycle length (days)	Pre-coital interval (days)	Male number	Pregnancy	Gestation length (days)
2301	4	4	2131	+	T
2302	4	1	2132	+	T
2303	4	1	2133	+	22
2304	4	2	2134	+	22½
2305	4	1	2135	+	22½
2306	4	1	2136	+	22½
2307	4	4	2137	-	T
2308	4	2	2138	+	22½
2309	4/5	2	2139	+	22½
2310	4	1	2140	+	T
2311	4/5	4	2141	+	T
2312	5	1	2142	+	T
2313	4	3	2143	+	22½
2314	4	3	2144	+	23
2315	5	3	2145	+	T
2316	4	3	2146	+	T
2317	4	2	2147	+	T
2318	4	1	2148	+	T
2319	4	3	2149	+	T
2320	4	3	2150	+	T

T Killed Day 20 post coitum for teratological examination.

APPENDIX 37

Individual bodyweights (g) of females after mating (F₁ - F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group Animal	Day post coitum				
/ Sex number	0	6	13	20	

1F	2161	246	276	303	383
	2162	307	337	371	429
	2163	260	290	322	379
	2164	273	297	323	389
	2165	286	316	306	413
	2166	272	301	327	414
	2167	294	315	348	418
	2168	328	359	395	483
	2169	358	388	410	465
	2170	301	335	372	470
	2171	268	309	350	443
	2172	317	351	375	439
	2173	283	308	325	396
	2174	274	297	315	378
	2175	243	276	297	376
	2176	275	299	329	411
	2177	268	302	330	401
	2178	309	339	365	400
	2179	253	289	316	394
	2180	238	267	301	371
	2181	280	316	334	401
	2182	252	284	310	381
	2183	285	311	366	412
	2184	309	336	359	435
	2185	304	332	371	427
	2186	262	292	322	403
	2187	270	301	334	429
	2188	319	350	378	441
	2189	307	330	366	388
	2190	294	334	381	473
	2191	290	329	365	417
	2193	321	345	374	448
	2194	258	291	314	388
	2195	236	258	288	359
	2196	262	289	321	398
	2198	278	321	338	381
	2200	285	328	363	434
	2192NP	325	352	378	385
	2197NP	276	302	314	302
	2199NP	280	319	351	353

NP Not pregnant.

APPENDIX 37 - continued

Individual bodyweights (g) of females after mating (F₁ - F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group Animal / Sex number	Day post 0	coitum 6	13	20
2F 2201	307	327	356	431
2202	263	296	323	396
2203	284	316	345	431
2204	261	291	321	409
2205	235	270	300	360
2206	240	273	309	373
2207	250	290	313	406
2208	258	290	323	416
2209	257	291	322	400
2210	273	301	328	402
2211	318	336	363	439
2212	274	298	327	402
2213	263	294	328	392
2214	271	305	331	359
2215	268	297	333	411
2216	304	335	361	443
2217	289	331	362	406
2218	246	276	308	394
2219	275	293	318	392
2220	297	321	356	430
2221	338	364	390	438
2222	285	328	362	425
2223	308	344	376	447
2224	278	308	337	436
2225	299	324	345	406
2226	231	253	279	344
2227	257	286	316	386
2228	255	281	317	391
2230	264	251	307	381
2232	237	261	293	359
2233	284	300	310	381
2234	287	311	339	408
2235	268	295	312	394
2236	307	336	362	430
2237	246	279	311	392
2239	300	328	365	435
2240	304	325	352	434
2229NP	301	323	337	328
2231NP	290	318	331	327
2238NP	278	310	340	338

NP Not pregnant.

APPENDIX 37 - continued

Individual bodyweights (g) of females after mating (F₁ - F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / Sex	Animal number	Day post coitum			
		0	6	13	20

3F	2241	290	314	349	428
	2242	288	305	331	418
	2243	262	292	321	399
	2244	234	259	284	352
	2245	296	322	364	432
	2246	294	321	352	426
	2247	261	286	313	381
	2249	291	316	346	423
	2250	284	316	342	416
	2251	319	344	371	459
	2252	286	303	300	401
	2253	296	331	351	419
	2254	316	343	368	454
	2255	272	301	328	370
	2256	272	308	341	394
	2257	283	323	355	432
	2258	284	334	371	426
	2259	249	280	302	377
	2260	322	334	355	411
	2261	289	308	339	400
	2262	288	309	338	409
	2263	250	267	298	371
	2264	264	291	314	366
	2265	221	243	264	323
	2266	263	293	315	390
	2267	252	286	301	386
	2268	258	291	313	386
	2269	262	288	317	401
	2270	288	308	336	407
	2271	299	327	371	468
	2272	264	294	321	388
	2273	284	322	348	402
	2274	237	270	294	361
	2275	266	302	322	387
	2276	316	357	399	488
	2277	304	347	374	444
	2278	312	349	383	467
	2279	256	284	312	367
	2280	265	289	316	390

2248NP	249	279	297	293
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NP Not pregnant.

APPENDIX 37 - continued

Individual bodyweights (g) of females after mating (F₁ - F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Animal	Day post coitum			
/ Sex	number	0	6	13	20

4F	2281	274	295	332	409
	2282	262	291	315	402
	2283	264	278	311	379
	2284	259	305	339	396
	2285	251	269	299	363
	2287	334	352	380	458
	2288	277	300	324	389
	2289	261	287	310	342
	2290	261	292	321	378
	2291	283	313	342	402
	2292	292	336	377	464
	2293	307	341	387	473
	2294	291	323	354	425
	2295	276	298	322	383
	2297	263	284	316	390
	2298	273	299	322	405
	2299	301	322	348	422
	2300	278	305	331	408
	2301	241	271	309	363
	2302	256	286	316	403
	2303	277	300	325	398
	2304	208	230	256	324
	2305	239	258	286	358
	2306	284	316	332	400
	2308	261	278	307	358
	2309	242	270	289	357
	2310	276	306	339	407
	2311	285	317	352	422
	2312	300	326	380	454
	2313	279	298	330	402
	2314	266	299	330	416
	2315	315	341	385	453
	2316	231	255	291	371
	2317	248	269	298	384
	2318	249	284	308	386
	2319	284	310	354	436
	2320	303	327	366	440

2286NP	282	300	319	315
2296NP	278	294	313	321
2307NP	259	287	311	311

NP Not pregnant

APPENDIX 38

Food intake (g/rat/day) -
individual values for females after mating (F_1 - F_2)

Group 1 : Control

Animal number	Days post coitum			Animal number	Days post coitum		
	0-5	6-12	13-19		0-5	6-12	13-19
2161	24	24	25	2181	22	23	23
2162	19	24	22	2182	20	22	22
2163	20	22	23	2183	23	29	24
2164	21	20	20	2184	24	25	27
2165	27	31	27	2185	23	25	27
2166	21	23	26	2186	28	31	25
2167	19	23	23	2187	21	24	25
2168	23	29	27	2188	21	25	25
2169	26	28	27	2189	20	24	22
2170	26	28	30	2190	24	26	30
2171	25	26	27	2191	26	27	26
2172	22	25	26	2193	29	27	24
2173	19	24	26	2194	28	28	23
2174	22	24	33	2195	17	19	21
2175	24	21	27	2196	17	18 ^a	26
2176	19	23	23	2198	21	24	26
2177	26	26	26	2200	21	27	29
2178	24	26	26				
2179	23	21	37	2192NP	24	26	23
2180	21	23	24	2197NP	21	21	20
				2199NP	24	28	23

a Based on 4 days only.

NP Not pregnant, excluded from group mean values.

APPENDIX 38 - continued

Food intake (g/rat/day) -
individual values for females after mating (F₁-F₂)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Days <u>post coitum</u>			Animal number	Days <u>post coitum</u>		
	0-5	6-12	13-19		0-5	6-12	13-19
2201	24	29	24	2221	21	24	24
2202	23	25	25	2222	31	27	32
2203	26	24	26	2223	25	28	30
2204	22	26	27	2224	23	30	31
2205	23	34	22	2225	27	30	29
2206	23	28	21	2226	17	22	23
2207	26	34	37	2227	20	23	25
2208	18	25	28	2228	21	26	25
2209	22	24	26	2230	15	22	27
2210	a	29	23	2232	17	22	23
2211	18	22	21	2233	16	22	22
2212	24	25	26	2234	20	30	26
2213	27	27	26	2235	20	23	24
2214	27	24	26	2236	21	29	25
2215	19	28	22	2237	24	27	26
2216	22	28	26	2239	25	29	30
2217	24	27	27	2240	22	26	22
2218	19	27	25				
2219	19	26	23	2229NP	19	20	22
2220	19	23	25	2231NP	21	22	21
				2238NP	28	32	27

a Data recording error, no value calculated.

NP Not pregnant, excluded from group mean values.

APPENDIX 38 - continued

Food intake (g/rat/day) -
individual values for females after mating (F₁-F₂)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	<u>Days post coitum</u>			Animal number	<u>Days post coitum</u>		
	0-5	6-12	13-19		0-5	6-12	13-19
2241	18	25	27	2262	24	24	24
2242	18	23	24	2263	18	21	22
2243	20	22	21	2264	23	22	25
2244	19	22	23	2265	26	26	27
2245	21	24	26	2266	17	19	22
2246	22	26	25	2267	20	22	22
2247	19	24	23	2268	18	26	25
2249	21	25	26	2269	24	36	26
2250	28	29	38	2270	20	23	24
2251	21	25	25	2271	24	29	28
2252	19	14	24	2272	23	36	27
2253	28	30	24	2273	29	33	39
2254	24	29	33	2274	24	30	27
2255	26	28	27	2275	21	24	28
2256	23	25	27	2276	27	30	33
2257	22	26	28	2277	24	26	26
2258	27	33	31	2278	30	32	31
2259	19	22	22	2279	22	24	24
2260	20	21	24	2280	25	26	26
2261	17	20	22				
				2248NP	21	36	28

NP Not pregnant, excluded from group mean values.

APPENDIX 38 - continued

Food intake (g/rat/day) -
individual values for females after mating (F_1 - F_2)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	<u>Days post coitum</u>			Animal number	<u>Days post coitum</u>		
	0-5	6-12	13-19		0-5	6-12	13-19
2281	18	22	25	2302	23	25	34
2282	21	21	24	2303	20	30	24
2283	17	29	23	2304	24	23	25
2284	26	36	31	2305	21	31	30
2285	19	20	22	2306	28	23	27
2287	a	24	28	2308	21	22	24
2288	18	22	22	2309	22	23	25
2289	22	27	26	2310	24	26	28
2290	29	29	35	2311	24	29	29
2291	24	29	24	2312	24	29	34
2292	24	31	31	2313	20	26	26
2293	23	29	31	2314	21	23	25
2294	27	24	28	2315	24	41	27
2295	22	26	23	2316	20	27	23
2297	17	26	30	2317	21	26	24
2298	22	21	23	2318	26	27	29
2299	22	23	23	2319	28	31	29
2300	22	27	29	2320	24	34	24
2301	22	24	28				
				2286NP	21	25	20
				2296NP	17	25	18
				2307NP	18	23	22

a Data recording error, no value calculated.

NP Not pregnant, excluded from group mean values.

APPENDIX 39

Achieved dosage (mg/kg/day) -
individual values for females after mating (F₁-F₂)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Days <u>post coitum</u>			Animal number	Days <u>post coitum</u>		
	0-5	6-12	13-19		0-5	6-12	13-19
2201	265	249	205	2221	209	187	195
2202	288	237	234	2222	354	230	273
2203	303	213	225	2223	268	228	245
2204	279	249	249	2224	275	273	269
2205	319	350	224	2225	303	263	259
2206	314	282	207	2226	246	243	248
2207	337	331	346	2227	258	224	239
2208	230	239	255	2228	274	255	237
2209	281	230	242	2230	204	231	264
2210	a	271	212	2232	239	233	237
2211	193	185	176	2233	192	212	214
2212	294	235	240	2234	234	271	234
2213	339	255	243	2235	249	222	228
2214	328	221	253	2236	229	244	212
2215	235	261	199	2237	320	269	249
2216	241	236	217	2239	279	246	252
2217	271	229	236	2240	245	225	188
2218	255	271	239				
2219	234	250	218	2229NP	213	178	222
2220	215	199	214	2231NP	242	199	214
				2238NP	333	289	268

a Data recording error, no value calculated.

NP Not pregnant, excluded from group mean values.

APPENDIX 39 - continued

Achieved dosage (mg/kg/day) -
individual values for females after mating (F₁-F₂)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	<u>Days post coitum</u>			Animal number	<u>Days post coitum</u>		
	0-5	6-12	13-19		0-5	6-12	13-19
2241	413	446	470	2262	557	438	434
2242	420	427	433	2263	482	439	444
2243	500	424	394	2264	574	430	497
2244	534	479	489	2265	776	606	622
2245	471	413	441	2266	423	369	422
2246	495	456	434	2267	515	443	433
2247	481	473	448	2268	454	509	483
2249	479	446	457	2269	604	703	489
2250	646	521	678	2270	465	422	437
2251	439	413	407	2271	531	491	451
2252	447	274	463	2272	571	692	515
2253	528	595	258	2273	663	582	703
2254	504	482	543	2274	656	629	557
2255	628	526	523	2275	512	454	534
2256	549	455	497	2276	556	469	503
2257	503	453	481	2277	511	426	430
2258	605	553	526	2278	629	517	493
2259	497	447	438	2279	564	476	478
2260	422	360	423	2280	625	508	498
2261	394	365	402				
				2248NP	551	739	641

NP Not pregnant, excluded from group mean values.

APPENDIX 39 - continued

Achieved dosage (mg/rat/day) -
individual values for females after mating (F₁-F₂)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Days <u>post coitum</u>			Animal number	Days <u>post coitum</u>		
	0-5	6-12	13-19		0-5	6-12	13-19
2281	652	614	677	2302	875	727	949
2282	783	606	672	2303	715	840	666
2283	647	862	669	2304	1130	828	865
2284	950	978	846	2305	871	997	935
2285	753	616	667	2306	962	621	740
2287	a	574	670	2308	803	658	724
2288	643	617	619	2309	886	720	776
2289	828	791	800	2310	850	705	753
2290	1081	828	1005	2311	822	759	752
2291	830	775	647	2312	790	719	818
2292	788	761	740	2313	715	724	713
2293	732	697	723	2314	766	640	672
2294	907	620	721	2315	754	988	646
2295	790	734	655	2216	848	865	697
2297	641	758	852	2217	837	802	706
2298	793	592	635	2218	1006	798	838
2299	728	601	599	2319	972	817	736
2300	778	743	787	2320	785	858	597
2301	886	724	836				
				2286NP	744	707	633
				2296NP	613	721	570
				2307NP	680	673	710

a Data recording error, no value calculated.

NP Not pregnant, excluded from group mean values.

APPENDIX 40

Individual litter data - females killed on Day 20 of gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a Small foetus (less than 2.70 g).
- b Large foetus (more than 4.00 g).
- c Shiny skin.
- d Abnormal pup (Siamese twin).
- e Subcutaneous haemorrhage on one ear.
- f Haemorrhage on palate.
- g Haemorrhage on limb.
- h Subcutaneous haemorrhage on tail.
- k Small placenta (less than 0.30 g).
- j Large placenta (more than 0.70 g).
- m Misshaped placenta.
- n Conjoined placentae.
- o Placenta with pale edges.
- p One thyroid haemorrhagic.
- q Ductus arteriosus 50 % closed, lungs not inflated.
- r Clotted blood in abdomen.
- s Unilateral hydroureter.
- t Bilateral hydroureter.
- u Unilateral hydronephrosis.
- v Bilateral hydronephrosis.

APPENDIX 40 - continued

Individual litter data - females killed on Day 20 of gestation (F₁-F₂)

Group 1 : Control

Animal number	Corpora lutea count	Implantations	Viable young		Resorptions		Implantation loss (%)		Foetal weight (g)		Placental weight (g)		Observations
			M	F	Total	Early	Late	Total	Pre-	Post-	Mean	S.D.	
2164	16	13	8	5	13	0	0	0	18.8	0.0	3.22	0.35	1a
2169 ^α	14	6	4	2	6	0	0	0	57.1	0.0	3.49	0.32	1b
2170	18	15	8	7	15	0	0	0	16.7	0.0	3.51	0.31	1a
2173	19	14	8	4	12	2	0	2	26.3	14.3	3.41	0.28	1t
2174	17	14	4	7	11	2	1	3	17.6	21.4	3.30	0.12	1q
2175	16	16	5	10	15	0	1	1	0.0	6.3	3.45	0.21	1s
2177	17	15	6	7	13	2	0	2	11.8	13.3	3.13	0.23	-
2180	16	14	5	7	12	2	0	2	12.5	14.3	3.25	0.14	1t
2182	15	13	6	6	12	1	0	1	13.3	7.7	3.03	0.44	1a,lsu
2183	20	17	8	8	16	0	1	1	15.0	5.9	3.18	0.22	1s
2185 ^α	17	9	4	5	9	0	0	0	47.1	0.0	3.40	0.23	1jtv
2186	15	15	8	5	13	2	0	2	0.0	13.3	3.41	0.34	1a
2188	18	8	3	5	8	0	0	0	55.6	0.0	3.17	0.18	-
2189	13	12	2	4	6	0	6	6	7.7	50.0	2.47	0.44	3am,1ajm,2jm
2191 ^α	12	6	3	2	5	1	0	1	50.0	16.7	3.28	0.38	-
2193	17	15	6	9	15	0	0	0	11.8	0.0	2.85	0.46	3a,1ac,1ace
2195	19	14	9	5	14	0	0	0	26.3	0.0	3.12	0.42	2a,1h
2200	17	14	7	6	13	1	0	1	17.6	7.1	3.39	0.25	1su,1sv

2192NP
2199NP

^α Unilateral implantation.
NP Not pregnant.

APPENDIX 40 - continued

Individual litter data - females killed on Day 20 of gestation (F₁-F₂)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Corpora lutea count	Implantations	Viable young		Resorptions		Implantation loss (%)		Foetal weight (g)		Placental weight (g)		Observations
			M	F	Total	Early	Late	Total	Pre-	Post-	Mean	S.D.	
2207	19	17	10	7	17	0	0	0	10.5	0.0	3.49	0.27	1a
2208	18	16	10	6	16	0	0	0	11.1	0.0	3.29	0.26	1r
2209	19	18	8	8	16	2	0	2	5.3	11.1	2.88	0.20	3a
2210	15	14	5	9	14	0	0	0	6.7	0.0	2.98	0.18	1a
2211	14	14	10	4	14	0	0	0	0.0	0.0	2.89	0.30	2a,laf
2216	17	15	9	5	14	1	0	1	11.8	6.7	3.42	0.22	-
2218	17	15	10	4	14	1	0	1	11.8	6.7	3.65	0.22	1bsu,lsu,lsv
2219	15	14	10	3	13	1	0	1	6.7	7.1	3.46	0.17	-
2224	22	19	10	9	19	0	0	0	13.6	0.0	2.84	0.25	4a,las
2225 ^a	24	7	4	3	7	0	0	0	70.8	0.0	3.31	0.18	-
2226	10 ^A	11	4	7	11	0	0	0	0.0	0.0	3.26	0.13	-
2227	13	12	6	6	12	0	0	0	7.7	0.0	3.14	0.27	-
2230	16	11	3	6	9	2	0	2	31.3	18.2	2.46	0.29	3a,lac,2acj
2232	15	14	8	5	13	1	0	1	6.7	7.1	3.31	0.28	-
2234	12 ^A	13	8	4	12	1	0	1	0.0	7.7	3.18	0.14	1j
2235	15 ^A	17	8	9	17	0	0	0	0.0	0.0	2.84	0.22	4a
2236	16	15	6	6	12	2	1	3	6.3	20.0	2.93	0.51	3a
2240	17	17	11	5	16	1	0	1	0.0	5.9	3.04	0.27	2a,ltv
2231NP													
2238NP													

^a Unilateral implantation.

^A Number of implantation sites substituted in calculation of pre-implantation loss.

NP Not pregnant.

APPENDIX 40 - continued

Individual litter data - females killed on Day 20 of gestation (F₁-F₂)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Corpora lutea count	Implantations	Viable young		Resorptions		Implantation loss (%)		Foetal weight (g)		Placental weight (g)		Observations
			M	F	Total	Early	Late	Total	Pre-	Post-	Mean	S.D.	
2242	15	15	6	9	15	0	0	0	0.0	0.0	3.46	0.19	-
2249	15	14	9	4	13	1	0	1	6.7	7.1	3.44	0.18	ltv
2250	18	16	9	6	15	0	1	1	11.1	6.3	3.25	0.17	-
2252	15	15	6	8	14	0	1	1	0.0	6.7	3.08	0.21	ln
2253	12	12	7	5	12	0	0	0	0.0	0.0	3.43	0.21	-
2255 ^a	14	3	2	1	3	0	0	0	78.6	0.0	3.79	0.15	lj
2257	15	13	4	8	12	1	0	1	13.3	7.7	2.94	0.27	2a
2258 ^a	20	8	4	4	8	0	0	0	60.0	0.0	3.29	0.27	-
2259	16 ^a	17	6	9	15	2	0	2	0.0	11.8	3.04	0.22	1a
2261	15	15	5	9	14	1	0	1	0.0	6.7	3.35	0.23	-
2263	14	14	5	8	13	1	0	1	0.0	7.1	2.82	0.32	lack
2265 ^a	15	8	4	4	8	0	0	0	46.7	0.0	3.41	0.19	-
2271	18	16	10	6	16	0	0	0	11.1	0.0	3.43	0.21	lt,ls,lp
2273	17	8	3	3	6	2	0	2	52.9	25.0	2.71	0.34	2a
2274	16	16	6	8	14	1	1	2	0.0	12.5	3.02	0.14	-
2275	18	14	7	5	12	1	1	2	22.2	14.3	3.13	0.18	lk
2278	16	15	8	7	15	0	0	0	6.3	0.0	3.12	0.29	1a,lj
2279 ^a	16	9	4	5	9	0	0	0	43.8	0.0	2.52	0.25	7a0,2o
2280	16	14	8	5	13	1	0	1	12.5	7.1	3.13	0.19	-

2248NP

^a Unilateral implantation.

^A Number of implantations substituted in calculation of pre-implantation loss.

* Excludes conjoined placentae.

NP Not pregnant.

