

SC-19192: SEGMENT III
PERINATAL WEANING STUDY IN THE RAT

P-T NO. 1011H72

FINAL REPORT

Submitted to

G. D. Searle and Company
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DATE: August 18, 1972

MATERIAL: SC-19192

LOT NO: IR

SUBJECT: FINAL REPORT
Segment III Perinatal Weaning Study in the Rat
Project No. 700-265

SUMMARY

This study was conducted to evaluate the potential effects of SC-19192 on the perinatal and postnatal phases of the reproductive process in albino rats, with emphasis on evaluation of parturition, neonatal viability, and growth of the newborn. Test diets prepared at 0.66%, 1.32%, and 2.63% weight-per-weight concentrations were administered to three test groups of 20 female rats each from Day 14 of gestation through weaning of the litters. A control group of 20 females received the basal diet only. Calculated mean actual dosage levels for the test groups from initiation of treatment through weaning of the litters were as follows: Group No. 2 - 0.67 g/kg/day, Group No. 3 - 1.31 g/kg/day, and Group No. 4 - 2.54 g/kg/day.

All control and test parental females survived the study. Appearance and behavior, group mean body weights and group mean body weight gains, and total group mean food consumption were comparable between the control and test animals. Statistical analysis of group mean body weights and total group mean food consumption values during the period of test diet administration showed no statistically significant differences between these control and test data.



Evaluation of the following parameters revealed no evidence of a compound-related effect among the test groups: gestation index and duration of the gestation period, live birth and weaning survival indices, litter size born, body weights and growth of pups, appearance and behavior of offspring, results of ophthalmoscopic examinations performed on Group No. 4 weanling rats, and results of visceral and skeletal examinations performed on stillbirths and on pups found dead during lactation.

In conclusion, dietary administration of SC-19192 to female albino rats from Day 14 of gestation through weaning of the litters at 0.66%, 1.32%, and 2.63% weight-per-weight concentrations had no discernible effect on the perinatal and postnatal phases of the reproductive process in albino rats in this study.

INTRODUCTION

The purpose of this study was to evaluate the potential effect of SC-19192 on the perinatal and postnatal phases of the reproductive process in albino rats. Mating of animals was initiated on March 21, 1972. Weaning of the litters was completed on May 16, 1972.

MATERIALS

Compound

Identification: SC-19192; Lot No. IR.

Receipt Date: August 18, 1971.

Description: A white, lumpy powder with no noticeable odor.

Purity: Assumed 100% active ingredient.



Animals

Species: Adult unproven male and female albino rats.

Strain: Charles River Caesarean-derived.

Supplier: Charles River Breeding Laboratories, Inc.

Basal Diet: Purina Laboratory Chow and water available ad libitum.

Stock Chemicals

Tissue Preservation: 10% neutral buffered formalin and 75% glycerin.

Skeletal Staining: 1.0% and 2.0% potassium hydroxide; alizarin red S and 0.5% potassium hydroxide solution; one part benzyl alcohol, one part glycerin, and two parts 70% alcohol; and 50% glycerin.

METHODS

Mating

Two females were placed with one male in a breeding cage. Using the vaginal douche method, each female was examined daily for the presence of spermatozoa. The day on which sperm (or copulatory plugs) were first observed was designated as Day 0 of gestation. Upon observation of sperm, females were individually housed. If no sperm were observed, females were omitted from the study.

Animal Groups

From a total of 80 females in which sperm were observed (a total of 104 females were used in mating), the animals were arbitrarily selected and placed into one control and three test groups to receive the indicated dosage



levels of compound. Males were used solely for breeding purposes and did not receive the test material. No observations were made and no records were maintained for the males.

| <u>Group No.</u> | <u>No. of Females</u> | <u>Diet</u> | <u>Dosage Levels (Females Only)</u> | |
|------------------|-----------------------|-----------------|-------------------------------------|----------------------------|
| | | | <u>Intended</u> g/kg/day | <u>Actual*</u> g/kg/day |
| 1 (Control) | 20 | basal diet only | 0 | 0 |
| 2 | 20 | 0.66% test diet | 0.5 | 0.67 |
| 3 | 20 | 1.32% test diet | 1.0 | 1.31 |
| 4 | 20 | 2.63% test diet | 2.0 | 2.54 |

* Calculated mean actual dosage levels from initiation of treatment through weaning of the litters. Group mean actual dosage levels for each week of the test diet administration (presented in text Figure No. 4) ranged from 0.50 to 0.89 g/kg/day for Group No. 2, from 1.04 to 1.70 g/kg/day for Group No. 3, and from 2.01 to 3.20 g/kg/day for Group No. 4. These data are further discussed in the Results section of this report (Page No.12).

Near time of delivery and throughout weaning, the females were housed in individual plastic nesting boxes with a commercial bedding of pine shavings (supplied by Shurfire Products Corporation, Washington, D. C.). At all other times, the animals were housed in Wahmann galvanized hanging cages.

Administration of Compound

The test material was incorporated into the basal laboratory diet at 0.66% (Group No. 2), 1.32% (Group No. 3), and 2.63% (Group No. 4) weight-per-weight concentrations and thoroughly mixed in a twin-shell, Patterson-Kelley blender to provide the appropriate dosage levels for each group. Fresh diets were prepared every week. Dosages were based on the mean body weight of the female "breeding pool" at initiation of breeding and "in house" control food



consumption for females of that specific weight. The test diets were administered from Day 14 of gestation through weaning of the litters. Prior to Day 14, the test animals received the basal diet only. Control females received the basal diet only throughout the study. The basal and test diets when administered were available ad libitum.

Parturition and Lactation

All females were allowed to litter naturally. Within 24 hours after birth, the litters were arbitrarily reduced to a maximum of eight pups and were carried through the 21-day lactation period to weaning.

Observations and Records

Mortality, appearance, and behavior of the females were observed daily during the study; observations were recorded weekly. Body weights were recorded at observation of sperm and at weekly intervals through weaning of the litters. Food consumption was recorded at weekly intervals.

Mortality, appearance, and behavior of the offspring were observed at birth, frequently during lactation, and at weaning. Individual pup weights were recorded at birth (within 24 hours), at four days postpartum, and at weaning (21 days postpartum). Records were kept of the number of pups born, number of stillbirths, and number of pups weaned.

Ophthalmoscopic Examination

Following completion of weaning, eye examinations utilizing a binocular indirect ophthalmoscope and Mydriacyl[®] as a mydriatic were performed on all Group No. 4 pups (average age - approximately 40 to 42 days); and subsequent



eye examinations utilizing a binocular magnifier and the focal beam light of a direct ophthalmoscope were performed on all control pups (average age - approximately 47 to 59 days).

Termination

All females and weanling pups were discarded following weaning of the litters and completion of ophthalmoscopic examination.

Postmortem Procedures

Unless precluded by mutilation, postmortem body weights were recorded for stillbirths and for pups found dead during lactation and these animals were preserved in 10% neutral buffered formalin.

Visceral Examination: Viscera of the preserved pups were examined grossly for anomalies; these pups were eviscerated; and the viscera was preserved in 10% neutral buffered formalin.

Skeletal Examination: The pups were skinned; and