APPENDIX 40 - continued

Individual litter data - females killed on Day 20 of gestation (F₁-F₂)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Corpora lutea count	Implantations	Viable young		Resorptions		Implantation loss (%)		Foetal weight (g)		Placental weight (g)		Observations
			M	F	Total	Early	Late	Total	Pre-	Post-	Mean	S.D.	
2281	14	11	7	4	11	0	0	0	21.4	0.0	3.06	0.30	1a
2288	14	13	10	3	13	0	0	0	7.1	0.0	3.04	0.38	2a
2289	19	4	2	1	3	1	0	1	78.9	25.0	3.05	0.28	-
2290 ^α	14	9	2	6	8	1	0	1	35.7	11.1	3.28	0.30	-
2291	17	16	4	9	13	3	0	3	5.9	18.8	2.93	0.26	2a,lt
2297	15	14	7	6	13	1	0	1	6.7	7.1	3.59	0.24	lbs
2298	15	15	8	6	14	1	0	1	0.0	6.7	3.04	0.29	2a
2301	13	11	6	4	10	1	0	1	15.4	9.1	3.11	0.46	lak,ltv
2302	18	17	6	11	17	0	0	0	5.6	0.0	3.27	0.26	ln
2310	15	14	7	6	13	1	0	1	6.7	7.1	3.04	0.28	2a
2311 ^α	19	9	5	4	9	0	0	0	52.6	0.0	3.51	0.21	lb,ls,lsu,ld
2312	13	13	6	4	10	3	0	3	0.0	23.1	3.50	0.35	lsu,lb,lt
2315	16	13	6	7	13	0	0	0	18.8	0.0	3.50	0.32	las,ls,lsv,2t,ltv
2316	15	17	6	8	14	3	0	3	0.0	17.6	3.19	0.40	lac,lg
2317	16	16	7	8	15	1	0	1	0.0	6.3	3.22	0.23	la
2318	15	15	5	9	14	1	0	1	0.0	6.7	2.90	0.30	4a
2319	19	17	4	11	15	1	1	2	10.5	11.8	3.18	0.21	ltv
2320	17	16	5	11	16	0	0	0	5.9	0.0	3.34	0.19	-

2296NP
2307NP

^α Unilateral implantation.
* Excludes conjoined placentae.
NP Not pregnant.

APPENDIX 41

Individual foetal observations at free-hand serial sectioning (F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a Haemorrhagic peritoneal fluid.
- b Subcutaneous oedema - trunk.
- c Subcutaneous scapular haemorrhage.
- d Hepatic haemorrhage.
- e Space between bodywall and organs.
- f Unilateral hydronephrosis.
- g Bilateral hydronephrosis.
- h Unilateral hydroureter.
- j Bilateral hydroureter.
- k Haemorrhagic abdomen.
- m Subcutaneous cranial haemorrhage.
- n Subcutaneous nasal haemorrhage.
- p Testis(es) displaced towards midline/cranially/ventrally.
- q Subcutaneous haemorrhage - fore/hind limb(s).
- r Blood in thoracic lymph duct at aortic arch level.
- s Localised internal abdominal haemorrhage.
- t Subcutaneous dorsal cervical haemorrhage.
- u Slightly distended bladder.
- v Intra-muscular haemorrhage - scapular region.
- w Subcutaneous haemorrhage - tail.
- x Depression on underside of tongue.
- y Intra-muscular haemorrhage - lower/side of jaw.
- z Blood in anus.
- A Bilateral microphthalmia.
- B Slightly increased dilatation of brain ventricle(s).
- C Slightly elongated genital tubercle.
- D Dilated umbilical arteries.

APPENDIX 41 - continued

Individual foetal observations at free-hand serial sectioning (F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations - continued

E	Subcutaneous dorsal/lateral/ventral thoracic haemorrhage.
F	Possible hairline septal defect.
G	Subcutaneous dorsal/lateral/abdominal haemorrhage.
H	Small haemorrhage - left eye lid.
J	Lower ribs appear unattached at sternal end.
K	Blood in nasal sinuses/nasopharynx/trachea.
M	Intra-muscular haemorrhage - tongue.
N	Petechial haemorrhages on right lower lung lobe.
P	Intra-muscular haemorrhage - nasal region.
Q	Haemorrhage between cerebral hemisphere and pia mater.
R	Intra-muscular haemorrhage - lateral cervical region.
S	Slightly distended lateral cervical lymph ducts.
T	Absence of innominate artery; right carotid and subclavian arteries arise directly from aortic arch.
U	Unilateral dilated orbital sinus.
V	Unilateral slight microphthalmia and reduction in thickness of retinal layer.
W	Subcutaneous haemorrhage - lower jaw.
X	Unilateral anophthalmia; severe internal hydrocephaly; pituitary gland reduced in size.
Y	Slightly increased amount of pericardial fluid.
Z	Haemorrhage surrounding dorsal cerebellar region.
α	Vacuole in adrenal gland without/containing blood.

APPENDIX 41 - continued

Individual foetal observations at free-hand serial sectioning (F₂)

Group 1 : Control

Animal number	Number of foetuses examined	Sex		Observations
		M	F	
2164	6	3	3	ladq, ldq, 2q, lqrs
2169	3	2	1	lc
2170	7	4	3	lcd, 2d, lt
2173	6	2	4	lh
2174	5	1	4	lcq
2175	7	2	5	3c, ld, lh
2177	6	2	4	ladvw, lcdkq, lcdq, ldenq, ldm, lu
2180	6	2	4	lcq, lq, lqz, lx
2182	6	5	1	lcdefkqwABC, lcepD, lcetW, ld, lem
2183	8	4	4	lac, 2cd, lt
2185	4	2	2	lc, ldk
2186	6	4	2	3c
2188	4	2	2	lc, lce, le
2189	3	1	2	lbemE, lde
2191	2	1	1	le
2193	7	2	5	lcJ, legqtCFG, lemngwB, lk, lm, lt
2195	7	4	3	lbemqC, lcd, ldk, ldkq, lq, lE
2200	6	3	3	2c, lcjq, lfp, lh
2192	NP			
2199	NP			

NP Not pregnant.

APPENDIX 41 - continued

Individual foetal observations at free-hand serial sectioning (F₂)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Number of foetuses examined	Sex		Observations
		M	F	
2207	8	4	4	1c
2208	8	7	1	1acd, 1c, 1cdkq, 1e
2209	8	5	3	1c, 3h
2210	7	4	3	2c, 1cd, 1d, 1de, 1eq
2211	7	6	1	1cen, 1d, 2e, 1eyD, 1eK, 1eR
2216	7	6	1	1cdq, 1d, 1h, 1m, 1pq, 1q
2218	7	4	3	1dM, 1p, 1GW
2219	6	5	1	1h, 1j
2224	9	4	5	1cG, 2e, 2eq, 2q
2225	3	1	2	1e, 1q
2226	5	2	3	1c, 1cd, 2d, 1p
2227	6	4	2	1c, 1h, 1hw
2230	4	1	3	1cenqBCN, 1ceqtBCEG, 1ceBD, 1em
2232	6	5	1	1d, 1j, 1q, 1y
2234	6	3	3	1bes, 2ce
2235	8	2	6	1ce, 2cq, 1cG, 1e, 1eq
2236	6	1	5	1ceqBCD, 1eC, 1eH, 1s
2240	8	7	1	1cds, 1cem, 1cptPQ, 1de, 1dz, 1t
2231	NP			
2238	NP			

NP Not pregnant.

APPENDIX 41 - continued

Individual foetal observations at free-hand serial sectioning (F₂)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Number of foetuses examined	Sex		Observations
		M	F	
2242	7	1	6	1c, 1d, 1Ra, 1S
2249	6	3	3	1fh, 1h
2250	7	5	2	1c, 1d, 1qt, 1y
2252	7	1	6	1c, 1cj, 1cja, 1egj, 1m
2253	5	3	2	1c
2255	1	-	1	-
2257	6	1	5	1adq, 1be, 1c, 1fh, 1E
2258	4	2	2	1c, 1q, 1E
2259	7	2	5	1ds, 1e, 1h, 1j
2261	7	2	5	3h, 1hx
2263	6	2	4	1c, 1cd
2265	4	3	1	1c, 1e, 1p
2271	8	5	3	1cdk, 1ch, 1jqT, 2u
2273	3	3	-	1dq, 1em, 1eK
2274	7	2	5	1ad
2275	6	2	4	2e, 1ejq
2278	7	4	3	2h, 1q
2279	4	3	1	1egjq, 1ef, 1emq, 1eDU
2280	6	4	2	1h, 1p
2248	NP			

NP Not pregnant.

APPENDIX 41 - continued

Individual foetal observations at free-hand serial sectioning (F₂)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Number of foetuses examined	Sex		Observations
		M	F	
2281	5	5	-	1beE, 1c, lcd, lcdn, lcy
2288	6	5	1	1c, lcdm, lcez, lemD
2289	1	1	-	1e
2290	4	1	3	1cn, 1e
2291	6	4	2	2c, lce, 1d, 1e, legj
2297	6	3	3	1e, 2q
2298	7	4	3	1d, 1dk, 2e, 1eV
2301	5	3	2	1cemnqX, 1ch, 1cE, 1E
2302	8	4	4	1cY
2310	6	5	1	1d, 1e, 1p
2311	4	1	3	1cgj, 1cq, 1e
2312	5	2	3	1cd, 1chq, 3h
2315	6	3	3	1chq, 1gj, 2h
2316	7	3	4	1a, 2c, 1q, 1E
2317	7	2	5	1c
2318	7	2	5	1b, 1be, 1bem, 1beK, 1bK, 1bq
2319	7	4	3	1c, 1dq, 1e, 1t
2320	8	3	5	1d, 1dk, 1dZ, 1y, 1Q
2296	NP			
2307	NP			

NP Not pregnant.

APPENDIX 42

Individual foetal observations at skeletal examination (F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a Incomplete ossification of supraoccipital bone.
- b Incomplete ossification of interparietal bone.
- c Incomplete ossification of one or both parietal bones.
- d Small additional plaque of bone in parietal suture.
- e Incomplete ossification of squamosal bones.
- f Frontal/nasal suture enlarged.
- g Incomplete ossification of hyoid bone.
- h Absence of hyoid bone.
- i 1st sternebra cleft.
- j Small discrete unossified area in frontal bone.
- k One or more sternebrae offset.
- n 13th rib(s) reduced in length or absent.
- p Incomplete ossification or absence of one or both pubic bones.
- q Apparent absence of inner corners of one or both scapulae.
- r Ossification of all cervical vertebral centra.
- s Incomplete ossification of caudal vertebrae, less than 5 vertebrae ossified.
- t Incomplete ossification of one or more thoracic vertebral centra.
- u Incomplete ossification of one or more lumbar vertebral centra.
- v Incomplete ossification of one or more sacral and/or lumbar vertebral arches.
- w Incomplete ossification or absence of metacarpals/metatarsals.
- x Ossification of one or more phalangeal bones.
- y Incomplete ossification of ischial bones.
- z Ossification of ventral arch of 1st cervical vertebra.

continued on next page

APPENDIX 42 - continued

Individual foetal observations at skeletal examination (F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

continued from previous page

Key to observations - continued

- A Asymmetric pelvis, ilia associated with different sacral vertebrae.
- B 25 presacral vertebrae.
- D Incomplete ossification of one or more cervical vertebral arches.
- E Slight medial thickening of right 9th and left 10th ribs.
- F Two or more sternebrae fused.
- G Small discrete unossified area in basioccipital bone.
- H Conjoined foetuses :- two foetuses joined ventrally between 2nd sternebra and umbilicus of major foetus, resulting in sternebral cleft with sternebral fusion. Minor foetus has no cranial structures, no sternebrae, vertebrae or ribs; hind limbs are normal, pubic bones absent; front limbs are fused to radius :- single fused scapula rudiment, fused humeri and fused radii (reduced), separate ulnae and forefeet. Major foetus otherwise normal.
- I Incomplete ossification of palatine bones (not cleft palate).
- J Incomplete ossification of basisphenoid.

APPENDIX 42 - continued

Individual foetal observations at skeletal examination (F₂)

Group 1 : Control

Animal number	Number of foetuses examined	Incomplete ossification of sternebrae: number of bones affected										Number of ribs of ribs			Number of meta carpals		Size of anterior fontanelle			Observations
		1 2 3 4 5 6										13	13/14	14	3/4	4/4	Small	Medium	Large	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
2164	7	-	6	-	-	-	1	7	-	-	-	-	3	3	3	-	7	-	lab, labchpt, labfpsw0, labp, lat	
2169	3	-	3	-	-	-	-	3	-	-	-	-	1	2	2	-	3	-	ltz	
2170	8	1	6	-	1	-	-	8	-	-	-	-	3	5	5	-	8	-	labh, lab, ldt, 2t	
2173	6	-	5	-	-	-	-	6	-	-	-	-	1	5	5	2	4	-	ln, lqt, lt, lz	
2174	6	-	6	-	-	-	-	5	1	-	-	-	6	-	-	-	6	-	labt, laht, lbp, lhp, lt	
2175	8	-	8	-	-	-	-	8	-	-	-	-	2	6	6	-	8	-	lab, 2t, lz	
2177	7	-	5	-	2	-	-	6	1	-	-	-	6	1	1	-	7	-	labkpf, lb, lkf	
2180	6	-	6	-	-	-	-	6	-	-	-	-	4	2	2	-	6	-	lqz, 2t, 2tz	
2182	6	-	3	3	-	-	-	6	-	-	-	-	5	1	1	-	6	-	lqz, lsz, ltz, lz	
2183	8	-	6	2	-	-	-	8	-	-	-	-	3	5	5	-	8	-	ln, lt	
2185	5	-	5	-	-	-	-	5	-	-	-	-	3	2	2	-	5	-	lq, 2t, lz	
2186	7	-	6	-	-	1	-	6	-	-	-	-	4	3	3	-	6	1	la, labnstBD, latz, lb, lbtz, lt	
2188	4	-	4	-	-	-	-	4	-	-	-	-	4	-	-	-	4	-	lkt, lt	
2189	3	-	2	-	-	-	1	3	-	-	-	-	1	-	-	-	1	2	labfpstw0, lb, lbfw0	
2191	3	-	3	-	-	-	-	3	-	-	-	-	2	1	1	-	3	-	lb	
2193	8	-	6	2	-	-	-	8	-	-	-	-	8	-	-	-	8	-	labhps, lah, lbs, ls, lt	
2195	7	-	2	3	2	-	-	6	-	1	-	-	6	1	1	-	7	-	labpst, lbj, 2lp, lit, lp, lt	
2200	7	2	4	1	-	-	-	7	-	-	-	-	2	5	5	1	6	-	lqt, lt, 2z	
2192	NP																			
2199	NP																			

NP Not pregnant.

APPENDIX 42 - continued

Individual foetal observations at skeletal examination (F₂)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Number of foetuses examined	Incomplete ossification of sternebrae: number of bones affected										Number of ribs		Number of meta carpals		Number of meta tarsals			Size of anterior fontanelle	Observations
		of sternebrae: number of bones affected										of ribs		meta carpals		meta tarsals				
		1	2	3	4	5	6	13	13/14	14	14	3/4	4/4	Small	Medium	Large				
2207	9	2	4	3	-	-	-	8	1	-	2	7	1	8	-	lgrxz, ltz, 3z				
2208	8	-	5	3	-	-	-	8	-	-	5	3	-	8	-	la, lx				
2209	8	-	7	1	-	-	-	8	-	-	8	-	-	8	-	4b, lbpw, lbs				
2210	7	-	5	2	-	-	-	7	-	-	7	-	-	7	-	labgt, labh, 3b, lt				
2211	7	-	5	2	-	-	-	7	-	-	5	2	-	7	-	lb, lbq, lk, lq				
2216	7	-	6	1	-	-	-	7	-	-	1	6	-	7	-	lbt, lt				
2218	7	1	5	-	-	-	-	7	-	-	-	7	-	7	-	lqx, lt, 2tx				
2219	7	-	7	-	-	-	-	6	1	-	2	5	-	7	-	lpq, lq, 2t				
2224	10	1	6	1	2	-	-	10	-	-	7	2	-	10	-	lbj, lbpswD, lbqs, lbs, lbsE, 1iAB, lqz				
2225	4	-	4	-	-	-	-	3	-	1	2	2	-	4	-	lab, lb, lptt, lqt				
2226	6	-	5	1	-	-	-	6	-	-	6	-	-	6	-	ln, 2t				
2227	6	-	6	-	-	-	-	6	-	-	4	2	-	6	-	lb				
2230	5	-	2	-	2	-	1	5	-	-	4	-	-	5	-	labfpswD, 2b, lbp				
2232	7	1	3	3	-	-	-	7	-	-	5	2	-	7	-	la, lf				
2234	6	-	4	2	-	-	-	6	-	-	5	1	-	6	-	lbgs, lpg, lt				
2235	9	-	4	3	2	-	-	9	-	-	9	-	-	9	-	labp4B, laps, 2p				
2236	6	-	5	1	-	-	-	6	-	-	2	4	-	5	1	lb, lt				
2240	8	-	3	3	2	-	-	8	-	-	5	3	-	8	-	labpst, lb, lbhps, lg, lpt, 2t				
2231	NP																			
2238	NP																			

NP Not pregnant.

APPENDIX 42 - continued

Individual foetal observations at skeletal examination (F₂)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Number of foetuses examined	Incomplete ossification of sternebrae: number of bones affected										Number of meta carpals			Number of meta tarsals			Size of anterior fontanelle	Observations	
		Number of ribs										3/4		4/4		Small	Medium			Large
		1	2	3	4	5	6	13	13/14	14	14	3/4	4/4	3/4	4/4					
2242	8	-	8	-	-	-	-	8	-	-	-	3	5	-	8	-	lhq, lht, lhtz, lq, 2t, lz			
2249	7	-	5	2	-	-	-	7	-	-	-	2	5	-	7	-	ln, lq, lt			
2250	8	-	6	2	-	-	-	8	-	-	-	4	4	-	8	-	2t, ltz, lz			
2252	7	-	4	2	1	-	-	7	-	-	-	7	-	-	7	-	la, lab, lb, 2t			
2253	7	1	5	1	-	-	-	7	-	-	-	2	5	-	7	-	3z			
2255	2	-	1	-	1	-	-	2	-	-	-	1	1	1	1	-	lab, lz			
2257	6	-	6	-	-	-	-	6	-	-	-	5	1	-	6	-	lab, lqt			
2258	4	1	3	-	-	-	-	3	1	-	-	4	-	-	4	-	lbt, lq, lt			
2259	8	-	4	3	1	-	-	8	-	-	-	7	1	-	8	-	last, lbt, lq, 2t			
2261	7	2	5	-	-	-	-	7	-	-	-	6	1	-	7	-	lt, ltz, lz			
2263	7	-	5	1	-	-	1	7	-	-	-	4	2	-	6	1	labfsw, 2b, lk, 2q			
2265	4	-	4	-	-	-	-	4	-	-	-	3	1	-	4	-	lht, lqt			
2271	8	-	8	-	-	-	-	8	-	-	-	3	5	-	8	-	lb, lh, lq, 2t			
2273	3	-	2	1	-	-	-	3	-	-	-	3	-	-	3	-	-			
2274	7	-	7	-	-	-	-	7	-	-	-	5	2	-	7	-	2t			
2275	6	-	6	-	-	-	-	6	-	-	-	5	-	-	6	-	labhpw, labp, lah, lg, lh			
2278	8	1	4	2	1	-	-	8	-	-	-	6	2	-	8	-	lab, lt			
2279	5	-	1	1	3	-	-	5	-	-	-	2	-	-	5	-	2abfsw0, labgsw0, 1sd			
2280	7	-	4	2	1	-	-	7	-	-	-	5	2	-	7	-	lhp, 2p, 2t			
2248	NP																			

NP Not pregnant.

APPENDIX 42 - continued

Individual foetal observations at skeletal examination (F₂)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Number of foetuses examined	Incomplete ossification of sternebrae: number of bones affected						Number of ribs			Number of meta carpals		Number of meta tarsals		Size of anterior fontanelle		Observations
								13 13/14 14			3/4		4/4		Small Medium Large		
2281	6	1	4	1	-	-	-	6	-	-	5	1	-	-	6	-	lbz, 2q, lt
2288	7	-	6	-	1	-	-	7	-	-	5	2	-	-	7	-	lbqsD, lh, 4t
2289	2	-	1	-	1	-	-	2	-	-	1	1	-	-	2	-	lb, lps,
2290	4	-	4	-	-	-	-	4	-	-	3	1	-	-	4	-	lb, 2t
2291	7	-	4	2	-	1	-	7	-	-	5	2	-	-	7	-	labi, 2b, lt, ltz, lz
2297	7	-	6	1	-	-	-	7	-	-	3	4	-	-	7	-	4t, ltz
2308	7	-	6	1	-	-	-	7	-	-	5	2	-	-	7	-	labt, lbt, 2t
2301	5	-	4	1	-	-	-	5	-	-	1	4	-	-	5	-	lt, lz
2302	9	-	7	1	1	-	-	9	-	-	8	1	-	-	9	-	lahqz, 3h, lnAB, 2z
2310	7	-	3	3	1	-	-	7	-	-	7	-	-	-	6	1	labfhikpt, labhpv, labptw, 2t
2311	5	1	2	-	-	-	-	5	-	-	3	2	-	-	5	-	lt, lh
2312	5	2	2	1	-	-	-	5	-	-	1	4	-	-	5	-	ldz, lt
2315	7	1	4	-	1	-	-	7	-	-	6	1	-	-	7	-	lab, 2it, lt, ltu
2316	7	-	5	-	-	1	1	7	-	-	5	-	-	-	6	1	labefhpstwdlJ, labgpwyD, lntAB, ltz
2317	8	1	7	-	-	-	-	8	-	-	7	1	-	-	8	-	lp, lpz, 2t
2318	7	1	4	2	-	-	-	7	-	-	7	-	-	-	7	-	labpt, 2t, lD
2319	8	-	6	1	1	-	-	8	-	-	4	4	-	-	8	-	-
2320	8	-	3	3	2	-	-	8	-	-	8	-	-	-	8	-	labhp, lbt, lqk, lnt, 2t
2296	NP																
2307	NP																

NP Not pregnant.

APPENDIX 43

Individual bodyweights (g) of females during lactation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group Animal / Sex number	Day post partum				
	1	4	7	14	21
1F 2161	293	306	297	315	307
2162	346	360	357	363	361
2163	301	301	302	309	321
2165	310	326	326	332	314
2166	318	336	329	339	323
2167	333	336	351	374	332
2168	369	373	363	373	339
2171	314	333	334	351	328
2172	360	375	374	385	339
2176	302	312	298	317	301
2178	376	360	355	367	350
2179	287	304	300	340	321
2181	290	324	329	336	320
2184	342	348	340	359	346
2187	289	304	307	325	304
2190	350	351	353	387	361
2194	297	311	311	330	296
2196	288	Litter died			
2198	338	328	331	335	318

2197NP

NP Not pregnant.

APPENDIX 43 - continued

Individual bodyweights (g) of females during lactation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / Sex	Animal number	Day post partum				
		1	4	7	14	21
2F	2201	343	352	350	359	340
	2202	311	330	319	341	302
	2203	322	339	341	358	329
	2204	276	315	309	343	315
	2205	296	295	Litter died		
	2206	286	292	295	313	286
	2212	329	330	324	333	324
	2213	299	298	295	316	293
	2214	339	Litter died			
	2215	313	326	328	339	318
	2217	351	352	349	350	327
	2220	343	348	341	358	327
	2221	391	371	370	368	349
	2222	343	346	350	365	336
	2223	372	368	355	367	339
	2228	305	312	312	310	299
	2233	305	309	310	324	315
	2237	286	306	308	318	304
	2239	361	349	347	343	330

2229NP

NP Not pregnant.

APPENDIX 43 - continued

Individual bodyweights (g) of females during lactation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group	Animal / Sex number	Day post partum				
		1	4	7	14	21
3F	2241	344	342	347	345	330
	2243	290	313	320	325	317
	2244	264	279	287	290	273
	2245	324	338	345	352	334
	2246	357	357	349	343	315
	2247	304	302	305	311	292
	2251	357	353	356	378	349
	2254	346	358	348	358	338
	2256	341	347	347	362	338
	2260	349	346	337	349	344
	2262	325	327	316	336	310
	2264	303	311	308	317	312
	2266	299	308	313	340	329
	2267	280	298	304	316	306
	2268	313	326	329	336	316
	2269	313	315	312	308	310
	2270	315	329	322	335	324
	2272	300	315	313	322	303
	2276	386	377	377	388	359
	2277	339	362	356	364	333

APPENDIX 43 - continued

Individual bodyweights (g) of females during lactation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / Sex	Animal number	Day post partum				
		1	4	7	14	21
4F	2282	279	304	296	309	294
	2283	280	311	301	327	306
	2284	343	342	333	345	308
	2285	296	296	294	308	296
	2287	357	364	363	370	349
	2292	391	373	371	371	349
	2293	398	392	384	379	328
	2294	343	345	341	351	331
	2295	328	Litter died			
	2299	322	331	324	342	326
	2300	325	326	324	337	312
	2303	311	313	328	333	322
	2304	237	249	248	265	261
	2305	268	279	290	295	294
	2306	325	329	335	339	310
	2308	301	307	308	312	300
2309	285	304	299	309	286	
2313	316	330	335	356	314	
2314	281	310	324	337	311	

2286NP

NP Not pregnant.

APPENDIX 44

Food intake (g/rat/day) - individual values for females during lactation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group 1				Group 2			
Animal number	Days post partum			Animal number	Days post partum		
	1-6	7-13	14-20 ^A		1-6	7-13	14-20 ^A
2161	32	47	64	2201	37	56	60
2162	39	48	62	2202	38	53	69
2163	24	41	53	2203	33	56	67
2165	33	50	63	2204	49	57	62
2166	36	54	62	2206	30	51	58
2167	34	58	70	2212	33	59	65
2168	33	48	68	2213	32	51	57
2171	34	46	63	2215	33	54	60
2172	28	51	63	2217	29	45	55
2176	30	55	67	2220	26	42	49
2178	20	28	55	2221	18	30	44
2179	34	62	71	2222	37	59	73
2181	32	60	73	2223	29	59	65
2184	34	51	65	2228	29	47	60
2187	29	46	60	2233	29	50	63
2190	33	58	69	2237	34	59	66
2194	39	59	69	2239	31	56	65
2198	28	41	51				
2196	LD			2205	LD		
2197	NP			2214	LD		
				2229	NP		

A Includes food eaten by offspring.

NP Not pregnant.

LD Litter died.

APPENDIX 44 - continued

Food intake (g/rat/day) - individual values for females during lactation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group 3				Group 4			
Animal number	Days post partum			Animal number	Days post partum		
	1-6	7-13	14-20 ^A		1-6	7-13	14-20 ^A
2241	37	49	63	2282	28	45	58
2243	30	49	57	2283	33	49	59
2244	29	49	54	2284	27	50	52
2245	27	35	37	2285	27	51	61
2246	33	46	63	2287	34	55	69
2247	32	58	65	2292	28	44	61
2251	42	54	66	2293	31	46	58
2254	35	58	70	2294	30	53	63
2256	37	51	65	2299	50	52	67
2260	30	53	72	2300	36	55	64
2262	32	52	60	2303	42	51	62
2264	36	61	71	2304	31	57	58
2266	37	54	65	2305	32	52	62
2267	39	55	65	2306	37	61	65
2268	36	55	67	2308	29	58	63
2269	29	44	56	2309	32	50	59
2270	38	59	73	2313	39	59	57
2272	43	58	66	2314	34	52	65
2276	33	58	67				
2277	42	56	68				
				2286	NP		
				2295	LD		

A Includes food eaten by offspring.

NP Not pregnant.

LD Litter died.

APPENDIX 45

Achieved dosage (mg/kg/day) - individual values for females during lactation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group 2				Group 3			
Animal number	Days post partum			Animal number	Days post partum		
	1-6	7-13	14-20 ^A		1-6	7-13	14-20 ^A
2201	220	257		2241	444	463	
2202	249	261		2243	408	497	
2203	205	260		2244	436	555	
2204	345	284		2245	335	328	
2206	213	273		2246	388	435	
2212	208	292		2247	436	616	
2213	222	271		2251	488	481	
2215	212	263		2254	418	537	
2217	171	209		2256	446	470	
2220	157	195		2260	363	505	
2221	97	132		2262	414	522	
2222	220	268		2264	489	638	
2223	164	266		2266	501	541	
2228	194	246		2267	554	580	
2233	194	256		2268	465	541	
2237	236	306		2269	385	464	
2239	180	264		2270	495	587	
				2272	582	597	
				2276	359	496	
				2277	501	509	
2205	LD						
2214	LD						
2229	NP						

A Offspring consuming diet, concentration of compound maintained at levels set for Days 7-13 post partum.
 NP Not pregnant.
 LD Litter died.

APPENDIX 45 - continued

Achieved dosage (mg/kg/day) - individual values for females during lactation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group 4			
Animal number	Days post partum		
	1-6	7-13	14-20 ^A
2282	598	721	
2283	697	756	
2284	490	715	
2285	562	821	
2287	580	727	
2292	451	575	
2293	487	584	
2294	539	742	
2299	950	757	
2300	681	806	
2303	807	748	
2304	785	1077	
2305	704	862	
2306	688	877	
2308	585	907	
2309	673	797	
2313	736	828	
2314	690	762	
2286	NP		
2295	LD		

A Offspring consuming diet, concentration of compound maintained at levels set for Days 7-13 post partum.

NP Not pregnant.

LD Litter died.

APPENDIX 46

Individual litter sizes (F₂)

Group 1 : Control

Animal number	Implan- tation sites	Total at Day 1 post partum	Number alive on Day post partum					
			1	4	4 ⁺	7	14	21
2161	14	14	14	14	8	8	8	8
2162	13	11	11	10	8	8	8	8
2163	11	11	11	10	8	7	7	7
2165	14	14	14	14	8	8	7	7
2166	15	14	14	14	8	8	8	8
2167	15	13	13	13	8	8	8	8
2168	18	16	16	15	8	8	8	8
2171	18	17	17	16	8	8	8	8
2172	13	12	11	9	8	8	8	8
2176	16	16	16	16	8	8	8	8
2178	3 [#]	3	3	3	3	3	3	3
2179	17	15	15	14	8	8	8	8
2181	14	12	12	9	8	8	8	8
2184	17	14	14	14	8	8	8	8
2187	18	17	17	13	8	8	8	8
2190	17	16	16	16	8	8	8	8
2194	16	14	14	14	8	8	8	8
2196	16	14	14	Litter died				
2198	6 [#]	5	5	5	5	5	5	5
2197	0	NP						

+ Following litter size adjustment.

Unilateral implantation.

NP Not pregnant.

APPENDIX 46 - continued

Individual litter sizes (F₂)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Implan- tation sites	Total at Day 1 post partum	Number alive on Day post partum					
			1	4	4 ⁺	7	14	21
2201	17	17	17	16	8	8	8	8
2202	15	14	14	14	8	8	8	8
2203	16	15	15	15	8	8	8	8
2204	17	16	16	15	8	8	8	8
2205	13	12	12	1	1	Litter died		
2206	14	14	14	13	8	8	8	8
2212	14	13	13	13	8	8	8	8
2213	17	16	16	16	8	8	8	8
2214	1\$	1	1	Litter died				
2215	15	14	14	14	8	8	8	8
2217	7\$	6	6	6	6	6	6	6
2220	15	15	15	12	8	6	6	6
2221	10	6	6	6	6	6	6	6
2222	14	14	14	13	8	8	8	8
2223	15	10	10	10	8	8	8	8
2228	13	13	13	12	8	8	8	8
2233	13 ^a	14	14	14	8	8	8	8
2237	16	15	14	13	8	8	8	8
2239	9	9	9	8	8	8	8	8
2229	0	NP						

+ Following litter size adjustment.

NP Not pregnant.

a Number of offspring at Day 1 substituted in calculation of post-implantation survival index.

\$ Unilateral implantation.

APPENDIX 46 - continued

Individual litter sizes (F₂)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Implan- tation sites	Total at Day 1 post partum	Number alive on Day post partum					
			1	4	4 ⁺	7	14	21
2241	16	13	13	13	8	8	8	8
2243	16	16	16	16	8	7	7	7
2244	14	13	12	12	8	8	8	8
2245	15	13	13	11	8	3	3	3
2246	13	10	10	10	8	8	8	8
2247	13	12	12	12	8	8	8	8
2251	15	14	14	14	8	8	7	7
2254	15	15	15	15	8	8	8	8
2256	8 ^{\$}	7	7	6	6	6	6	6
2260	10	9	9	9	8	8	8	8
2262	15	13	13	10	8	8	8	8
2264	15	13	13	13	8	8	8	8
2266	13 ^a	14	14	14	8	8	8	8
2267	15	15	15	15	8	8	7	7
2268	14	14	14	14	8	8	8	8
2269	16	14	14	14	8	8	8	8
2270	16	15	15	15	8	8	8	8
2272	15	13	13	12	8	8	8	8
2276	16	15	15	15	8	8	8	8
2277	17	14	14	14	8	8	8	8

+ Following litter size adjustment.

\$ Unilateral implantation.

a Number of offspring at Day 1 substituted in calculation of post-implantation survival index.

APPENDIX 46 - continued

Individual litter sizes (F₂)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Implan- tation sites	Total at Day 1 post partum	Number alive on Day post partum					
			1	4	4 ⁺	7	14	21
2282	17 ^a	18	18	18	8	8	8	8
2283	16	14	14	14	8	8	8	8
2284	6 ^{\$}	6	6	6	6	6	6	6
2285	12	12	12	11	8	8	8	8
2287	16	15	15	15	8	8	8	8
2292	13	13	13	13	8	8	8	8
2293	13	12	12	11	8	8	8	8
2294	13	12	12	12	8	8	8	8
2295	11	11	11	Litter died				
2299	15	13	13	13	8	8	8	8
2300	15	14	14	14	8	8	8	8
2303	16	14	14	12	8	8	8	8
2304	14 ^a	15	15	15	8	8	8	8
2305	13	13	13	11	8	8	8	8
2306	13	11	11	11	8	8	8	8
2308	15	8	8	8	8	8	8	8
2309	13	13	13	13	8	8	8	8
2313	13	12	12	12	8	8	8	8
2314	17	16	16	15	8	8	8	8
2286	0	NP						

+ Following litter size adjustment.

a Number of offspring at Day 1 substituted in calculation of post-implantation survival index.

\$ Unilateral implantation.

NP Not pregnant.

APPENDIX 47

Individual litter mean bodyweights (g) of offspring (F₂)

Group 1 : Control

Animal number		Day post partum				
		1	4	7	14	21
2161	Mean	5.6	8.0	14.5	31.2	52.8
	S.D.	0.4	0.8	1.1	1.6	3.5
2162	Mean	5.7	6.7	10.7	25.4	43.5
	S.D.	0.5	0.8	2.0	3.7	7.0
2163	Mean	5.6	6.7	10.6	26.0	41.7
	S.D.	0.4	0.8	1.9	5.5	8.5
2165	Mean	6.1	7.5	10.8	28.3	46.6
	S.D.	0.4	0.8	1.9	3.7	5.2
2166	Mean	5.6	7.9	13.7	30.6	50.3
	S.D.	0.3	0.6	0.9	1.3	2.3
2167	Mean	5.6	8.1	13.4	32.1	52.5
	S.D.	0.3	0.8	1.4	2.2	4.3
2168	Mean	6.0	9.2	17.0	35.3	59.6
	S.D.	0.5	1.1	1.5	1.8	4.2
2171	Mean	5.7	8.2	13.0	28.5	50.0
	S.D.	0.4	0.4	1.1	2.2	2.8
2172	Mean	5.2	6.9	12.3	29.4	49.4
	S.D.	0.3	0.8	1.1	2.4	4.8
2176	Mean	5.7	7.2	14.0	31.0	51.9
	S.D.	0.6	1.0	0.9	1.4	1.6
2178	Mean	7.1	9.5	14.5	32.4	58.5
	S.D.	0.2	0.5	0.5	1.1	1.5
2179	Mean	6.2	8.8	14.8	32.5	53.3
	S.D.	0.7	1.3	2.2	4.0	6.8
2181	Mean	6.7	10.2	17.6	37.4	62.5
	S.D.	0.8	1.3	1.9	2.3	3.9
2184	Mean	5.9	8.4	14.0	31.6	53.4
	S.D.	0.3	0.5	1.0	1.2	2.9
2187	Mean	5.0	7.2	12.4	28.0	48.0
	S.D.	0.4	1.1	2.3	4.1	6.0
2190	Mean	6.5	8.5	14.2	32.3	54.8
	S.D.	0.5	1.2	1.0	3.1	3.6
2194	Mean	5.9	8.5	14.8	31.3	51.0
	S.D.	0.4	0.7	1.4	2.8	4.4
2196	Mean	5.3	Litter died			
	S.D.	0.4				
2198	Mean	7.9	12.3	18.7	37.6	59.7
	S.D.	1.3	2.8	4.1	6.1	11.8
2197	NP					

NP Not pregnant.
SD Standard deviation.

APPENDIX 47 - continued

Individual litter mean bodyweights (g) of offspring (F₂)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number		Day post partum				
		1	4	7	14	21
2201	Mean	5.1	7.3	13.2	31.0	49.2
	S.D.	0.4	0.8	1.6	2.0	3.3
2202	Mean	6.5	9.7	15.8	31.7	55.4
	S.D.	0.4	0.8	1.3	1.5	2.7
2203	Mean	5.8	7.6	13.7	31.3	49.8
	S.D.	0.4	0.6	0.7	1.3	3.1
2204	Mean	5.9	8.0	13.6	32.3	52.7
	S.D.	0.4	0.6	0.8	1.3	2.7
2205	Mean	5.1	3.8	Litter died		
	S.D.	0.3	-			
2206	Mean	5.4	6.9	12.0	26.6	44.1
	S.D.	0.5	1.2	2.8	5.4	7.4
2212	Mean	6.2	7.9	14.0	30.1	49.3
	S.D.	0.7	1.2	2.0	4.0	7.2
2213	Mean	6.0	7.6	12.1	25.4	43.3
	S.D.	0.6	1.3	2.7	4.0	6.1
2214	Mean	7.4	Litter died			
	S.D.	-				
2215	Mean	6.5	8.1	13.8	31.0	50.3
	S.D.	0.4	0.7	2.0	2.8	4.1
2217	Mean	8.3	12.7	19.5	36.8	62.5
	S.D.	0.3	0.4	0.7	1.2	2.4
2220	Mean	5.5	6.9	11.4	28.2	48.5
	S.D.	0.6	0.7	1.6	3.2	4.6
2221	Mean	5.7	7.7	11.8	25.2	39.6
	S.D.	0.4	0.9	1.7	2.8	5.0
2222	Mean	5.8	8.2	14.3	32.1	53.1
	S.D.	0.4	0.8	1.7	2.3	4.0
2223	Mean	6.3	9.7	17.0	34.8	56.6
	S.D.	0.4	0.9	1.6	2.0	2.9
2228	Mean	5.6	6.3	10.6	25.7	41.6
	S.D.	0.6	1.0	2.0	3.9	7.9
2233	Mean	6.1	8.6	14.0	30.5	51.3
	S.D.	0.3	0.8	1.2	1.2	2.7
2237	Mean	5.1	7.6	13.4	30.1	49.5
	S.D.	0.4	0.7	1.5	2.7	3.9
2239	Mean	7.5	11.7	18.1	33.4	55.6
	S.D.	0.4	0.5	0.7	0.7	2.5
2229	NP					

NP Not pregnant.

SD Standard deviation.

APPENDIX 47 - continued

Individual litter mean bodyweights (g) of offspring (F₂)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number		Day post partum				
		1	4	7	14	21
2241	Mean	5.7	8.7	14.6	31.7	53.6
	S.D.	0.4	0.8	1.3	2.4	5.0
2243	Mean	5.5	5.6	10.2	27.1	44.3
	S.D.	0.5	1.0	1.8	4.0	5.2
2244	Mean	6.1	7.7	12.0	26.2	41.0
	S.D.	0.2	0.8	1.0	1.9	2.4
2245	Mean	6.3	6.6	12.6	29.9	49.7
	S.D.	0.5	1.0	3.0	4.6	8.7
2246	Mean	7.1	10.7	16.0	32.4	55.8
	S.D.	0.8	1.2	2.4	2.5	3.9
2247	Mean	6.1	7.7	14.1	30.5	51.4
	S.D.	0.5	0.7	1.2	1.6	2.8
2251	Mean	6.2	8.8	13.6	32.8	54.5
	S.D.	0.5	0.8	0.7	1.6	1.8
2254	Mean	6.6	9.0	17.0	35.5	57.4
	S.D.	0.5	0.6	0.6	1.5	3.8
2256	Mean	7.9	12.5	19.1	38.7	66.1
	S.D.	0.3	0.4	0.5	1.1	3.1
2260	Mean	6.4	10.0	16.6	33.7	57.2
	S.D.	0.6	0.8	1.3	2.4	3.5
2262	Mean	5.2	8.2	13.5	28.7	46.6
	S.D.	0.8	0.9	1.4	2.2	3.2
2264	Mean	6.7	9.3	16.3	34.4	58.1
	S.D.	0.6	0.7	1.4	1.9	3.8
2266	Mean	6.0	7.3	12.0	27.7	45.7
	S.D.	0.5	1.4	4.0	8.7	15.1
2267	Mean	6.7	8.8	15.4	35.2	56.0
	S.D.	0.6	1.3	2.3	3.6	6.5
2268	Mean	6.0	8.3	15.3	31.7	50.7
	S.D.	0.9	1.8	3.9	8.2	14.2
2269	Mean	5.5	7.3	13.0	27.7	43.1
	S.D.	0.4	1.0	1.8	2.9	4.2
2270	Mean	6.5	9.4	16.6	36.2	59.8
	S.D.	0.4	0.7	1.0	1.6	2.7
2272	Mean	6.1	10.0	16.5	35.0	57.9
	S.D.	0.8	0.6	0.9	1.1	3.9
2276	Mean	7.0	10.0	16.8	35.4	57.8
	S.D.	0.3	0.8	1.4	1.4	2.8
2277	Mean	6.3	9.0	15.6	33.4	55.0
	S.D.	0.3	1.0	2.0	2.5	4.6

SD Standard deviation.

APPENDIX 47 - continued

Individual litter mean bodyweights (g) of offspring (F₂)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number		Day post partum				
		1	4	7	14	21
2282	Mean	5.4	7.0	12.1	28.7	46.3
	S.D.	0.4	0.5	1.4	3.4	4.5
2283	Mean	5.6	7.6	13.4	29.7	47.1
	S.D.	0.7	1.0	2.0	3.3	6.2
2284	Mean	7.4	11.2	17.5	32.2	53.8
	S.D.	0.2	0.4	0.8	0.9	2.0
2285	Mean	5.4	8.1	13.7	30.0	48.6
	S.D.	0.3	0.6	0.7	1.2	2.8
2287	Mean	6.4	9.2	16.1	35.3	57.0
	S.D.	0.3	0.7	0.7	1.1	1.6
2292	Mean	6.1	7.1	12.8	28.3	47.2
	S.D.	0.3	0.8	1.0	1.7	2.7
2293	Mean	6.6	10.0	16.1	32.8	53.7
	S.D.	1.0	0.8	1.2	1.2	2.4
2294	Mean	5.9	8.4	14.5	29.2	48.3
	S.D.	0.5	1.1	2.2	3.3	5.4
2295	Mean	4.5	Litter died			
	S.D.	0.3				
2299	Mean	7.0	9.2	16.4	34.0	58.3
	S.D.	0.3	0.6	1.0	1.4	2.1
2300	Mean	5.8	8.1	13.4	29.6	50.5
	S.D.	0.3	0.6	0.7	1.4	3.4
2303	Mean	5.8	8.6	14.1	31.7	52.0
	S.D.	0.4	0.7	1.2	1.7	3.5
2304	Mean	5.5	7.1	12.4	27.8	46.2
	S.D.	0.5	0.8	1.7	2.5	3.5
2305	Mean	5.9	8.4	14.2	32.1	49.9
	S.D.	0.6	0.9	1.3	2.1	3.7
2306	Mean	6.3	9.6	15.7	34.0	51.0
	S.D.	0.4	0.8	1.2	2.2	3.0
2308	Mean	6.6	8.1	13.4	29.5	48.7
	S.D.	0.5	0.6	0.7	2.0	3.0
2309	Mean	6.2	8.4	14.3	31.6	49.9
	S.D.	0.6	0.7	1.4	2.0	3.0
2313	Mean	6.3	8.3	13.7	30.6	51.0
	S.D.	0.7	1.2	2.9	4.7	8.0
2314	Mean	5.7	7.7	12.7	30.2	51.5
	S.D.	0.4	0.6	1.4	2.7	3.7
2286	NP					

NP Not pregnant.

SD Standard deviation.

APPENDIX 48

Individual litter sex ratios (F₂)

Group 1 : Control

Animal number	Total at Day 1		Number alive at Day 1		Number alive Day 4 (pre-cull)		Number alive Day 4 (post-cull)		Number alive Day 21	
	M	F	M	F	M	F	M	F	M	F
2161	10	4	10	4	10	4	4	4	4	4
2162	7	4	7	4	7	3	5	3	5	3
2163	6	5	6	5	5	5	4	4	4	3
2165	9	5	9	5	9	5	4	4	3	4
2166	6	8	6	8	6	8	4	4	4	4
2167	5	8	5	8	5	8	4	4	4	4
2168	7	9	7	9	7	8	4	4	4	4
2171	8	9	8	9	7	9	4	4	4	4
2172	2	10	2	9	2	7	4	4	2	6
2176	5	11	5	11	5	11	4	4	4	4
2178	2	1	2	1	2	1	2	1	2	1
2179	8	7	8	7	8	6	4	4	4	4
2181	8	4	8	4	7	2	6	2	6	2
2184	6	8	6	8	6	8	4	4	4	4
2187	13	4	13	4	9	4	4	4	4	4
2190	10	6	10	6	10	6	4	4	4	4
2194	8	6	8	6	8	6	4	4	4	4
2196	5	9	5	9	5	9	4	4	4	4
2198	2	3	2	3	Litter died	3	2	3	2	3
2197	NP									

NP Not pregnant.

APPENDIX 48 - continued

Individual litter sex ratios (F₂)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Total at Day 1		Number alive at Day 1		Number alive Day 4 (pre-cull)		Number alive Day 4 (post-cull)		Number alive Day 21	
	M	F	M	F	M	F	M	F	M	F
2201	8	9	8	9	8	8	4	4	4	4
2202	4	10	4	10	4	10	4	4	4	4
2203	7	8	7	8	7	8	4	4	4	4
2204	11	5	11	5	10	5	4	4	4	4
2205	7	5	7	5	1	0	1	0	Litter died	4
2206	7	7	7	7	7	6	4	4	4	4
2212	3	10	3	10	3	10	3	5	3	5
2213	8	8	8	8	8	8	4	4	4	4
2214	0	1	0	1	Litter died					
2215	8	6	8	6	8	6	4	4	4	4
2217	4	2	4	2	4	2	4	2	4	2
2220	11	4	11	4	8	4	4	4	3	3
2221	4	2	4	2	4	2	4	2	4	2
2222	11	3	11	3	10	3	5	3	5	3
2223	6	4	6	4	6	4	4	4	4	4
2228	6	7	6	7	5	7	4	4	4	4
2233	7	7	7	7	7	7	4	4	4	4
2237	5	10	5	9	5	8	4	4	4	4
2239	3	6	3	6	3	5	3	5	3	5
2229	NP									

NP Not pregnant.

APPENDIX 48 - continued

Individual litter sex ratios (F₂)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Total at Day 1		Number alive at Day 1		Number alive Day 4 (pre-cull)		Number alive Day 4 (post-cull)		Number alive Day 21	
	M	F	M	F	M	F	M	F	M	F
2241	5	8	5	8	5	8	4	4	4	4
2243	9	7	9	7	9	7	4	4	4	3
2244	7	6	6	6	6	6	4	4	4	4
2245	6	7	6	7	5	6	4	4	1	2
2246	8	2	8	2	8	2	6	2	6	2
2247	9	3	9	3	9	3	5	3	5	3
2251	6	8	6	8	6	8	4	4	3	4
2254	8	7	8	7	8	7	4	4	4	4
2256	3	4	3	4	2	4	2	4	2	4
2260	5	4	5	4	5	4	4	4	4	4
2262	7	6	7	6	5	5	4	4	4	4
2264	5	8	5	8	5	8	4	4	4	4
2266	8	6	8	6	8	6	4	4	4	4
2267	8	7	8	7	8	7	4	4	4	4
2268	9	5	9	5	9	5	4	4	3	4
2269	7	7	7	7	7	7	4	4	4	4
2270	7	8	7	8	7	8	4	4	4	4
2272	7	6	7	6	7	5	4	4	4	4
2276	7	8	7	8	7	8	4	4	4	4
2277	4	10	4	10	4	10	4	4	4	4

APPENDIX 48 - continued

Individual litter sex ratios (F₂)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Total at Day 1		Number alive at Day 1		Number alive Day 4 (pre-cull)		Number alive Day 4 (post-cull)		Number alive Day 21	
	M	F	M	F	M	F	M	F	M	F
2282	13	5	13	5	13	5	4	4	4	4
2283	7	7	7	7	7	7	4	4	4	4
2284	2	4	2	4	2	4	2	4	2	4
2285	6	6	6	6	6	5	4	4	4	4
2287	10	5	10	5	10	5	4	4	4	4
2292	4	9	4	9	4	9	4	4	4	4
2293	8	4	8	4	7	4	4	4	4	4
2294	7	5	7	5	7	5	4	4	4	4
2295	4	7	4	7	Litter died		4	4	4	4
2299	6	7	6	7	6	7	4	4	4	4
2300	4	10	4	10	4	10	4	4	4	4
2303	10	4	10	4	9	3	5	3	5	3
2304	7	8	7	8	7	8	4	4	4	4
2305	9	4	9	4	8	3	5	3	5	3
2306	2	9	2	9	2	9	2	6	2	6
2308	2	6	2	6	2	6	2	6	2	6
2309	8	5	8	5	8	5	4	4	4	4
2313	7	5	7	5	7	5	4	4	4	4
2314	5	11	5	11	5	10	4	4	4	4
2286	NP									

NP Not pregnant.

APPENDIX 49

Individual observations at necropsy of offspring (F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a Appearance - small pup for age.
- b Brain - unilateral dilation of lateral ventricles.
- c Brain - hydrocephaly, head slightly domed.
- d Epididymis - unilateral rudimentary organ.
- e Eye - one eye missing.
- f Eye - one pupil constricted, both eyes cloudy.
- g Head - wound above left eye.
- h Kidney - unilateral hydronephrosis.
- j Kidney - bilateral hydronephrosis.
- k Kidney - punctate cyst(s) on surface of one kidney.
- m Kidney - pale raised areas (to 5 mm diameter) on one kidney.
- n Kidney - pale areas (to 2 mm diameter) on both kidneys.
- o Liver - pale punctate areas on left median lobe.
- p Palate - pale areas on palate.
- q Palate - dark areas on palate.
- r Palate - haemorrhage on one side of palate.
- s Stomach - no milk in stomach.
- t Stomach/Intestines - distended with gas.
- u Testis - unilateral rudimentary organ.
- v Ureter - unilateral hydroureter.
- w Ureter - bilateral hydroureter.
- x Urinary bladder - full.
- y Urinary bladder - distended.

APPENDIX 49 - continued

Individual observations at necropsy of offspring (F₂)

Group 1 : Control

Animal number	Offspring dying before weaning ^Δ		Offspring killed Day 4		Offspring killed after weaning	
	Number examined	Observations	Number examined	Observations	Number examined	Observations
2161	0	-	6	-	8	-
2162	1	1hs	2	2x	8	-
2163	1	1h	2	-	7	-
2165	0	-	6	-	7	-
2166	0	-	6	1hv, 1j	8	-
2167	0	-	5	-	8	-
2168	1	-	7	-	8	-
2171	0	-	8	-	8	-
2172	3	3s	1	-	8	-
2176	0	-	8	1a, 1v, 1vx, 1w	8	-
2178	0	-	0	-	3	1h
2179	0	-	6	1x	8	-
2181	0	-	1	-	8	-
2184	0	-	6	-	8	-
2187	3	1hs, 1jrs, 1jst	5	-	8	-
2190*	0	-	8	1jw, 1v	8	-
2194	0	-	6	-	8	-
2196	8	1hs, 4s	Litter died	-	8	1m
2198	0	-	0	-	5	1e
2197	NP					

Δ Excludes missing, autolysed and grossly cannibalised offspring.

NP Not pregnant.

APPENDIX 49 - continued

Individual observations at necropsy of offspring(F₂)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Offspring dying before weaning ^A		Offspring killed Day 4		Offspring killed after weaning	
	Number examined	Observations	Number examined	Observations	Number examined	Observations
2201	1	-	8	-	8	1h
2202	0	-	6	1j	8	-
2203	0	-	7	-	8	-
2204	1	1qs	7	-	8	-
2205	11	1hs, 1ps, 9s	Litter died			
2206	1	1s	5	1a	8	1a
2212	0	-	5	-	8	-
2213	0	-	8	1x	8	1a
2215	0	-	6	-	8	1k
2217	0	-	0	-	6	1h
2220	3	1hs, 2s	4	-	6	-
2221	0	-	0	-	6	-
2222	1	-	5	-	8	-
2223	0	-	2	-	8	-
2228	1	1js	4	-	8	-
2233	0	-	6	-	8	-
2237	1	1s	5	-	8	-
2239	1	-	0	-	8	-
2214	LD					
2229	NP					

^A Excludes missing, autolysed and grossly cannibalised offspring.

LD Litter died; no offspring available for examination.

NP Not pregnant.

APPENDIX 49 - continued

Individual observations at necropsy of offspring(F₂)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Offspring dying before weaning ^A		Offspring killed Day 4		Offspring killed after weaning	
	Number examined	Observations	Number examined	Observations	Number examined	Observations
2241	0	-	5	4x	8	-
2243	1	-	8	1ox	7	-
2244	0	-	4	-	8	-
2245	7	1qs, 5s	3	1jswy, 1s, 1x	3	1n
2246	0	-	2	1x	8	1b
2247	0	-	4	-	8	-
2251	0	-	6	-	7	1fk
2254	0	-	7	-	8	-
2256	0	-	0	-	6	-
2260	0	-	1	-	8	-
2262	3	3s	2	-	8	-
2264	0	-	5	2q, 1qy	8	2a, 1du
2266	0	-	6	-	8	-
2267	0	-	7	-	7	-
2268	0	-	6	1y	8	1a
2269	0	-	6	-	8	-
2270	0	-	7	2s, 2sx, 1x	8	1h
2272	1	1s	4	-	8	-
2276	0	-	7	-	8	-
2277	0	-	6	-	8	-

^A Excludes missing, autolysed and grossly cannibalised offspring.

APPENDIX 49 - continued

Individual observations at necropsy of offspring (F₂)

Group 4 : SC-19129 : 750 mg/kg/day (Intended)

Animal number	Offspring dying before weaning ^Δ		Offspring killed Day 4		Offspring killed after weaning	
	Number examined	Observations	Number examined	Observations	Number examined	Observations
2282	0	-	10	1x, 1y	8	1h
2283	0	-	6	-	8	1c, 1h
2284	0	-	0	-	6	-
2285	0	-	3	-	8	-
2287	0	-	7	7x	8	-
2292	0	-	5	1v	8	-
2293	1	1aqs	3	-	8	-
2294	0	-	4	-	8	-
2295	7	1gs, 6s	Litter died	-	8	-
2299	0	-	5	1vy, 1x	8	-
2300	0	-	6	-	8	-
2303	0	-	4	1x, 1y	8	-
2304	0	-	7	-	8	-
2305	0	-	3	-	8	-
2306	0	-	3	-	8	-
2308	0	-	0	-	8	-
2309	0	-	5	-	8	-
2313	0	-	4	-	8	-
2314	0	-	7	1w, 2x	8	-
2286	NP	-				

^Δ Excludes missing, autolysed or grossly cannibalised offspring.
NP Not pregnant.

APPENDIX 50

Individual observations at necropsy of males (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a Appearance - hairloss, face.
- b Epididymis - blue and/or reduced, unilateral.
- c Epididymis - slightly enlarged, unilateral.
- d Fat pads - creamy or yellow body in testicular fat pad.
- e Intestine - section of walls of small intestine red, contents yellow and fluid.
- f Kidney - unilateral hydronephrosis.
- g Pancreas - pedunculate body attached to pancreas.
- h Prostate - reduced.
- j Testis - small and/or blue and/or flaccid, unilateral.
- k Testis - large, blue and flaccid, unilateral.
- m Testis - large (1½-2 x normal) unilateral.
- n Testis - large (2 x normal) bilateral.
- p Testis - yellow body (2 x 2 mm) under tunica membrane.

APPENDIX 50 - continued

Individual observations at necropsy of males (F₁)

Group 1 : Control

Animal number	Obser- vations	Animal number	Obser- vations
2001	-	2021	m
2002	-	2022	-
2003	-	2023	-
2004	-	2024	-
2005	-	2025	-
2006	-	2026	-
2007	-	2027	-
2008	-	2028	-
2009	-	2029	m
2010	-	2030	-
2011	-	2031	-
2012	-	2032	-
2013	-	2033	-
2014	-	2034	-
2015	-	2035	-
2016	bjp	2036	e
2017	-	2037	djm
2018	-	2038	-
2019	-	2039	-
2020	bk	2040	-

APPENDIX 50 - continued

Individual observations at necropsy of males (F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Obser- vations	Animal number	Obser- vations
2041	-	2061	-
2042	-	2062	-
2043	bj	2063	-
2044	-	2064	-
2045	-	2065	-
2046	-	2066	g
2047	bjm	2067	-
2048	-	2068	f
2049	-	2069	-
2050	-	2070	-
2051	-	2071	-
2052	-	2072	hm
2053	-	2073	-
2054	-	2074	-
2055	-	2075	-
2056	-	2076	-
2057	-	2077	-
2058	-	2078	h
2059	bj	2079	-
2060	-	2080	d

APPENDIX 50 - continued

Individual observations at necropsy of males (F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Obser- vations	Animal number	Obser- vations
2081	-	2101	-
2082	-	2102	-
2083	-	2103	-
2084	m	2104	-
2085	-	2105	-
2086	-	2106	-
2087	-	2107	-
2088	-	2108	-
2089	-	2109	-
2090	-	2110	-
2091	-	2111	-
2092	-	2112	-
2093	d	2113	-
2094	f	2114	-
2095	-	2115	-
2096	-	2116	-
2097	-	2117	-
2098	bj	2118	-
2099	f	2119	-
2100	-	2120	-

APPENDIX 50 - continued

Individual observations at necropsy of males (F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Obser- vations	Animal number	Obser- vations
2121	-	2141	-
2122	-	2142	-
2123	-	2143	-
2124	-	2144	abj
2125	-	2145	-
2126	-	2146	-
2127	-	2147	-
2128	-	2148	-
2129	-	2149	f
2130	-	2150	-
2131	d	2151	-
2132	-	2152	-
2133	n	2153	-
2134	-	2154	-
2135	-	2155	-
2136	bcj	2156	-
2137	-	2157	-
2138	-	2158	-
2139	h	2159	-
2140	-	2160	-

APPENDIX 51

Individual observations at necropsy of females (F₁)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Key to observations

- a Appearance - hairloss, ventral surface.
- b Appearance - hairloss, limbs.
- c Appearance - one ear missing.
- d Heart - enlarged, twice normal size.
- e Kidney - unilateral hydronephrosis.
- f Kidney - bilateral hydronephrosis.
- g Mammary tissue - pale and/or inactive.
- h Mammary tissue - swollen region (30 x 15 mm) : cut surface shows pale-green amorphous material.
- j Thymus - areas of congestion (4 x 7 mm).
- k Uterus - unilateral implantation sites.
- m Uterus - no implantation sites.
- n Uterus - clotted blood in gravid horn of uterus.

APPENDIX 51 - continued

Individual observations at necropsy of females (F₁)

Group 1 : Control

Animal number	Stage of study	Observations	Animal number	Stage of study	Observations
2161	W	ab	2181	W	-
2162	W	-	2182	T	-
2163	W	-	2183	T	-
2164	T	-	2184	W	-
2165	W	-	2185	T	-
2166	W	-	2186	T	-
2167	W	-	2187	W	-
2168	W	-	2188	T	-
2169	T	k	2189	T	dj
2170	T	-	2190	W	-
2171	W	-	2191	T	k
2172	W	c	2192	T	m
2173	T	-	2193	T	-
2174	T	-	2194	W	-
2175	T	-	2195	T	-
2176	W	-	2196	LD	g
2177	T	-	2197	NP	m
2178	W	k	2198	W	k
2179	W	-	2199	T	m
2180	T	-	2200	T	e

T Sacrificed on Day 20 post coitum for teratological examination.

NP Sacrificed when no litter produced by Day 25 post coitum.

LD Sacrificed after litter died.

W Sacrificed after litter weaned.

APPENDIX 51 - continued

Individual observations at necropsy of females (F₁)

Group 2 : SC-19129 : 250 mg/kg/day (intended)

Animal number	Stage of study	Observations	Animal number	Stage of study	Observations
2201	W	-	2221	W	-
2202	W	-	2222	W	-
2203	W	-	2223	W	-
2204	W	-	2224	T	-
2205	LD	-	2225	T	k
2206	W	-	2226	T	-
2207	T	-	2227	T	-
2208	T	-	2228	W	-
2209	T	-	2229	NP	m
2210	T	-	2230	T	-
2211	T	-	2231	T	m
2212	W	-	2232	T	-
2213	W	-	2233	W	-
2214	LD	gk	2234	T	-
2215	W	-	2235	T	-
2216	T	-	2236	T	-
2217	W	k	2237	W	-
2218	T	-	2238	T	m
2219	T	-	2239	W	-
2220	W	-	2240	T	-

T Sacrificed on Day 20 post coitum for teratological examination.

NP Sacrificed when no litter produced by Day 25 post coitum.

LD Sacrificed after litter died.

W Sacrificed after litter weaned.

APPENDIX 51 - continued

Individual observations at necropsy of females (F₁)

Group 3 : SC-19129 : 500 mg/kg/day (intended)

Animal number	Stage of study	Observations	Animal number	Stage of study	Observations
2241	W	a	2261	T	-
2242	T	-	2262	W	-
2243	W	-	2263	T	-
2244	W	-	2264	W	-
2245	W	-	2265	T	k
2246	W	-	2266	W	-
2247	W	-	2267	W	-
2248	T	m	2268	W	-
2249	T	-	2269	W	-
2250	T	-	2270	W	-
2251	W	-	2271	T	-
2252	T	-	2272	W	ab
2253	T	-	2273	T	-
2254	W	-	2274	T	-
2255	T	k	2275	T	-
2256	W	k	2276	W	-
2257	T	-	2277	W	-
2258	T	k	2278	T	-
2259	T	-	2279	T	kn
2260	W	-	2280	T	-

T Sacrificed on Day 20 post coitum for teratological examination.
W Sacrificed after litter weaned.

APPENDIX 51 - continued

Individual observations at necropsy of females (F₁)

Group 4 : SC-19129 : 750 mg/kg/day (intended)

Animal number	Stage of study	Observations	Animal number	Stage of study	Observations
2281	T	-	2301	T	-
2282	W	-	2302	T	-
2283	W	a	2303	W	-
2284	W	k	2304	W	-
2285	W	-	2305	W	-
2286	NP	gm	2306	W	-
2287	W	-	2307	T	m
2288	T	-	2308	W	-
2289	T	-	2309	W	-
2290	T	k	2310	T	-
2291	T	-	2311	T	k
2292	W	-	2312	T	f
2293	W	-	2313	W	h
2294	W	-	2314	W	-
2295	LD	g	2315	T	-
2296	T	m	2316	T	-
2297	T	-	2317	T	-
2298	T	-	2318	T	-
2299	W	-	2319	T	-
2300	W	-	2320	T	-

T Sacrificed on Day 20 post coitum for teratological examination.

NP Sacrificed when no litter produced by Day 25 post coitum.

LD Sacrificed after litter died.

W Sacrificed after litter weaned.

APPENDIX 52

Individual absolute weights (g) of male reproductive organs (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Prostate	Seminal Vesicles	Testes	Epididymides
1M	2001	625	0.62	3.06	3.57	1.37
	2002	545	0.58	2.75	3.78	1.38
	2003	554	0.54	2.86	3.27	1.28
	2004	555	1.02	2.71	3.15	1.23
	2005	550	0.68	2.66	3.64	1.40
	2006	551	0.55	1.73	3.59	1.33
	2007	536	0.66	2.77	3.90	1.43
	2008	589	0.52	3.18	3.47	1.26
	2009	562	0.61	2.28*	3.63	1.18
	2010	542	0.54	2.88	3.30	1.20
	2011	533	0.31	1.98	3.09	1.13
	2012	576	0.49	2.67	3.66	1.28
	2013	671	0.34	2.15	3.40	1.30
	2014	587	0.32	2.16	2.89	1.21
	2015	594	1.06	1.77	3.25	1.20
	2016	508	0.70	2.31*	2.77	0.98
	2017	534	0.63	2.38	3.62	1.31
	2018	550	0.48	2.11*	3.37	1.27
	2019	517	0.45	2.23	3.28	1.18
	2020	454	0.65	2.82	3.81	1.00
	2021	556	0.64	2.52	4.94	1.23
	2022	584	0.57	1.85*	3.27	1.20
	2023	546	0.48	2.26	3.67	1.17
	2024	485	0.46	2.04	3.85	1.27
	2025	612	0.40	2.31	4.00	1.32
	2026	493	0.75	2.96	3.11	1.09
	2027	677	0.60	2.93	3.56	1.35
	2028	602	0.72	2.53	3.74	1.28
	2029	647	0.61	2.37	4.96	1.13
	2030	533	0.55	2.89	3.66	1.28
	2031	582	0.63	2.64	3.41	1.17
	2032	589	0.47	2.44	3.92	1.45
	2033	656	0.86	2.75	3.83	1.29
	2034	658	0.87	3.24	4.19	1.52
	2035	453	0.50	2.58	3.87	1.29
	2036	528	0.40	2.90	3.75	1.27
	2037	570	0.47	2.33	4.03	0.97
	2038	630	0.71	2.77	3.55	1.26
	2039	640	0.37	2.12	4.01	1.17
	2040	580	0.51	2.16	3.80	1.33

* Damaged at necropsy, excluded from group mean values.

APPENDIX 52 - continued

Individual absolute weights (g) of male reproductive organs (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Prostate	Seminal Vesicles	Testes	Epididymides
2M	2041	530	0.50	2.63	4.14	1.52
	2042	547	0.74	2.78	3.41	1.33
	2043	499	0.56	2.48	2.58	0.79
	2044	499	0.46	2.97	3.20	1.29
	2045	607	0.50	2.73	3.55	1.38
	2046	584	0.50	2.89	4.38	1.45
	2047	586	0.84	2.64	4.03	1.25
	2048	572	0.52	2.11	3.48	1.27
	2049	618	0.88	2.70	4.04	1.40
	2050	504	0.62	3.11	3.66	1.24
	2051	485	0.83	2.84	3.58	1.21
	2052	575	0.45	2.26	3.74	1.31
	2053	567	0.69	2.82	4.14	1.35*
	2054	498	0.45	3.04	3.78	1.49
	2055	581	0.55	2.44	3.48	1.19
	2056	622	0.38	2.79	3.82	1.33
	2057	489	0.35	1.63*	4.07	1.26
	2058	570	0.43	3.14	4.18	1.43
	2059	558	0.39	2.47*	3.16	0.98
	2060	552	0.70	2.56	3.41	1.16
	2061	484	0.61	2.42	3.49	1.25
	2062	608	0.74	2.65	3.72	1.29
	2063	506	0.63	2.59	3.63	1.30
	2064	496	0.40	2.50	3.46	1.29
	2065	511	0.48	2.19	2.30	1.12
	2066	667	0.44	2.36	3.77	1.23
	2067	568	0.60	2.37	3.93	1.45
	2068	605	0.76	2.38	3.73	1.34
	2069	565	0.70	2.62*	4.01	1.37
	2070	564	0.61	3.09	3.69	1.36
	2071	497	0.33	3.23	3.39	1.23
	2072	483	0.23	2.39	4.72	1.10
	2073	445	0.43	2.52	3.74	1.26
	2074	460	0.61	1.78*	3.12	1.20
	2075	585	0.74	2.44	3.45	1.28
	2076	607	0.60	2.18	3.78	1.37
	2077	603	0.40	2.23	3.70	1.24
	2078	588	0.24	2.94	3.60	1.40
	2079	598	0.65	2.91	4.37	1.44
	2080	553	0.68	2.68	3.55	1.32

* Damaged at necropsy, excluded from group mean values.

APPENDIX 52 - continued

Individual absolute weights (g) of male reproductive organs (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Prostate	Seminal Vesicles	Testes	Epidid-ymides
3M	2081	580	0.58	2.99	3.40	1.32
	2082	570	0.59	2.94	3.82	1.35
	2083	556	0.43	3.03	3.70	1.22
	2084	549	0.80	2.61	5.28	1.57
	2085	547	0.59	1.78	3.45	1.33*
	2086	562	0.65	2.55	3.51	1.38
	2087	502	0.63	2.74	3.28	1.18
	2088	600	1.05	2.71	3.76	1.31
	2089	587	0.44	3.01	4.02	1.45
	2090	578	0.31	2.63	3.46	1.27
	2091	518	0.78	2.42	3.65	1.33
	2092	518	0.89	2.80	3.47	1.22
	2093	576	0.91	2.55	3.73	1.26
	2094	527	0.78	2.51	3.09	1.14
	2095	579	0.42	2.85	3.70	1.19
	2096	601	0.53	2.03	3.62	1.20
	2097	567	0.27	2.43	3.82	1.23
	2098	552	0.73	2.66	2.57	0.83
	2099	526	0.52	2.46	2.98	1.16
	2100	491	0.49	2.64	3.21	1.05
	2101	561	1.00	2.43	3.43	1.23
	2102	560	0.45	2.38	3.76	1.26
	2103	563	0.29	2.33	3.87	1.18
	2104	555	0.40	1.75	3.62	1.18
	2105	507	0.53	2.57	3.48	1.36
	2106	464	0.74	2.20	3.33	1.38
	2107	442	0.59	1.76	3.01	1.20
	2108	474	0.47	2.05	3.57	1.28
	2109	606	0.79	2.95	3.80	1.36
	2110	586	0.48	2.31	3.98	1.35
	2111	670	0.55	3.07	3.93	1.37
	2112	600	0.58	2.50	3.56	1.27
	2113	588	0.86	3.09	4.10	1.46
	2114	492	0.73	3.02	3.73	1.34
	2115	595	0.57	2.99	3.59	1.27
	2116	605	0.34	2.37	3.77	1.51
	2117	517	0.48	2.60	3.92	1.48
	2118	671	0.33	1.88	3.77	1.29
	2119	497	0.51	2.59	3.73	1.33
	2120	542	0.61	2.38	3.39	1.26

* Damaged at necropsy, excluded from group mean values.

APPENDIX 52 - continued

Individual absolute weights (g) of male reproductive organs (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Prostate	Seminal Vesicles	Testes	Epididymides
4M	2121	527	0.36	1.54*	3.80	1.34
	2122	461	0.67	2.30	3.16	1.22
	2123	334	0.54	2.74	3.47	1.25
	2124	509	0.74	2.24	3.36	1.26
	2125	556	0.53	2.23	3.51	1.06
	2126	585	0.60	2.76	3.31	1.24
	2127	565	0.59	2.99	3.74	1.39
	2128	513	0.52	1.60	3.36	1.00
	2129	561	0.88	2.71*	3.70	1.30
	2130	491	0.45	2.64	3.82	1.39
	2131	615	0.51	2.67	2.39 ^α	1.13
	2132	597	0.37	2.60	3.27	1.16
	2133	510	0.53	2.42*	6.57	1.21
	2134	630	0.39	2.69	3.66	1.39
	2135	631	0.55	3.06	4.44	1.40
	2136	543	0.72	2.72	3.79	1.25
	2137	564	0.42	2.10	3.64	1.23
	2138	551	0.31	2.95	3.52	1.20
	2139	469	0.07	1.99*	3.64	1.28
	2140	520	0.39	2.14	4.23	1.35
	2141	497	0.65	2.90	4.01	1.22
	2142	563	0.81	2.38	3.78	1.31
	2143	436	0.62	2.13	3.63	1.25
	2144	499	0.49	2.39	3.14	1.02
	2145	544	0.48	3.11	4.11	1.27
	2146	503	0.52	2.53	2.76	1.12
	2147	520	0.75	2.85	3.40	1.26
	2148	498	0.54	2.47	3.68	1.34
	2149	495	0.85	2.26	3.10	1.13
	2150	500	0.51	2.25	3.48	1.07
	2151	575	0.72	3.49	4.07	1.38
	2152	531	1.10	3.13	3.64	1.27
	2153	593	0.53	3.25	4.36	1.38
	2154	574	0.67	2.23	3.40	1.23
	2155	470	0.54	2.65	3.31	1.15
	2156	448	0.33	2.04	3.62	1.28
	2157	452	0.26	3.19	3.13	1.29
	2158	475	0.59	2.85	3.21	1.21
	2159	655	0.39	2.38	3.99	1.44
	2160	608	0.51	3.18	3.97	1.34

* Damaged at necropsy, excluded from group mean values.

α One testis misweighed, excluded from group mean value.

APPENDIX 53

Individual relative weights^Δ of male reproductive organs (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Prostate	Seminal Vesicles	Testes	Epididymides
1M	2001	625	0.10	0.49	0.57	0.22
	2002	545	0.11	0.50	0.69	0.25
	2003	554	0.10	0.52	0.59	0.23
	2004	555	0.18	0.49	0.57	0.22
	2005	550	0.12	0.48	0.66	0.25
	2006	551	0.10	0.31	0.65	0.24
	2007	536	0.12	0.52	0.73	0.27
	2008	589	0.09	0.54	0.59	0.21
	2009	562	0.11	0.41*	0.65	0.21
	2010	542	0.10	0.53	0.61	0.22
	2011	533	0.06	0.37	0.58	0.21
	2012	576	0.09	0.46	0.63	0.22
	2013	671	0.05	0.32	0.51	0.19
	2014	587	0.05	0.37	0.49	0.21
	2015	594	0.18	0.30	0.55	0.20
	2016	508	0.14	0.45*	0.55	0.19
	2017	534	0.12	0.45	0.68	0.25
	2018	550	0.09	0.38*	0.61	0.23
	2019	517	0.09	0.43	0.63	0.23
	2020	454	0.14	0.62	0.84	0.22
	2021	556	0.12	0.45	0.89	0.22
	2022	584	0.10	0.32*	0.56	0.21
	2023	546	0.09	0.41	0.67	0.21
	2024	485	0.09	0.42	0.79	0.26
	2025	612	0.07	0.38	0.65	0.22
	2026	493	0.15	0.60	0.63	0.22
	2027	677	0.09	0.43	0.53	0.20
	2028	602	0.12	0.42	0.62	0.21
	2029	647	0.09	0.37	0.77	0.17
	2030	533	0.10	0.54	0.69	0.24
	2031	582	0.11	0.45	0.59	0.20
	2032	589	0.08	0.41	0.67	0.25
	2033	656	0.13	0.42	0.58	0.20
	2034	658	0.13	0.49	0.64	0.23
	2035	453	0.11	0.57	0.85	0.28
	2036	528	0.08	0.55	0.71	0.24
	2037	570	0.08	0.41	0.71	0.17
	2038	630	0.11	0.44	0.56	0.20
	2039	640	0.06	0.33	0.63	0.18
	2040	580	0.09	0.37	0.66	0.23

* Damaged at necropsy, excluded from group mean values.

Δ Expressed as a percentage of bodyweight.

APPENDIX 53 - continued

Individual relative weights^Δ of male reproductive organs (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Prostate	Seminal Vesicles	Testes	Epididymides
2M	2041	530	0.09	0.50	0.78	0.29
	2042	547	0.14	0.51	0.62	0.24
	2043	499	0.11	0.50	0.52	0.16
	2044	499	0.09	0.60	0.64	0.26
	2045	607	0.08	0.45	0.58	0.23
	2046	584	0.09	0.49	0.75	0.25
	2047	586	0.14	0.45	0.69	0.21
	2048	572	0.09	0.37	0.61	0.22
	2049	618	0.14	0.44	0.65	0.23
	2050	504	0.12	0.62	0.73	0.25
	2051	485	0.17	0.59	0.74	0.25
	2052	575	0.08	0.39	0.65	0.23
	2053	567	0.12	0.50	0.73	0.24*
	2054	498	0.09	0.61	0.76	0.30
	2055	581	0.09	0.42	0.60	0.20
	2056	622	0.06	0.45	0.61	0.21
	2057	489	0.07	0.33*	0.83	0.26
	2058	570	0.08	0.55	0.73	0.25
	2059	558	0.07	0.44*	0.57	0.18
	2060	552	0.13	0.46	0.62	0.21
	2061	484	0.13	0.50	0.72	0.26
	2062	608	0.12	0.44	0.61	0.21
	2063	506	0.12	0.51	0.72	0.26
	2064	496	0.08	0.50	0.70	0.26
	2065	511	0.09	0.43	0.45	0.22
	2066	667	0.07	0.35	0.57	0.18
	2067	568	0.11	0.42	0.69	0.26
	2068	605	0.13	0.39	0.62	0.22
	2069	565	0.12	0.46*	0.71	0.24
	2070	564	0.11	0.55	0.65	0.24
	2071	497	0.07	0.65	0.68	0.25
	2072	483	0.05	0.49	0.98	0.23
	2073	445	0.10	0.57	0.84	0.28
	2074	460	0.13	0.39*	0.68	0.26
	2075	585	0.13	0.42	0.59	0.22
	2076	607	0.10	0.36	0.62	0.23
	2077	603	0.07	0.37	0.61	0.21
	2078	588	0.04	0.50	0.61	0.24
	2079	598	0.11	0.49	0.73	0.24
	2080	553	0.12	0.48	0.64	0.24

* Damaged at necropsy, excluded from group mean values.

Δ Expressed as a percentage of bodyweight.

APPENDIX 53 - continued

Individual relative weights^Δ of male reproductive organs (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Prostate	Seminal Vesicles	Testes	Epididymides
3M	2081	580	0.10	0.52	0.59	0.23
	2082	570	0.10	0.52	0.67	0.24
	2083	556	0.08	0.54	0.67	0.22
	2084	549	0.15	0.48	0.96	0.29
	2085	547	0.11	0.33	0.63	0.24*
	2086	562	0.12	0.45	0.62	0.25
	2087	502	0.13	0.55	0.65	0.24
	2088	600	0.18	0.45	0.63	0.22
	2089	587	0.07	0.51	0.68	0.25
	2090	578	0.05	0.46	0.60	0.22
	2091	518	0.15	0.47	0.70	0.26
	2092	518	0.17	0.54	0.67	0.24
	2093	576	0.16	0.44	0.65	0.22
	2094	527	0.15	0.48	0.59	0.22
	2095	579	0.07	0.49	0.64	0.21
	2096	601	0.09	0.34	0.60	0.20
	2097	567	0.05	0.43	0.67	0.22
	2098	552	0.13	0.48	0.47	0.15
	2099	526	0.10	0.47	0.57	0.22
	2100	491	0.10	0.54	0.65	0.21
	2101	561	0.18	0.43	0.61	0.22
	2102	560	0.08	0.43	0.67	0.23
	2103	563	0.05	0.41	0.69	0.21
	2104	555	0.07	0.32	0.65	0.21
	2105	507	0.10	0.51	0.69	0.27
	2106	464	0.16	0.47	0.72	0.30
	2107	442	0.13	0.40	0.68	0.27
	2108	474	0.10	0.43	0.75	0.27
	2109	606	0.13	0.49	0.63	0.22
	2110	586	0.08	0.39	0.68	0.23
	2111	670	0.08	0.46	0.59	0.20
	2112	600	0.10	0.42	0.59	0.21
	2113	588	0.15	0.53	0.70	0.25
	2114	492	0.15	0.61	0.76	0.27
	2115	595	0.10	0.50	0.60	0.21
	2116	605	0.06	0.39	0.62	0.25
	2117	517	0.09	0.50	0.76	0.29
	2118	671	0.05	0.28	0.56	0.19
	2119	497	0.10	0.52	0.75	0.27
	2120	542	0.11	0.44	0.63	0.23

* Damaged at necropsy, excluded from group mean values.

Δ Expressed as a percentage of bodyweight.

APPENDIX 53 - continued

Individual relative weights^Δ of male reproductive organs (F₁)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Prostate	Seminal Vesicles	Testes	Epididymides
4M	2121	527	0.07	0.29*	0.72	0.25
	2122	461	0.15	0.50	0.69	0.26
	2123	334	0.16	0.82	1.04	0.37
	2124	509	0.15	0.44	0.66	0.25
	2125	556	0.10	0.40	0.63	0.19
	2126	585	0.10	0.47	0.57	0.21
	2127	565	0.10	0.53	0.66	0.25
	2128	513	0.10	0.31	0.65	0.19
	2129	561	0.16	0.48*	0.66	0.23
	2130	491	0.09	0.54	0.78	0.28
	2131	615	0.08	0.43	0.39*	0.18
	2132	597	0.06	0.44	0.55	0.19
	2133	510	0.10	0.47*	1.29	0.24
	2134	630	0.06	0.43	0.58	0.22
	2135	631	0.09	0.48	0.70	0.22
	2136	543	0.13	0.50	0.70	0.23
	2137	564	0.07	0.37	0.65	0.22
	2138	551	0.06	0.54	0.64	0.22
	2139	469	0.01	0.42*	0.78	0.27
	2140	520	0.08	0.41	0.81	0.26
	2141	497	0.13	0.58	0.81	0.25
	2142	563	0.14	0.42	0.67	0.23
	2143	436	0.14	0.49	0.83	0.29
	2144	499	0.10	0.48	0.63	0.20
	2145	544	0.09	0.57	0.76	0.23
	2146	503	0.10	0.50	0.55	0.22
	2147	520	0.14	0.55	0.65	0.24
	2148	498	0.11	0.50	0.74	0.27
	2149	495	0.17	0.46	0.63	0.23
	2150	500	0.10	0.45	0.70	0.21
	2151	575	0.13	0.61	0.71	0.24
	2152	531	0.21	0.59	0.69	0.24
	2153	593	0.09	0.55	0.74	0.23
	2154	574	0.12	0.39	0.59	0.21
	2155	470	0.11	0.56	0.70	0.24
	2156	448	0.07	0.46	0.81	0.29
	2157	452	0.06	0.71	0.69	0.29
	2158	475	0.12	0.60	0.68	0.26
	2159	655	0.06	0.36	0.61	0.22
	2160	608	0.08	0.52	0.65	0.22

* Damaged at necropsy, excluded from group mean values.

Δ Expressed as a percentage of bodyweight.

APPENDIX 54

Individual absolute weights (g) of female
reproductive organs at Day 20 of gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Gravid Uterus	Uterus	Ovaries
1F	2164	380	66	4.22	0.103
	2169	458 ^a	NW	NW	NW
	2170	462	80	4.27	0.130
	2173	385	61	3.32	0.110
	2174	365	NW	3.81	0.130
	2175	366	79	4.69	0.100
	2177	391	66	4.37	0.250
	2180	365	NW	4.15	0.106
	2182	371	60	3.78	0.099
	2183	406	77	4.19	0.120
	2185	420	NW	3.28	0.134
	2186	394	69	4.41	0.123
	2188	429	41	3.42	0.140
	2189	380	39	3.65	0.080
	2191	407	29	2.73	0.120
	2193	440	70	5.21	0.120
	2195	357	68	4.30	0.170
	2200	428	70	4.53	0.100
	2192NP	372	-	0.46	0.070
	2199NP	352	-	0.67	0.087

a Organs not weighed, bodyweight excluded from group mean value.

NW Not weighed.

NP Not pregnant, data excluded from group mean value.

APPENDIX 54 - continued

Individual absolute weights (g) of female reproductive organs at Day 20 of gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	---	SC-19129	---
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Gravid Uterus	Uterus	Ovaries
2F	2207	404	91	4.57	0.109
	2208	407	85	5.37	0.110
	2209	395	74	4.71	0.140
	2210	396	67	4.05	0.106
	2211	431	69	5.27	0.100
	2216	433	74	4.67	0.116
	2218	389	84	5.06	0.115
	2219	387	66	3.99	0.110
	2224	427	91	5.49	0.140
	2225	296	37	2.75	0.164
	2226	334	55	3.71	0.104
	2227	376	60	3.92	0.080
	2230	375	43	4.09	0.118
	2232	359	65	4.10	0.106
	2234	400	60	4.12	0.120
	2235	385	78	4.88	0.120
	2236	417	59	3.75	0.114
	2240	433	78	4.72	0.140
	2231NP	317	-	0.37	0.080
	2238NP	329	-	0.89	0.076

NP Not pregnant, data excluded from group mean values.

APPENDIX 54 - continued

Individual absolute weights (g) of female reproductive organs at Day 20 of gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Gravid Uterus	Uterus	Ovaries
3F	2242	412	77	4.62	0.117
	2249	409	67	4.16	0.099
	2250	410	76	4.70	0.120
	2252	395	70	4.22	0.133
	2253	411	63	3.77	0.090
	2255	365	19	2.14	0.090
	2257	423	55	3.77	0.210
	2258	416	41	3.11	0.160
	2259	370	71	4.82	0.130
	2261	391	72	4.64	0.110
	2263	363	61	4.02	0.080
	2265	313	43	3.02	0.110
	2271	454	83	4.47	0.100
	2273	395	29	2.20	0.128
	2274	353	68	4.27	0.110
	2275	378	57	3.48	0.093
	2278	454	77	4.65	0.110
	2279	364	44	2.98	0.093
	2280	278 ^b	66	4.35	0.101
	2248NP	287	-	0.93	0.120

NP Not pregnant, data excluded from group mean values.

b Suspected weighing error, excluded from group mean value.

APPENDIX 54 - continued

Individual absolute weights (g) of female reproductive organs at Day 20 of gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight	Gravid Uterus	Uterus	Ovaries
4F	2281	398	58	3.97	0.100
	2288	384	64	4.34	0.150
	2289	336	16	1.59	0.120
	2290	368	43	3.04	0.110
	2291	394	63	4.21	0.109
	2297	384	72	4.49	0.082
	2298	400	73	4.61	c
	2301	362	50	3.46	0.131
	2302	295 ^b	86	4.46	0.100
	2310	397	63	4.74	0.100
	2311	414	49	3.37	0.120
	2312	445	54	3.09	0.112
	2315	445	67	3.86	0.145
	2316	366	70	4.25	0.100
	2317	378	NW	4.33	0.120
	2318	380	68	3.87	0.090
	2319	427	67	4.68	0.133
	2320	432	85	4.69	0.090
	2296NP	311	-	0.43	0.096
	2307NP	306	-	0.61	0.091

b Suspected recording error, excluded from group mean value.

c One ovary not weighed.

NW Not weighed.

NP Not pregnant, data excluded from group mean values.

APPENDIX 55

Individual relative weights^A of female reproductive organs at Day 20 of gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Gravid Uterus	Uterus	Ovaries ⁺
-------------	---------------	-----------------	---------------	--------	----------------------

1F	2164	380	17.37	1.11	27.1
	2169	458 ^a	NW	NW	NW
	2170	462	17.32	0.92	28.1
	2173	385	15.84	0.86	28.6
	2174	365	NW	1.04	35.6
	2175	366	21.58	1.28	27.3
	2177	391	16.88	1.12	63.9
	2180	365	NW	1.14	29.0
	2182	371	16.17	1.02	26.7
	2183	406	18.97	1.03	29.6
	2185	420	NW	0.78	31.9
	2186	394	17.51	1.12	31.2
	2188	429	9.56	0.80	32.6
	2189	380	10.26	0.96	21.1
	2191	407	7.13	0.67	29.5
	2193	440	15.91	1.18	27.3
	2195	357	19.05	1.20	47.6
	2200	428	16.36	1.06	23.4
	2192NP	372	-	0.12	18.8
	2199NP	352	-	0.19	24.7

a Organs not weighed, bodyweight excluded from group mean value.

NW Not weighed.

NP Not pregnant, data excluded from group mean values.

Δ Expressed as a percentage of bodyweight unless otherwise indicated.

+ Ovaries : percentage value multiplied by 1000.

APPENDIX 55 - continued

Individual relative weights^Δ of female reproductive organs at Day 20 of gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Gravid Uterus	Uterus	Ovaries ⁺
2F	2207	404	22.52	1.13	27.0
	2208	407	20.88	1.32	27.0
	2209	395	18.73	1.19	35.4
	2210	396	16.92	1.02	26.8
	2211	431	16.01	1.22	23.2
	2216	433	17.09	1.08	26.8
	2218	389	21.59	1.30	29.6
	2219	387	17.05	1.03	28.4
	2224	427	21.31	1.29	32.8
	2225	296	12.50	0.93	55.4
	2226	334	16.47	1.11	31.1
	2227	376	15.96	1.04	21.3
	2230	375	11.47	1.09	31.5
	2232	359	18.11	1.14	29.5
	2234	400	15.00	1.03	30.0
	2235	385	20.26	1.27	31.2
	2236	417	14.15	0.90	27.3
	2240	433	18.01	1.09	32.3
	2231NP	317	-	0.12	25.2
	2238NP	329	-	0.27	23.1

NP Not pregnant, data excluded from group mean values.

Δ Expressed as a percentage of bodyweight unless otherwise indicated.

+ Ovaries : percentage value multiplied by 1000.

APPENDIX 55 - continued

Individual relative weights^Δ of female
reproductive organs at Day 20 of gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Gravid Uterus	Uterus	Ovaries ⁺
3F	2242	412	18.69	1.12	28.4
	2249	409	16.38	1.02	24.2
	2250	410	18.54	1.15	29.3
	2252	395	17.72	1.07	33.7
	2253	411	15.33	0.92	21.9
	2255	365	5.21	0.59	24.7
	2257	423	13.00	0.89	49.6
	2258	416	9.86	0.75	38.5
	2259	370	19.19	1.30	35.1
	2261	391	18.41	1.19	28.1
	2263	363	16.80	1.11	22.0
	2265	313	13.74	0.96	35.1
	2271	454	18.28	0.98	22.0
	2273	395	7.34	0.56	32.4
	2274	353	19.26	1.21	31.2
	2275	378	15.08	0.92	24.6
	2278	454	16.96	1.02	24.2
	2279	364	12.09 ^d	0.82 ^d	25.5
	2280	278 ^b	23.74 ^d	1.56 ^d	36.3 ^d
2248NP	287	-	-	0.32	41.8

b Suspected weighing error, excluded from group mean value.

d Relative weights excluded from group mean value.

NP Not pregnant, data excluded from group mean values.

Δ Expressed as a percentage of bodyweight unless otherwise indicated.

+ Ovaries : percentage value multiplied by 1000.

APPENDIX 55 - continued

Individual relative weights^Δ of female
reproductive organs at Day 20 of gestation (F₁-F₂)

Group	:	1	2	3	4
Compound	:	Control	-----	SC-19129	-----
Intended dosage (mg/kg/day)	:	0	250	500	750

Group / sex	Animal number	Body weight (g)	Gravid Uterus	Uterus	Ovaries ⁺
----------------	------------------	-----------------------	------------------	--------	----------------------

4F	2281	398	14.57	1.00	25.1
	2288	384	16.67	1.13	39.1
	2289	336	4.76	0.47	35.7
	2290	368	11.68	0.83	29.9
	2291	394	15.99	1.07	27.7
	2297	384	18.75	1.17	21.4
	2298	400	18.25	1.15	c
	2301	362	13.81	0.96	36.2
	2302	295 ^b	29.15 ^d	1.51 ^d	33.9 ^d
	2310	397	15.87	1.19	25.2
	2311	414	11.84	0.81	29.0
	2312	445	12.13	0.69	25.2
	2315	445	15.06	0.87	32.6
	2316	366	19.13	1.16	27.3
	2317	378	NW	1.15	31.7
	2318	380	17.89	1.02	23.7
	2319	427	15.69	1.10	31.1
	2320	432	19.68	1.09	20.8
	2296NP	321	-	0.14	30.9
	2307NP	306	-	0.20	29.7

b Suspected recording error, excluded from group mean value.

c One ovary not weighed.

d Relative weights excluded from group mean values.

NW Not weighed.

NP Not pregnant, data excluded from group mean values.

Δ Expressed as a percentage of bodyweight unless
otherwise indicated.

+ Ovaries : percentage value multiplied by 1000.

ADDENDUM 1

Room temperature and humidity

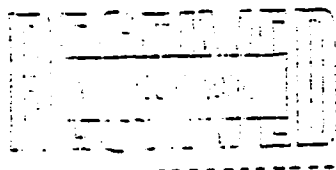
Month	Temperature °C				Relative humidity	
	Minimum		Maximum		(%)	
	Mean	95% range	Mean	95% range	Mean	95% range
1984						
November ^a	20	1	22	1	63	8
December	20	1	22	1	60	12
1985						
January	20	0.4	22	1	59	13
February	21	1	23	1	60	13
March	20	1	22	2	61	10
April	20	1	22	1	66	7
May	21	2	23	2	66	9
June	21	1	24	1	67	8
July ^b	20	0.5	24	1	69	14

a Mean of 24 days only - animals arrived 7 November 1984.

b Mean of 8 days only - live animal work completed 8 July 1985.

ADDENDUM 2

Protocol and amendments



LSR Schedule No.

SEA 043

LSR Enquiry No.

ZZZ/0150 A

TWO GENERATION REPRODUCTION STUDY
OF SC-19129 IN RATS, S.A. NO. 2473

Revised protocol prepared for
G.D. SEARLE AND COMPANY
by
Life Science Research
Eye, Suffolk, England
30 October 1984

MANAGEMENT OF STUDY

Project co-ordinator : Peter A. McAnulty, B.Sc., M. Phil.,
Ph.D., C. Biol., M.I. Biol.

Study director : Christopher R. Willoughby, B.Sc., M.P.S.

Staff reproductive biologist : Roger C. Secker, B.Sc., C. Biol.,
M.I. Biol.

Sponsor : G.D. Searle and Company
Box 5110
Chicago
Illinois 60680
U.S.A.

Monitor : Dr. J.W. Noveroske

PROTOCOL APPROVAL

For LIFE SCIENCE RESEARCH LIMITED

Issued by : *John G. Smith* Date : *30/10/84*

Released by : *John G. Smith* Date : *30 Oct 84*

For G.D. SEARLE AND COMPANY

No modifications required

This protocol is accepted without revision and my signature authorises the study to proceed as described in this document. The document becomes the FINAL PROTOCOL for the study, and will be reproduced in the final report.

Approved by : *John G. Smith* Date : *Nov. 6, 1984*

Study Co-ordinator

..... *John G. Smith* Date : *11/6/84*

Director of Toxicology

..... *Frank E. Kuhn* Date : *11/6/84*

Senior Director, PSA

STUDY DIRECTOR

The Sponsor has approved the initiation of the study according to the procedures described in this document. My signature below denotes that I have read and agreed the contents of this document.

..... *Ch. W. Houghton* Date : *15. Nov. 1984*

(Study Director)

TWO GENERATION REPRODUCTION STUDY
OF SC-19129 IN RATS, S.A. NO. 2473

1. INTRODUCTION

1.1 Objective

The aim of this investigation will be to assess the influence of continuously administered SC-19129 upon the reproductive capacity of two successive generations of rats.

1.2 Choice of species

The rat will be selected because of the requirement for its use by regulatory authorities. The Charles River CD Rat (of Sprague-Dawley origin) will be selected because of the background data available on this strain in these laboratories.

1.3 Choice of route of administration and treatment levels

SC-19129 will be administered by the dietary route to simulate the route of human exposure.

Dosages will be based on information provided by the Sponsor, by reference to the expected levels of human exposure, or on the results of a preliminary study.

1.4 Location of study

: Life Science Research
Eye
Suffolk IP23 7PX
England
Telephone: Diss (0379) 4122
Telex : 975389

2. REPRODUCTIVE AND TREATMENT SEQUENCE

<u>Study week</u> <u>(approximate)</u>	<u>F₀</u>	<u>F₁</u>	<u>F₂</u>
1	Treatment of F ₀ males begins		
9	Treatment of F ₀ females begins		
11-13	F ₀ mating period		
14-16	Treatment of F ₀ males terminated and animals killed	F ₁ born and litter size adjusted to 8 offspring	
17-20	Treatment of F ₀ females is terminated	F ₁ weaned; treatment of selected F ₁ animals begins	
	F ₀ females are killed	F ₁ unselected offspring are killed	
27-30		F ₁ mating period	
30-33		Treatment of F ₁ males terminated and animals killed	F ₂ born and litter size adjusted to 8 offspring
33-37		Treatment of F ₁ females terminated and animals killed	F ₂ weaned and killed

3. SCHEDULED TIME PLAN

3.1 Treatment commences : 12 November 1984

3.2 Draft report to Sponsor : November 1985

4. DESIGN CONDITIONS

4.1 Animals

Rats of the CD strain (of Sprague-Dawley origin) will be obtained from Charles River U.K. Limited, Margate, Kent, England to form the F_0 generation.

Males will be 5 weeks old at arrival, and in the approximate weight range of 115-135 g; females will be 8-9 weeks old at arrival, and in the approximate weight range of 180-200 g. They will be allowed approximately one week's acclimatisation in type RCI cages (as described in Section 4.6) during which time they will be maintained on basal laboratory diet (Labsure Laboratory Animal Diet No.1) and tap water and examined daily to check their physical condition.

4.2 Environmental control

The animals will be housed inside a barriered, limited access, rodent facility.

Each animal room has its own supply of filtered air which is passed to atmosphere without re-circulation, providing approximately 15 room air changes per hour. The temperature and relative humidity in the animal room are recorded daily and records retained. A 12-hour light : 12-hour dark cycle operates throughout. A stand-by power supply is automatically brought into operation should the mains supply fail.

4.3 Water supply

Tap water will be supplied to the cages via polythene bottles and chromium-plated sipper tubes. The East Anglian Water Company monitor the quality of the water supply at approximately six-monthly intervals and copies of the relevant analyses will be retained with the raw data.

4.4 Basal diet

A commercially-available laboratory animal diet (Labsure Laboratory Animal Diet No.2 ground) will be fed ad libitum throughout the study. This is a heat treated diet supplied in a discardable outer paper sack and sealed inner sterilisable polythene bag. It contains no added antibiotic or other chemotherapeutic or prophylactic agent. The manufacturers, Labsure, K. and K. Greeff Chemicals Limited, Croydon, Surrey, England, supply a certificate of analysis with every batch and copies of the relevant certificates will be retained with the raw data.

4.5 Contaminants

There are no contaminants in the diet, water or bedding supplied that are reasonably expected to be present at levels that are known to be capable of interfering with the purpose or conduct of the study.

4.6 Caging

Rats will be housed in RC1, RM2 modified, and RB3 cages from North Kent Plastics Limited, Dartford, Kent, England. The cages consist of high density polypropylene bodies with stainless steel lids and mesh floors (if present). Cages with mesh floors will be suspended in batteries over trays covered with crepe absorbent paper; the latter will be changed on alternate week days. Autoclaved wood shavings will be provided for bedding during the littering phase. Cages will be changed at approximately two-week intervals.

At various stages of the study the maximum number of rats per cage will be:

<u>Stage</u>	<u>No. of animals</u>		<u>Cage type</u>
	<u>M</u>	<u>F</u>	
Pre-mating	5	5	RC1
Mating	1	: 1	RM2 (modified)
Males to termination) Females to Day 16-18 p.c.)	5	5	RC1
Littering (from Day 16-18 p.c. to Day 14-18 p.p.)	-	1 + litter	RB3
Lactation (Day 14-18 p.p until weaning)	-	1 + litter	RC1
Post weaning	5	5	RC1

4.7 Test substance

4.7.1 Compound identity

The identity, strength, purity and composition or other characteristics which appropriately define the batch from which the test substance for this study is drawn are determined by the Sponsor before the test substance is used. The test substance is stored at room temperature and subject to artificial illumination unless other conditions are specified by the Sponsor. Stability of the test substance is determined by the Sponsor. Methods of synthesis, fabrication or derivation of the test substance are documented by the Sponsor.

At or before initiation of the study, a 10 g reserve sample of the test substance is taken and stored in a well-closed glass container under the conditions specified for storage of the bulk supply of the test substance.

In order to demonstrate that the test substance remains satisfactory under the conditions in which it is stored at these laboratories, a 5 g sample from the container in current use is returned to the Sponsor for analysis on completion of the treatment period or at depletion of the batch, whichever occurs first.

Similar procedures are adopted for any additional batches of test substance used during the course of the study.

Results of these analyses are communicated to Life Science Research for inclusion in the final report.

4.7.2 Absorption of compound

The assessment of the absorption of the compound by the animals will be responsibility of the Sponsor.

4.8 Treatment

4.8.1 Constitution of treatment groups

On receipt, animals are allocated to cages by sex. Before commencement of treatment, each animal will be examined; individual offspring showing signs of ill-health, or at the extremes of the bodyweight range, will be rejected; remaining offspring will be distributed among the groups by a random replicate selection procedure which ensures an even distribution of animals among the groups.

Each animal will be given an identity number and receive an ear notch corresponding to the last three digits of the identity number.

Cage labels, identifying the occupants by experiment, animal number, sex and treatment group, are colour-coded to match the correspondingly colour-coded diet bins.

The four groups, consisting of an untreated control group and three graded dosage groups will be treated as follows:

<u>Group</u>	<u>Treatment</u>	<u>Dose levels</u> (mg/kg/day)	<u>Number of animals</u>		<u>Animal numbering</u>	
			M	F	M	F
1	Control	0	34	34	1001-1034	1137-1170
2	SC-19129	250	34	34	1035-1068	1171-1204
3	SC-19129	500	34	34	1069-1102	1205-1238
4	SC-19129	1000	34	34	1103-1136	1239-1272

4.8.2 Route and duration

SC-19129 (Lot No. 84K-047-101) will be administered orally, mixed with the food. Dietary concentrations will be calculated weekly for each sex to achieve a close approximation to the dose levels specified.

F₀ males will receive the experimental diets for 71 days before pairing for mating (see Section 4.9), and females for 15 days before pairing. Treatment of F₀ males will continue throughout mating, but with the diet prepared for the females. Following successful mating, the males will return to their own diet, and treatment will continue until termination at the time that the majority of females have littered successfully. Treatment of F₀ females will continue throughout mating and gestation, and will cease at the end of the second week of lactation. All females will receive untreated diet during the remainder of lactation up to termination at weaning of the offspring. F₁ animals will receive the experimental diets from the time of weaning for a minimum of 10 weeks. They will then be paired for mating and treatment continued according to the same schedule as for the F₀ animals.

*SC-19129 treated diets will be removed to prevent pups from ingesting SC-19129 directly as they start consuming food prior to weaning.

4.8.3 Test diets

4.8.3.1 Preparation

Assuming no stability problem batches of each test diet will be prepared weekly and issued in sealed polythene bags. Diets unused at the end of each week will be incinerated.

100 g aliquots of each test diet, other than those being analysed for achieved concentration in accordance with Section 4.8.3.2 will be sealed into aluminium foil laminate sachets and stored at room temperature. The aliquots will be discarded following authorisation from the Sponsor.

4.8.3.2 Quality control

On each day that quantities of test substance are weighed out for test diet preparation, the stock container will be weighed before the first and after the last removal of part of its contents. The reduction in the weight of the stock container will be documented as an independent check that the correct weight of test substance has been used.

Diet samples will be taken in respect of the following:

Homogeneity

During the first week of treatment, duplicate 1 g diet samples from nine positions in the mixer will be taken from each diet prepared, and stored deep frozen. One set of samples will be despatched to the Sponsor at a later date for determination of homogeneity and achieved concentration.

Achieved concentration

For the F_0 generation, duplicate 1 g diet samples will be taken from each diet prepared during the fourth and ninth weeks of treatment, and during the second week of both gestation and lactation. For the F_1 generation, similar samples will be taken during the first, fourth and ninth weeks of treatment, and during the second week of both gestation and lactation. All samples will be stored deep frozen, and one set will be despatched to the Sponsor at a later date for determination of achieved concentration.

4.9 Mating procedure

After the appropriate treatment period the females will be paired on a one-to-one basis with males from the same treatment group. Each morning following pairing, the trays beneath the cages will be checked for ejected copulation plugs and a vaginal smear will be prepared from each female and examined for the presence of spermatozoa. The day on which evidence of mating is found will be designated Day 0 of gestation. Once mating has occurred, the males and females will be separated and vaginal smearing discontinued.

If mating has not been detected within 7 days of pairing, the female will be removed and placed with a second male that has also failed to mate from the same treatment group. Should only one pair fail to mate no changeover will occur. Females that have not mated within 14 days will be paired with a male of proven mating ability from the same treatment group, provided that the males being replaced have been in pairing with an oestrous female on at least one occasion.

The same mating procedure will be adopted for the F_1 animals after 10 weeks of treatment (13-14 weeks of age).

F_1 males and females will be paired within treatment groups avoiding mating between siblings.

5. SERIAL OBSERVATIONS (PARENTAL)

5.1 Signs

All animals will be examined daily throughout the study, and any visible signs of reaction to treatment will be recorded, with details of type, severity, time of onset and duration.

5.2 Mortality

Any animals found dead or killed in extremis will be subjected to a thorough macroscopic examination of the visceral organs with the object of identifying the cause of death. Specimens of abnormal tissues will be retained.

5.3 Bodyweight

Males will be weighed at commencement of treatment and weekly until termination. Females will be weighed at commencement of treatment and weekly until mating is detected, on Days 0, 6, 13 and 20 post coitum and on Days 1, 4, 7, 14 and 21 post partum.

5.4 Food consumption

Food consumption will be recorded weekly for each generation throughout the study, with the exception of the mating periods and the last week of lactation.

5.5 Vaginal smears

For 10 days before the scheduled day of pairing, daily vaginal smears will be taken from all groups to establish the normality or otherwise of oestrus. This will be continued after pairing with the male until evidence of mating is observed.

6. ASSESSMENT OF REPRODUCTIVE PERFORMANCE (F₀ GENERATION)

6.1 Pre-coital interval (females only)

The time elapsing between initial pairing and detection of mating will be noted.

6.2 Litter response

Approximately twelve of the females from each treatment group will be necropsied on Day 20 of gestation for examination of their uterine contents as described below in Sections 6.2.1-6.2.3. The remaining females will be allowed to deliver and raise their young naturally to Day 21 post partum as detailed in Sections 6.3 and 6.4.

6.2.1 Teratology phase

On Day 20 of gestation, approximately twelve of the females from each group will be killed by inhaled carbon dioxide for examination of their uterine contents. Each animal will first be examined macroscopically for evidence of disease or adverse reaction to treatment. The reproductive tract, complete with ovaries, will be dissected out and the following recorded:

- a) Number of corpora lutea in each ovary;
- b) Number of implantation sites. In apparently non-pregnant animals, presence of implantation sites will be checked using the Salewski staining technique (Salewski, E., Arch. exp. Pathol. Pharmacol., 247, 367, 1964);
- c) Number of resorption sites (classified as early or late);
- d) Number and distribution of live and dead fetuses in each uterine horn;
- e) Weight and sex of individual fetuses;
- f) Individual placental weights;
- g) External abnormalities of individual fetuses.

6.2.2 Skeletal examination : the neck and thoracic and abdominal cavities of approximately half of the fetuses from each litter will be dissected and examined. Low-power magnification will be used if necessary. Following examination and evisceration, the fetuses will be placed in industrial methylated spirit (74 o.p.) before processing, which utilises a modification of the Dawson staining technique (Tesh, J.M., Ph.D. Thesis, Faculty of Veterinary Science, University of Liverpool, 1968) and subsequent skeletal examination.

6.2.3 Visceral examinations : the remaining fetuses will be placed in Bouin's fixative for subsequent free-hand sectioning following the technique of Wilson (in Teratology : Principles and Techniques, p.251, University of Chicago Press, 1965).

6.3 Serial observations (Maternal, Post-natal)

6.3.1 Duration of gestation

The time elapsing between the detection of mating and commencement of parturition will be recorded.

6.3.2 Duration of parturition

If labour difficulties are observed, an attempt will be made to record the duration of the parturition process.

6.3.3 Bodyweight

Females will be weighed on Days 1, 4, 7, 14 and 21 post partum.

6.4 Serial observations (Offspring)

6.4.1 Observations on Day 1 post partum

All litters will be observed at approximately 24 hours after birth. Each individual offspring will be toe marked.

6.4.2 Mortality and litter size

Daily records will be maintained of mortality and consequent changes in litter size. On Day 4 post partum, litter size will be reduced to eight to give, where possible, four males and four females per litter. Offspring within each sex will be selected randomly. Where litter size is eight or less, no adjustment will be made.

Offspring culled at Day 4 post partum, and any found dead, will be examined externally and internally for abnormalities. Specimens of abnormal tissues will be retained.

6.4.3 Bodyweight (F_1 offspring)

Individual bodyweights of offspring will be recorded on Days 1, 4, 7, 14 and 21 post partum. Animals continuing the study from this point will be weighed weekly after selection.

6.4.4 Sex ratio (F_1 offspring)

The offspring will be sexed on Days 1, 4 (before and after culling), 14 and 21 post partum.

6.4.5 Physical development (F_1 offspring)

The speed of physical development of the offspring will be assessed by maintaining records of the days on which the onset of and completion of the following parameters occur:

- a) Pinna unfolding
Detachment of the edge of the pinna;
- b) Hair growth
Macroscopic observation of generalised growth of body hair;
- c) Tooth eruption
Eruption of upper incisors through the gum;
- d) Eye opening
Separation of the upper and lower eyelids;

- e) Testes descent
Testes palpable in the scrotum;
- f) Vaginal opening
Separation of the vaginal edges.

6.4.6 Auditory and visual function (F₁ offspring)

On Day 21 post partum, auditory and visual responses of the progeny will be examined in a qualitative manner by means of the following techniques:

- a) Auditory function
Auditory function will be assessed using the startle response to a sudden sharp noise.
- b) Visual function
Visual function will be assessed by:
 - i) examination of the pupil closure response to a bright point source of light.
 - ii) assessment of the visual placing response.

6.4.7 Behaviour studies

- a) Activity
After weaning at Day 21 post partum, each litter will be separated into males and females and placed in clear plastic cages; following a period of acclimatisation the activity of each litter will be measured for 12 hours overnight. For this purpose a system incorporating a pair of infra-red light sources and detectors will be used to monitor within-cage activity, the frequency with which the light beams are interrupted producing an activity score (Tesh, J.M., in Methods in Pre-natal Toxicology, ed. Neubert et al, Thieme Verlag, Stuttgart, 1977).
- b) Water-filled maze
A water-filled Y-maze will be used to evaluate learning ability of the offspring (Tesh J.M., ibid). The times taken by each animal to swim through the maze in six successive trials will be measured. A maximum of 60 seconds will be allowed for each trial; any animal exceeding this time will be removed and will be considered to have failed the test. Maintained improvement in swimming time will be taken as an indication of learning.

The water-filled maze test may be repeated if equivocal results are obtained.

7. ASSESSMENT OF DEVELOPMENT AND REPRODUCTIVE PERFORMANCE (F₁ GENERATION)

7.1 Selection

Following weaning a minimum of 40 male and 40 female offspring will be selected from each group using random number tables, after grossly atypical offspring have been excluded. These will constitute the F₁ generation.

Where possible, two male and two females will be selected from each litter. Each animal will be given an identity number and receive an ear notch corresponding to the last three digits of the identity number.

Animal identity numbers will be as follows:

<u>Group</u>	<u>M</u>	<u>F</u>
1	2001-2040	2161-2200
2	2041-2080	2201-2240
3	2081-2120	2241-2280
4	2121-2160	2281-2320

7.2 Serial observations

Serial observations and mating procedures will be as described for the first generation (Sections 4.9-6.4.4), except that 20 females per group will be used in the Teratology Phase and the remaining 20 females per group will be allowed to deliver their young.

8. TERMINAL STUDIES

8.1 Parental animals (F₀ and F₁)

Males will be killed when the majority of females have littered successfully.

Females that litter and rear offspring to weaning will be killed on Day 21 post partum. Females that litter but whose litters die before weaning will be killed on the day that their last offspring dies.

Females allocated to litter that mate but do not give birth will be killed on Day 25 post coitum. Females that fail to mate will be killed 25 days after the last day of pairing.

All parental animals will be subjected to necropsy as described in Section 8.4.

8.2 Offspring (unselected F₁ and F₂)

F₁ offspring not selected for continuation of the study will be killed on completion of behavioural studies and examined externally and internally for macroscopic abnormalities. F₂ offspring will be killed after weaning and examined externally and internally for macroscopic abnormalities. Specimens of abnormal tissues will be retained.

8.3 Euthanasia

All animals, including those killed in extremis, will be killed by carbon dioxide inhalation.

8.4 Macroscopic pathology

All parental animals killed and any found dead will be subjected to a detailed necropsy.

The necropsy procedure will include a review of the history of each animal and a detailed examination of the cranial, thoracic, abdominal and pelvic cavities and their viscera. The external and cut surfaces of the organs and tissues will be examined either before or after weighing, as appropriate. The number of uterine implantation sites will be recorded in all females. Abnormalities, interactions and changes will be noted, the requisite organs weighed and the required tissue samples preserved in fixative (see below).

Before disposal of the carcass, the retained tissues are checked against the Protocol and the Senior Prosector reviews the necropsy report.

8.5 Organ weights

The organs specified in column A of the Pathology Procedures Table appended will be dissected free of adjacent fat and other contiguous tissue and the weights recorded.

8.6 Tissues preserved in fixative

Samples of the tissues specified in column B of the Pathology Procedures Table will be preserved in buffered 4% formal saline. In those cases where a lesion is not clearly delineated, contiguous tissue is fixed with the grossly affected region and sectioned as appropriate.

PATHOLOGY PROCEDURES

Species : CD rat

Process and examine microscopically* (P and E): Only required if macroscopic or reproductive abnormalities are observed, and initially limited to rats from Groups 1 and 4. The examination is extended to all rats from Groups 2 and 3 in respect of any tissues affected at the high dose (additional cost).

List	A		B	C *
Organ/Tissue	Weigh		Fix	P and E
Abnormalities	T if possible		T	P *
Epididymides	L	M	M	M
	R	M	M	M
Mammary glands	Cranial		O	O *
	Caudal		O	
Ovaries	L	F	F	F
	R	F	F	F
Pituitary			S	S *
Prostate	M		M	M
Seminal vesicles	L	M	M	M
	R	M	M	M
Testes	L	M	M	M
	R	M	M	M
Uterus	F		F	F
Vagina			F	F
Target organs (specify)	P * (if possible)		P *	P *

Key

F All females killed for
teratological examination
L Left
M All parental males
O Parental females with total
litter loss
P All parental animals

R Right
S Parental animals
with suspect fertility
T All animals (including
offspring)
* Additional cost

8.7 Histology*

The tissue samples specified in column C of the Pathology Procedures Table, taken from all animals, will be dehydrated and embedded in paraffin wax.

8.8 Microscopy*

The paraffin wax blocks of the organs retained in Section 8.7 will be sectioned at 5 μ thickness and stained with haematoxylin and eosin.

Microscopic examination will be performed on the tissue sections specified in column C of the Pathology Procedures Table as follows:-

- i) From all rats of Groups 1 and 4.
- ii) From all rats killed in extremis or dying during the study (additional cost for rats of Groups 2 and 3).
- iii) From all rats of Groups 2 and 3 in respect of tissues considered to exhibit a reaction to treatment at the high dosage (additional cost).

9. PHOTOGRAPHY*

Where possible, colour photographs will be prepared showing a representative sample of treatment-related macroscopic and microscopic abnormalities.

10. TREATMENT OF DATA

- 10.1 Data will be expressed as group mean values and standard deviations unless other wise indicated.

Standard deviations will be calculated as:

$$\sqrt{\frac{\sum (x - \bar{x})^2}{n-1}}$$

*Optional extra at additional charge.

- 10.2 Food conversion efficiency will be calculated weekly during the periods that food consumption is measured from the formula:

$$\text{F.C.E.} = \frac{\text{Group mean bodyweight gain in week}}{\text{Group mean food consumption (g/rat/week)}} \times 100$$

- 10.3 Chemical intake will be calculated weekly during the periods that food consumption is measured.

10.4 Mating performance and fertility

For each group and sex the following will be calculated:

$$\text{Percentage mating} = \frac{\text{Animals mated}}{\text{Animals paired}} \times 100$$

$$\text{Conception rate} = \frac{\text{Animals pregnant or siring a pregnancy}}{\text{Animals mated}} \times 100$$

$$\text{Fertility index} = \frac{\text{Animals pregnant or siring a pregnancy}}{\text{Animals paired}} \times 100$$

10.5 Teratology data

- 10.5.1 Pre-natal losses will be considered separately for the pre- and post-implantation phases.

a) Pre-implantation loss

Pre-implantation loss includes losses due to non-fertilisation of ova and very early post-implantation deaths (i.e. those occurring up to Days 7-8 of gestation), in addition to true pre-implantation loss. It will be calculated for each litter from the formula:

$$\frac{\text{No. corpora lutea} - \text{No. implantations}}{\text{No. corpora lutea}} \times 100$$

Group values will be calculated as a mean of the individual litter values.

b) Post-implantation loss

Post-implantation loss covers only the period between Days 7 and 20 of gestation; it does not include the first 2-3 days post-implantation as any deaths that occur in this phase leave no remains that may be detected at Day 20. It will be calculated for each litter from the formula:

$$\frac{\text{No. implantations} - \text{No. viable foetuses}}{\text{No. implantations}} \times 100$$

Group values will be calculated as a mean of the individual litter values.

c) Resorptions

Resorptions (classified as early, late and total) will be calculated as group means and the standard deviations will be calculated as:

$$\sqrt{\bar{x}}$$

since resorptions approximate to a Poisson distribution.

- 10.5.2 Group mean foetal and placental weights and standard deviations will be calculated as:

$$\frac{\text{Total of individual litter mean foetal/placental weights}}{\text{Number of litters}}$$

- 10.5.3 Observations on foetuses at examination post mortem and at skeletal evaluations and free-hand serial sections will be calculated on a group basis for each abnormality observed as:

$$\frac{\text{No. foetuses with a particular abnormality}}{\text{Total No. foetuses examined in group}} \times 100$$

In addition, the total number of litters within each group containing foetuses with a particular observation will be calculated and expressed as a percentage of the total number of litters in the group.

10.6 Post-natal data (F_0 and F_1 generations)

- 10.6.1 Gestation length will be presented to the nearest 1/2 day with Day 1 = day of mating. If parturition starts overnight gestation length will be the Day post coitum when the litter was first observed minus half a day.

- 10.6.2 Post-implantation survival index will be calculated for each litter as:

$$\frac{\text{No. offspring born}}{\text{No. uterine implantation sites}} \times 100$$

Group values will be calculated as a mean of the individual litter values.

- 10.6.3 Live birth index will be calculated for each litter as:

$$\frac{\text{No. live offspring at Day 1 post partum}}{\text{No. offspring born}} \times 100$$

Group values will be calculated as a mean of the individual litter values.

- 10.6.4 Viability index will be calculated for each litter as:

$$\frac{\text{No. live offspring on day of examination}}{\text{No. live offspring at Day 1 post partum}} \times 100$$

Group values will be calculated as a mean of the individual litter values.

- 10.6.5 Offspring development timing

A continuity correction of half a day will be subtracted from the age (day post partum) of litters born overnight.

- 10.6.6 Group mean activity score will be calculated as:

$$\frac{\text{Total of individual litter means}}{\text{Number of litters}}$$

- 10.6.7 Group mean swimming time will be calculated as:

$$\frac{\text{Summed individual litter mean swimming times}}{\text{Total number of litters}}$$

10.7 Statistical evaluation

The significance of suggestive inter-group difference will be tested using appropriate statistical tests, each of which will be specified where significance is found. The following tests will be used:

One-way analysis of variance
and/or t-test

Bodyweights
Bodyweight change
Food consumption
Foetal weight
Placental weight
Water-maze swimming times
Male reproductive organ weights

Mann-Whitney U-test

Corpora lutea count
Implantation count
Resorption count
Pre-coital interval
Gestation length
Physical activity scores
Pre-implantation loss
Post-implantation loss
Post-implantation survival index
Litter size
Live birth index
Viability index
Sex ratio

Chi-squared test, Fishers
Exact Probability test or
Mann-Whitney U-test

Fertility index
Gestation index
Mating performance
Conception rate

11. REPORTING

The information and data required in Section 163.80-4 of the EPA guidelines will be included in the final report.

12. RECORDS

All raw data, original records, slides, blocks and any wet tissues will be retained until management decides they should be discarded.

Documents and samples to be stored

1. Compound : reserve samples, analytical certificates and records of use.
2. Environment : records of temperature and humidity of animal room.
3. Animals : records of identification numbers.
4. Cages : cage plan and position of animals and groups on rack.
5. Physical examination records.
6. Bodyweight : weight records of each animal.
7. Food consumption.
8. Mating evidence.

9. Parturition and litter data.
10. Records of selection of F₁ generation.
11. Histopathology findings.*
12. Terminal findings.

All records will be inspected by the Responsible Scientist and lodged with central records at Life Science Research.

*Optional extra at additional charge.



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LSR Schedule No. SEA/043/19129

LSR Enquiry No. ZZZ/0150A

TWO GENERATION REPRODUCTION STUDY
OF SC-19129 IN RATS, S.A. No. 2473

FIRST AMENDMENT TO PROTOCOL

Sponsor : G.D. Searle and Company
Study Director : C.R. Willoughby
Purpose of Amendment : To update and correct protocol
Date of Amendment : 12 November 1984
Source of Amendment : Sponsor and Staff Biologist

AMENDMENTS

The LSR Schedule Number is SEA/043/19129

Section 4.1 Animals

The animal diet to be used during acclimatisation is amended to Labsure Laboratory Animal Diet No. 2., ground.

Section 4.6 Caging

Amend to read:

	<u>No. of animals</u>		<u>Cage type</u>
	M	F	
Pre-mating	5	5	RC1
Mating	1	1	RM2 (modified)
Males to termination	5	-	RC1
Females <u>post coitum</u>	-	1 (+ litter)	RB3
and to <u>Day 14-18 post partum</u>			
Lactation (Day 14-18 <u>post partum</u>	-	1 (+ litter)	RC1
until weaning)			
Post - weaning	1 litter	1 litter	RC1

Section 4.7.1 Compound identity

Amend second sentence of first paragraph to read:

The test substance is stored at room temperature and protected from light.

Insert at end of third paragraph:

All unused material will be returned to the Sponsor.

Delete fifth paragraph.

Section 4.8.1 Constitution of treatment groups

Amend first paragraph to read:

On receipt, animals are allocated to cages by sex. Before commencement of treatment, each animal will be examined; individuals showing signs of ill health, or at the extremes of the bodyweight range, will be rejected; remaining rats will be distributed among the groups by a random replicate selection procedure which ensures an even distribution of animals among the groups.

Amend Group 4 dose level to 750 mg/kg/day.

Section 4.8.3.1 Preparation

Insert:

SC-19129 will be incorporated into the ground animal diet at the required concentrations by initial preparation of a milled premix followed by dilution with further quantities of diet and mixing in an electrically grounded mixer.

Section 4.8.3.2 Homogeneity and Achieved concentration

Delete : 1g
Insert : 10g

Sections 6.4.3 and 6.4.4 Bodyweight (F₁ offspring) and
Sex ratio (F₁ offspring)

Delete : "(F₁ offspring)" from these headings.

Section 6.4.5 Physical development (F₁ offspring)

Amend first paragraph to read:

The speed of physical development of the offspring will be assessed on an individual offspring basis but reported on a total litter basis by maintaining records of the days on which the onset of and completion of the following parameters occur:
Continues unchanged.

Section 6.4.7 Behaviour studies

Amend heading to read : Behaviour studies (F₁ offspring)

Section 8.2 Offspring (Unselected F₁ and F₂)

Amend first sentence to read:

F₁ offspring not selected for continuation of the study will be killed following behavioural studies and completion of vaginal opening and examined externally and internally for macroscopic abnormalities.

Section 11. REPORTING

Amend to read:

The information and data required in Section 58.185 of the Good Laboratory Practice Regulations published by the U.S. Food and Drug Administration in the Federal Register (Vol. 43. No. 247, 22 December 1978) are included in the final report.

FOR LIFE SCIENCE RESEARCH LIMITED

Issued by : *C. Willoughby* Date: *3 Dec. 1984*

Released by : *Bill Anulty* Date: *3/12/84*

FOR G.D. SEARLE AND COMPANY

Accepted by *John G. Munn* Date: *Dec. 12, 1984*



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LSR Schedule No.

SEA/043 19129

TWO GENERATION REPRODUCTION STUDY
OF SC-19129 IN RATS, S.A. No. 2473

SECOND AMENDMENT TO PROTOCOL

<u>Sponsor</u>	: G D Searle and Company
<u>Study Director</u>	: C R Willoughby B.Sc., M.P.S.
<u>Purpose of amendment</u>	: To extend the treatment period for females during lactation
<u>Date of amendment</u>	: 5 February 1985
<u>Source of amendment</u>	: Sponsor in consultation with Life Science Research

Amendment

Section 4.8.2 Route and duration

Paragraph 2 : fourth and fifth sentences deleted and
replaced by:

"Treatment of F₀ females will continue throughout mating,
gestation and lactation up to termination after
weaning of the offspring."

For LIFE SCIENCE RESEARCH

Issued by : *C. W. Houghton* Date: *S. Feb 85*
Released by : *A. L. Smith* Date: *5/2/85*

For G D SEARLE AND COMPANY

Accepted by *James E. Seaver* Date: *Feb. 5, 1985*



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LSR Schedule No. SEA/043/19129

LSR Enquiry No. ZZZ/0150A

TWO GENERATION REPRODUCTION STUDY OF

SC-19129 IN RATS, S.A. No. 2473

THIRD AMENDMENT TO PROTOCOL

Sponsor : G D Searle and Company
Study Director : C R Willoughby
Purpose of Amendment : To update and correct protocol
Effective Date of Amendment : 18 February 1985
Source of Amendment : Sponsor and Staff Biologist

Amendments

Insert new Section:

4.7.3 Stability

The assessment of stability of the compound incorporated into the diet will be the responsibility of the Sponsor.

4.8.2 Route and duration

Delete footnote from the bottom of the page.

4.8.3.2 Achieved concentration

The number of samples to be taken is increased to 6 x 10g samples from the fourth week of the F₁ generation onwards.

Last sentence amended to:

All samples will be stored deep frozen and three samples per group will be despatched to the Sponsor at a later date for determination of achieved concentration.

Insert new section:

Stability

One 10g sample will be taken from the diet tins of the first two cages of males in each group after 7 days in the animal room (Week 14 F₀ generation) and the first two cages of males and females after 14 days in the animal room (Week 9 F₁ generation). The samples will be stored deep frozen before despatch to the Sponsor for determination of stability of the test compound in the diet.

For LIFE SCIENCE RESEARCH LIMITED

Issued by : *C. Willoughby* Date: *10.4.85*

Released by : *A. H. Smith* Date: *10/4/85*

For G D SEARLE AND COMPANY

Accepted by : *David G. Searle* Date: *April 10, 1985*



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LSR Schedule No. SEA/043/19129

TWO GENERATION REPRODUCTION STUDY
OF SC-19129 IN RATS S.A. NO. 2473

FOURTH AMENDMENT TO PROTOCOL

Sponsor	:	G D Searle and Company
Study Director	:	C R Willoughby
Purpose of amendment	:	To amend timings of stability assay sampling
Date of amendment	:	23 August 1985
Source of amendment	:	Study Director

AMENDMENT

Section 4.8.3.2 Quality control

Third amendment to protocol : Stability

The first sentence is replaced by :

One 10g sample will be taken from the diet tins of the first two cages of males in each group after 7 days in the animal room (Week 14 Fo generation)

One 10g sample will be taken from the diet tins of the first two cages of males and the first two females in each group after 14 days in the animal room
(Week 28 of study = Week 12 F₁ generation / 2nd week of gestation).

For LIFE SCIENCE RESEARCH LIMITED

Issued by Ch. Willoughby Date 29 August 85

Released by Attn: Analty Date 29/8/85

For G D SEARLE & COMPANY

Accepted by John G. Hancock Date Sept 10, 1985



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LSR Enquiry No. ZZZ/0150 A

TWO GENERATION REPRODUCTION STUDY OF
SC-19129 IN RATS, S.A.No. 2473

FIFTH AMENDMENT TO PROTOCOL

Sponsor	: G D Searle and Company
Study Director	: C R Willoughby
Purpose of amendment	: To add details of certain data processing methods.
Date of amendment	: 22 November 1985
Source of amendment	: Sponsor request of 20 November 1985

AMENDMENTS

Section 10.6 Post-natal data (Fo and F1 generations)

New sub-section

10.6.2 Gestation index will be calculated for all females allowed to give birth as:

$$\text{Gestation index} = \frac{\text{Number of live litters born} \times 100}{\text{Number pregnant}}$$

Subsections re-numbered as :

10.6.3 Post implantation survival index

10.6.4 Live birth index

10.6.5 Viability index

New subsection

- 10.6.6 Lactation index will be calculated for each group on a litter basis as:

$$\frac{\text{Number of live offspring on Day of examination} \times 100}{\text{Number of live offspring after culling on Day 4 post partum}}$$

Group mean values will be calculated as a mean of the individual litter values.

New subsection

- 10.6.7 Group mean offspring weight will be calculated

as:

$$\frac{\text{Total of individual litter mean offspring weights}}{\text{Number of litters on day of examination}}$$

Subsections re-numbered as:-

- 10.6.8 Offspring development timing

- 10.6.9 Group mean activity scores

- 10.6.10 Group mean swimming time

Section 10.7 Statistical evaluation

- i) Reference to "Male reproductive organ weights" amended to "Reproductive organ weights"
- ii) Oestrous cycle distribution added to the list of data to be analysed by the Chi squared test, Fishers Exact test or Mann-Whitney U-test.

For LIFE SCIENCE RESEARCH LIMITED

Issued by : CL Willoughby Date : 28/11/85

Released by : Bill Anubly Date : 28/11/85

For G.D. SEARLE AND COMPANY

Accepted by : [Signature] Date : Dec 3, 1985

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R&D PRODUCT DEVELOPMENT FUNCTION
REPORT REVIEW AND RELEASE

Page 1 of 32

DEPARTMENT: Product Development Analytical

DOCUMENT NUMBER: F-358-034-13

TITLE OF REPORT: SC-19129

TYPE OF REPORT: Analytical Summary in Support of Product Safety
Assessment Study Number 2473

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NORTH AMERICAN PRECLINICAL RESEARCH AND DEVELOPMENT
SEARLE PHARMACEUTICALS AND CONSUMER PRODUCTS
SKOKIE, ILLINOIS

Subject: SC-19129

Summary Number: F-358-034-13

Applicable to SA Study Number: 2473

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Subject: SC-19129

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I. Test Article Characterization and Stability

Lot 84K-047-101 and 84K-052-101 of SC-19129 were analyzed using the release methods of testing, released against the current specifications (NS-S84-015-A), and given a re-evaluation period of one year prior to use in this study. The results of analysis are presented in Tables 1 and 2.

Table 1

SC-19129, Lot 84K-047-101

	Pre-Study	Post-Study
Report of Analysis	84N1058	85N0682
Completion Date	10/16/84	08/20/85
Identity (HPLC)	Conforms to standard	Conforms to standard
Assay (HPLC) (on Dried Basis)	100.0% n = 3 s = 0.2	99.7% n = 3 s = 0.2
Water	9.8%	9.3%

Table 2

SC-19129, Lot 84K-052-101

	Pre-Study	Post-Study
Report of Analysis	84N1138	85N0681
Completion Date	12/18/84	08/20/85
Identity (HPLC)	Conforms to standard	Conforms to standard
Assay (HPLC) (on Dried Basis)	98.8% n = 3 s = 0.2	100.1% n = 3 s = 0.3
Water	9.7%	9.1%

These results and all other results, coupled with the use of lots 84K-047-101 and 84K-052-101 within their re-evaluation periods indicate that these lots of SC-19129 were suitable for use in this study.

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II. On-Shelf Stability of Test Article in Carrier

The on-shelf stability of SC-19129 in diet admixture (Labsure Animal Diet Number 2) at ambient conditions was determined at 1,000 and 50,000 parts per million (ppm) using a stability indicating HPLC method (M84-045-B0185). Samples were prepared on selected days over a 16 day period. In order to analyze all of the samples at one time, the samples were prepared in reverse order. For example, the Day 16 stability samples were prepared sixteen days before they were analyzed. Two 1 gram samples of each concentration were prepared on Day 1, 2, 4, 7, 11, 15, and 16 time points, while for the Day 0 time point, four 1 gram samples of each concentration were prepared.

For the 1,000 ppm dosing concentration, the linear regression analysis (MINITAB, Reference 1) for the percent recovery of SC-19129 versus time gave a t-value for the slope that was less than the table value (Reference 2), indicating no significant downward trend. The results indicate that at a concentration of 1,000 ppm, SC-19129 in diet admixture is considered to be stable for at least 16 days when stored at ambient conditions.

For the 50,000 ppm dosing concentration, the linear regression analysis (MINITAB, Reference 1) for the percent recovery of SC-19129 versus time gave a t-value for the slope that was less than the table value (Reference 2), indicating no significant downward trend. The results indicate that at a concentration of 50,000 ppm, SC-19129 in diet admixture is considered to be stable for at least 16 days when stored at ambient conditions.

Since SC-19129 in diet admixture at 1,000 ppm and 50,000 ppm is stable when stored at ambient conditions, all dosing concentrations between 1,000 ppm and 50,000 ppm are considered to be stable for at least 16 days when stored at ambient conditions.

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Table 3

On-Shelf Stability Study
SC-19129 in Diet Admixture

Report of Analysis		85-0252	85-0253
Dosing Concentration		1,000 ppm	50,000 ppm
Time (Days)	Sample Number	% SC-19129 Recovered	% SC-19129 Recovered
0	1	99.9	99.6
	2	99.8	100.5
	3	99.8	101.2
	4	99.6	102.0
1	1	97.6	101.2
	2	100.0	101.0
2	1	100.4	101.5
	2	100.3	101.0
4	1	100.3	100.8
	2	100.2	101.3
7	1	99.4	100.0
	2	98.0	102.0
11	1	100.2	101.2
	2	99.2	100.8
15	1	99.0	99.1
	2	99.2	98.9
16	1	101.7	102.3
	2	99.5	102.7
Intercept		99.6	101.0
Slope		0.008	- 0.007
t-Ratio		0.21	- 0.18
t(0.95, 16)		1.746	1.746

Notebook Reference: K. Klimovitz, PDAD0061, pp. 276-294

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III. Homogeneity of Mixing for Test Article in Carrier

The homogeneity of mixing of SC-19129 in diet admixture (Labsure Animal Diet Number 2) was determined at the low male dosing concentration (2,076 ppm) and the high male dosing concentration (6,237 ppm) during Study Week 1. Nine 10 gram samples for each dosing concentration were removed from the appropriate container. For each 10 gram sample, one 1 gram subsample was submitted for analysis. The calculated tolerance interval for this determination was 29.3% for the low male dosing concentration and 44.3% for the high male dosing concentration. Due to the high variance, this analysis was repeated (see Endnote, page 29). For the repeat analysis, three 1 gram subsamples were analyzed for each of the original 10 gram samples. The analysis was conducted using a stability indicating HPLC method (M84-045-B0185). The results of the analyses are presented in Tables 4 and 5.

The results for the 2,079 ppm dosing concentration were shown to be normally distributed ($\alpha = 0.05$, $n = 9$), having a normality correlation coefficient of $r = 0.951$ as compared to the table value of $r = 0.912$ (Reference 3). The calculated tolerance interval (Reference 2, Table A-6) indicates that with 95% confidence at least 95% of future samples should be between $\pm 5.5\%$ of the average dosing concentration. At a dosing concentration of 2,079 ppm, SC-19129 is considered to be homogeneous in the diet admixture.

The results for the 6,237 ppm dosing concentration were shown to be normally distributed ($\alpha = 0.05$, $n = 9$), having a normality correlation coefficient of $r = 0.955$ as compared to the table value of $r = 0.912$ (Reference 3). The calculated tolerance interval (Reference 2, Table A-6) indicates that with 95% confidence at least 95% of future samples should be between $\pm 9.2\%$ of the average dosing concentration. At a dosing concentration of 6,237 ppm, SC-19129 is considered to be homogeneous in the diet admixture.

Since SC-19129 in diet admixture at the low male dosing concentration (2,079 ppm) and the high male dosing concentration (6,237 ppm) is homogeneous, all dosing concentrations used in this study are considered to be homogeneous.

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Table 4

Homogeneity Study
SC-19129 in Diet Admixture, ppm

Study Week 1⁽¹⁾

Report of Analysis

85-0692

Dose Group

Low Male

Designated
Dosing
Concentration

2,079

Sample Number	Subsample Number	Concentration (ppm)	Mean (ppm)
1	1	2,107	2,062
	2	2,073	
	3	2,005	
2	1	2,018	1,990
	2	1,921	
	3	2,031	
3	1	1,925	1,976
	2	2,022	
	3	1,980	
4	1	2,064	1,993
	2	2,056	
	3	1,859	
5	1	1,997	2,031
	2	2,159	
	3	1,937	
6	1	2,004	2,012
	2	2,008	
	3	2,024	
7	1	1,969	1,988
	2	1,962	
	3	2,034	
8	1	1,907	1,962
	2	1,955	
	3	2,025	
9	1	2,078	1,981
	2	1,855	
	3	1,980	

Mean

1,999

Standard Deviation

31

Correlation Coefficient

0.951

Tolerance Interval

± 109 (5.5%)

(1) See Endnote

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Table 5

Homogeneity Study
SC-19129 in Diet Admixture, ppm
Study Week 1⁽¹⁾Report of Analysis 85-0618
Dose Group High Male
Designated Dosage Concentration 6,237

Sample Number	Subsample Number	Concentration (ppm)	Mean (ppm)
1	1	6,340	6,204
	2	6,029	
	3	6,244	
2	1	5,820	5,748
	2	5,567	
	3	5,857	
3	1	5,680	5,993
	2	6,064	
	3	6,235	
4	1	5,435	5,717
	2	5,880	
	3	5,835	
5	1	6,446	6,122
	2	6,085	
	3	5,834	
6	1	5,881	5,972
	2	5,904	
	3	6,131	
7	1	5,776	5,977
	2	6,106	
	3	6,050	
8	1	5,878	5,949
	2	5,992	
	3	5,978	
9	1	5,949	5,960
	2	5,852	
	3	6,079	
Mean			5,960
Standard Deviation			155
Correlation Coefficient			0.955
Tolerance Interval			± 547 (9.2%)

(1) See Endnote

Notebook Reference: K. Klimovitz, PDAD0096 pp. 62-86

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IV. In-Cage Characterization of Test Article "in Carrier

The in-cage stability and homogeneity of SC-19129 in diet admixture (Labsure Animal Diet Number 2) was determined at the low (2,934 ppm), medium (5,908 ppm), and high (8,749 ppm) female dosing concentrations, as well as the low (4,428 ppm), medium (8,742 ppm), and high (13,124 ppm) male dosing concentrations during Study Week 28. Three samples were selected from the storage container on Day 0. Two samples were selected from the rat feeders on Day 14. These feeders were stored in the cage with the animals for one week, then removed from the cage and stored for an additional week (Day 14). All samples were approximately 10 grams each, and were analyzed using a stability indicating HPLC method (M85-022-A). See Endnote, page 29. The results of the analyses are presented in Tables 6 and 7.

For the female dosing concentrations of 2,934, 5,908, and 8,749 ppm, all the Day 14 results are within a tolerance interval of $\pm 15\%$ of the mean dosing concentration for Day 0, indicating the SC-19129 did not significantly change over the 14 day period. The female dosing concentrations are considered to be stable and homogeneous in the diet admixture, in-cage, for at least 14 days.

For the male dosing concentrations of 4,428, 8,742, and 13,214 ppm, all the Day 14 results except for the second sample of the 8,742 ppm dosing concentration are within a tolerance interval of $\pm 15\%$ of the mean dosing concentration for Day 0, indicating the SC-19129 did not significantly change over the 14 day period. The male dosing concentrations are considered to be stable and homogeneous in the diet admixture, in-cage, for at least 14 days.

Since SC-19129 in diet admixture at the low, medium, and high female dosing concentrations, as well as the low, medium, and high male dosing concentrations are stable and homogeneous in-cage, for at least 14 days, all dosing concentrations used in this study are considered stable and homogeneous in cage for at least 14 days.

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Table 6

In-Cage Stability and Homogeneity Study
SC-19129 in Diet Admixture, ppm
Study Week 28 (1)

Dose Group		Low Female	Medium Female	High Female
Designated Dosing Concentration		2,934	5,908	8,749
Report of Analysis		85-1478	85-1480	85-1482
Time (Days)	Sample Number			
0	1	2,786	5,656	8,670
	2	2,770	5,589	8,433
	3	2,718	5,594	8,639
Report of Analysis		85-1486	85-1488	85-1490
14	1	2,533	5,386	8,192
	2	2,743	5,511	7,817
Tolerance Interval of + of the Mean Dosing Concentra- tion of the Day 0 Samples		2,344 to 3,172	4,771 to 6,455	7,294 to 9,868

(1) See Endnote

Notebook Reference: K. Klimovitz PDAD0137 pp. 11-49

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Table 7

In-Cage Stability and Homogeneity Study

SC-19129 in Diet Admixture, ppm

Study Week 28 (1)

Dose Group		Low Male	Medium Male	High Male
Designated Dosing Concentration		4,428	8,742	13,214
Report of Analysis		85-1479	85-1481	85-1483
Time (Days)	Sample Number			
0	1	4,209	8,299	12,780
	2	4,249	8,600	12,834
	3	4,223	8,588	12,789
Report of Analysis		85-1487	85-1489	85-1491
14	1	3,594	7,574	11,929
	2	3,710	6,640	11,564
Tolerance Interval of + of the Mean Dosing Concentra- tion of the Day 0 Samples		3,593 to 4,861	7,222 to 9,770	10,881 to 14,721

(1) See Endnote

Notebook Reference: K. Klimovitz PDAD0137 pp. 11-49

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V. Concentration of Test Article in Carrier

The concentration of SC-19129 in diet admixture (Labsure Animal Diet Number 2) was determined for Study Weeks 1, 4, 9, 12, 15, 17, 20, 25, 28, and 31. The samples that were shipped from the contract lab contained 10 grams of diet admixture (see Endnote, page 29). For Study Weeks 1, 4, and 9, the concentration of SC-19129 in diet admixture was determined using HPLC method (M84-045-B0185). The sample size requirement for this method is 1 gram. Therefore, each 10 gram sample had to be subsampled to obtain a 1 gram sample for analysis. For Study Week 1, three 1 gram subsamples were removed from each ten gram sample and analyzed. For Study Weeks 4 and 9, ten 1 gram subsamples were removed from each 10 gram sample and analyzed. For Study Weeks 12, 15, 17, 20, 25, 28 and 31, the concentration of SC-19129 was determined using HPLC method (M85-022-A). The sample size requirement for this method is 10 grams, therefore, subsampling was not required prior to analysis.

For Study Week 1, nine 10 gram samples for each dosing concentration were submitted by the contract lab for analysis. For the low male dosing concentration and the high male dosing concentration, all nine samples were analyzed. For the dosing control concentration and the medium male dosing concentration, three samples were randomly selected for analysis. For Study Weeks 4, 9, 12, 15, and 17, one 10 gram sample was submitted by the contract lab for analysis. For Study Weeks 20, 25, 28, and 31, three 10 gram samples were submitted by the contract lab for analysis. The dosing control samples were prepared by mixing the diet chow in a mixer with no test article. The results of analyses are presented in Tables 8 through 17.

The mean percent values for each Study Week are summarized for each dose group in Tables 18 through 23. For each dosing concentration, all the mean percent recovery values fall within $\pm 13\%$ of the designated dosing concentration (100%).

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Table 8

Diet Admixture Concentrations

Study Week 1 (1)

SC-19129, ppm

Report of Analysis	85-0497	85-0692	85-1002	85-0618
Dose Group	Dosing Control	Low Male	Medium Male	High Male
Designated Dosing Concentration	0.00	2,079	4,158	6,237
Sample Number				
1	< 50	2,062	3,922	6,204
2	< 50	1,990	3,863	5,748
3	< 50	1,976	3,784	5,993
4		1,993		5,717
5		2,031		6,122
6		2,012		5,972
7		1,988		5,977
8		1,962		5,949
9		1,981		5,960
\bar{X}	NA	1,999	3,856	5,960
s	NA	31	69	155

(1) Reported values are the average from the results of three 1 gram subsamples

NA = Not applicable

Notebook Reference: K. Klimovitz, PDAD0096 pp. 62-86, 179-192

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Table 9

Diet Admixture Concentrations

Study Week 4 (1)

SC-19129, ppm

Report of Analysis	85-0377	85-0378	85-0379
Dose Group	Low Male	Medium Male	High Male
Designated Dosing Concentration	3,052	6,228	9,263
Sample Number			
1	2,893	5,859	8,508

(1) Reported values are the average from the results of ten 1 gram subsamples

Notebook Reference: K. Klimovitz, PDAD0096, pp. 25-45

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Table 10

Diet Admixture Concentrations

Study Week 9 (1)

SC-19129, ppm

Report of Analysis	85-0582 85-1003	85-0584 85-0879	85-0586 85-1006	85-0588 85-1008
Dose Group	Control Female	Low Female	Medium Female	High Female
Designated Dosing Concentration	0.00	2,853	5,706	8,557
Sample Number				
1	< 50	2,709	5,286	7,891

Report of Analysis	85-0583 85-1004	85-0585 85-1005	85-0587 85-1007	85-0589 85-0878
Dose Group	Control Male	Low Male	Medium Male	High Male
Designated Dosing Concentration	0.00	4,466	8,705	13,112
Sample Number				
1	< 50	4,220	7,810	11,480

(1) Reported values are the average from the results of ten 1 gram subsamples

Notebook Reference: K. Klimovitz, PDAD0096, pp. 112-192

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Table 11
Diet Admixture Concentrations
Study Week 12 (1)
SC-19129, ppm

Report of Analysis	85-1357	85-1359	85-1361	85-1363
Dose Group	Control Female	Low Female	Medium Female	High Female
Designated Dosing Concentration	0.00	2,850	5,700	8,550
Sample Number				
1	< 50	2,811	5,498	8,364

Report of Analysis	85-1358	85-1360	85-1362	85-1364
Dose Group	Control Male	Low Male	Medium Male	High Male
Designated Dosing Concentration	0.00	4,777	9,511	14,332
Sample Number				
1	< 50	4,676	9,587	14,034

(1) Reported values are from one 10 gram sample

Notebook Reference: K. Klimovitz, PDAD0096, pp. 222-262

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Table 12

Diet Admixture Concentrations

Study Week 15 (1)

SC-19129, ppm

Report of Analysis	85-1369	85-1371	85-1373	85-1375
Dose Group	Control Female	Low Female	Medium Female	High Female
Designated Dosing Concentration	0.00	1,520	3,040	4,562
Sample Number				
1	< 50	1,457	2,845	4,145

Report of Analysis	85-1370	85-1372	85-1374	85-1376
Dose Group	Control Male	Low Male	Medium Male	High Male
Designated Dosing Concentration	0.00	5,012	10,168	15,199
Sample Number				
1	< 50	4,849	9,928	13,964

(1) Reported values are from one 10 gram sample

Notebook Reference: K. Klimovitz, PDAD0096, pp. 222-262

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Table 13

Diet Admixture Concentrations

Study Week 17 (1)

SC-19129, ppm

Report of Analysis	85-1899	85-1901	85-1903	85-1905
Dose Group	Control Female	Low Female	Medium Female	High Female
Designated Dosing Concentration	0.00	1,244	2,489	3,734
Sample Number				
1	< 50	1,163	2,278	3,535

Report of Analysis	85-1900	85-1902	85-1904	85-1906
Dose Group	Control Male	Low Male	Medium Male	High Male
Designated Dosing Concentration	0.00	1,208	2,414	3,624
Sample Number				
1	< 50	1,157	2,238	3,599

(1) Reported values are from one 10 gram sample

Notebook Reference: M. Yin, PDAD0132, pp. 48-65

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Table 14

Diet Admixture Concentrations

Study Week 20 (1)

SC-19129, ppm

Report of Analysis	85-1462	85-1463	85-1465	85-1467
Dose Group	Control Female/Male	Low Female	Medium Female	High Female
Designated Dosing Concentration	0.00	2,194	4,387	6,581
Sample Number				
1	< 50	2,093	4,283	6,507
2	< 50	2,092	4,263	6,340
3	< 50	2,095	4,228	6,214
\bar{X}	NA	2,093	4,258	6,354
s	NA	2	28	147

Report of Analysis	85-1464	85-1466	85-1468
Dose Group	Low Male	Medium Male	High Male
Designated Dosing Concentration	2,309	4,619	6,928
Sample Number			
1	2,237	4,587	6,982
2	2,207	4,541	6,774
3	2,224	4,522	6,834
\bar{X}	2,223	4,550	6,863
s	15	33	107

(1) Reported values are from three 10 gram samples

NA = Not applicable

Notebook Reference: K. Klimovitz, PDAD0096, pp. 263-278

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Table 15

Diet Admixture Concentrations

Study Week 25 (1)

SC-19129, ppm

Report of Analysis	85-1469	85-1470	85-1472	85-1474
Dose Group	Control Female/ Male	Low Female	Medium Female	High Female
Designated Dosing Concentration	0.00	3,135	6,297	9,449
Sample Number				
1	< 50	2,988	6,269	9,212
2	< 50	3,026	6,223	9,058
3	< 50	3,020	6,209	9,241
\bar{X}	NA	3,011	6,234	9,170
s	NA	20	31	98

Report of Analysis	85-1471	85-1473	85-1475
Dose Group	Low Male	Medium Male	High Male
Designated Dosing Concentration	3,846	7,631	11,545
Sample Number			
1	3,651	6,864	10,998
2	3,642	6,927	10,888
3	3,590	6,968	10,958
\bar{X}	3,628	6,920	10,948
s	33	52	56

(1) Reported values are from three 10 gram samples

NA = Not applicable

Notebook Reference: K. Klimovitz, PDAD0096, pp. 279-295

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Table 16
Diet Admixture Concentrations
Study Week 28 (1)
SC-19129, ppm

Report of Analysis	85-1476	85-1478	85-1480	85-1482
Dose Group	Control Female	Low Female	Medium Female	High Female
Designated Dosing Concentration	0.00	2,934	5,908	8,749
Sample Number				
1	< 50	2,786	5,656	8,670
2	< 50	2,770	5,589	8,433
3	< 50	2,718	5,594	8,639
\bar{X}	NA	2,758	5,613	8,581
s	NA	36	37	129

Report of Analysis	85-1477	85-1479	85-1481	85-1483
Dose Group	Control Male	Low Male	Medium Male	High Male
Designated Dosing Concentration	0.00	4,428	8,742	13,214
Sample Number				
1	< 50	4,209	8,299	12,780
2	< 50	4,249	8,600	12,834
3	< 50	4,223	8,588	12,789
\bar{X}	NA	4,227	8,496	12,801
s	NA	20	170	29

(1) Reported values are from three 10 gram samples

NA = Not applicable

Notebook Reference: K. Klimovitz, PDAD0137, pp. 11-42

Subject: SC-19129

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Table 17

Diet Admixture Concentrations

Study Week 31 (1)

SC-19129, ppm

Report of Analysis	85-1492	85-1493	85-1494	85-1495
Dose Group	Control Female	Low Female	Medium Female	High Female
Designated Dosing Concentration	0.00	1,625	3,270	4,846
Sample Number				
1	< 50	1,582	3,220	4,677
2	< 50	1,609	3,163	4,732
3	< 50	1,616	3,166	4,660
\bar{X}	NA	1,602	3,183	4,690
s	NA	18	32	38

(1) Reported values are from three 10 gram samples

NA = Not applicable

Notebook Reference: M. Yin, PDAD0132, pp. 11-28

Subject: SC-19129

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VI. Tabulation of Concentration Data

Table 18

Summary of Concentration Data

Low Female Dose Group

Study Week	Designated Dosing Concentration (ppm)	Mean % Recovery
1	*	*
4	*	*
9	2,853	95.0
12	2,850	98.6
15	1,520	95.9
17	1,244	93.5
20	2,194	95.4
25	3,135	96.0
28	2,934	94.0
31	1,625	98.6
\bar{X}		95.9
s		1.9

* = Female dosing concentration analysis not required until Study Week 9

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Summary Number: F-358-034-13

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Table 19

Summary of Concentration Data

Medium Female Dose Group

Study Week	Designated Dosing Concentration (ppm)	Mean % Recovery
1	*	*
4	*	*
9	5,706	92.6
12	5,700	96.5
15	3,040	93.6
17	2,489	91.5
20	4,387	97.1
25	6,297	99.0
28	5,908	95.0
31	3,270	97.3
\bar{X}		95.3
s		2.6

* = Female dosing concentration analysis not required until Study Week 9

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Table 20

Summary of Concentration Data

High Female Dose Group

Study Week	Designated Dosing Concentration (ppm)	Mean % Recovery
1	*	*
4	*	*
9	8,557	92.2
12	8,550	97.8
15	4,562	90.9
17	3,734	94.7
20	6,581	96.6
25	9,449	97.0
28	8,749	98.1
31	4,846	96.8
\bar{X}	.	95.5
s		2.7

* = Female dosing concentration analysis not required until Study Week 9

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Table 21

Summary of Concentration Data

Low Male Dose Group

Study Week	Designated Dosing Concentration (ppm)	Mean % Recovery
1	2,079	96.2
4	3,052	94.8
9	4,466	94.5
12	4,777	97.9
15	5,012	96.7
17	1,208	95.8
20	2,309	96.3
25	3,846	94.3
28	4,428	95.5
31	*	*
\bar{X}		95.8
S		1.2

* = Male dosing concentration analysis not required on
Study Week 31

Subject: SC-19129

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Table 22

Summary of Concentration Data

Medium Male Dose Group

Study Week	Designated Dosing Concentration (ppm)	Mean % Recovery
1	4,158	92.7
4	6,228	94.1
9	8,705	89.7
12	9,511	100.8
15	10,165	97.7
17	2,414	92.7
20	4,619	98.5
25	7,631	90.7
28	8,742	97.2
31	*	*
\bar{X}		94.9
s		3.8

* = Male dosing concentration analysis not required on
Study Week 31

Subject: SC-19129

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Table 23

Summary of Concentration Data

High Male Dose Group

Study Week	Designated Dosing Concentration (ppm)	Mean % Recovery
1	6,237	95.6
4	9,263	91.8
9	13,112	87.6
12	14,332	97.9
15	15,199	91.9
17	3,624	99.3
20	6,928	99.1
25	11,545	94.8
28	13,214	96.9
31	*	*
\bar{X}		95.0
S		3.9

* = Male dosing concentration analysis not required on Study Week 31

Subject: SC-19129

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VII. Endnote

The analyses for the homogeneity and concentration of SC-19129 in diet admixture (Labsure Animal Diet Number 2) for Study Weeks 1, 4, and 9 as well as the on-shelf stability were conducted using HPLC method (M84-045-B0185). This method was developed and validated for the analysis of a 1 gram sample. The samples that were shipped from the contract lab contained 10 grams of diet admixture. To utilize method (M84-045-B0185) for the analysis of SC-19129, each 10 gram sample had to be subsampled to obtain a 1 gram sample for analysis. The results of the analysis for the 1 gram subsamples (first determination for homogeneity) exhibited a higher than normal degree of variability. The possible causes for this high variability could be:

1. subsample variance
2. sample size
3. stratification of sample content

To reduce the variability of the analysis, three 1 gram subsamples for Study Week 1, and ten 1 gram subsamples for Study Week 4 and 9 were analyzed. The average values are reported.

To expedite the sample preparation procedure and to further reduce the subsampling variance, an HPLC method (M85-022-A) was developed and validated for the analysis of a 10 gram sample. Beginning with Study Week 12, the analysis of SC-19129 in diet admixture was conducted using HPLC method (M85-022-A). One sample was analyzed for each dosing concentration on Study Weeks 1, 4, 9, 12, 15, and 17, and three samples were analyzed for each dosing concentration on Study Weeks 20, 25, 28, and 31 (see Chart 1 for the sampling scheme).

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Chart 1

Sampling Scheme for SA 2473 (1)

Study Week	Number of 10 Gram Samples	Mass of Samples Analyzed	Number of Subsamples Analyzed
1	9	1 g	3
4	1	1 g	10
9	1	1 g	10
12	1	10 g	NA
15	1	10 g	NA
17	1	10 g	NA
20	3	10 g	NA
28			
t = 0 (Days)	3	10 g	NA
t = 14 (Days)	2	10 g	NA
31	3	10 g	NA

(1) Method M84-045-B0185 used for the analysis of the 1 g samples

Method M85-022-A used for the analysis of the 10 g samples

NA = Not applicable

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VIII. Bibliographic References

1. Ryan, Jr., T. A., Joiner, B. L., and Ryan, B. F., "MINITAB Student Handbook", 1976, Wadsworth Publishing Co., Inc.
2. Natrella, M. G., "Experimental Statistics, National Bureau of Standards Handbook 91", 1963, US Government Printing Office
3. Filliben, J., Technometrics, 17 (1), 111 (1975)

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IX. GLP Compliance Statement

To the best of our knowledge, the support activities provided by the Product Development Analytical Department for this study were conducted in compliance with the Good Laboratory Practices Regulations, as set forth in part 58, 21 CFR.

DEPARTMENT OF PRODUCT SAFETY ASSESSMENT
G. D. Searle & Co., Skokie, IL

Title: Segment II Teratology Evaluation of SC-19129
in Rabbits

Authors: J.M. Tesh, F.W. Ross, T.J. Wightman, O.K. Wilby,
and S.A. Tesh
(Life Science Research, Suffolk, England)

Study No.: S.A. 2643

Date: January 6, 1986

Type of Report: Final

Summary:

SC-19129 was administered by gavage to pregnant New Zealand White rabbits during organogenesis from Day 6 to Day 19 of gestation inclusive, at dosages of 250, 500 or 750 mg/kg/day. A fourth group, serving as controls, received the vehicle 0.5% (w/v) methylcellulose and 0.1% (w/v) Tween 80 at the same volume-dosage during the same treatment period. On Day 29 of gestation, females were killed to allow examination of their uterine contents.

Females receiving 750 mg/kg/day showed a reduction in food intake and faecal output and three females also exhibited a post-dosing increase in respiration rate on the first day of treatment only.

Five of fifteen females receiving 750 mg/kg/day died or were killed in extremis; two of five necropsied females showed respiratory problems and most had gastro-intestinal tract disorders.

There was no indication of any adverse treatment-related effect upon maternal bodyweight performance.

No adverse treatment-related effects upon litter parameters and foetal morphogenesis were observed.

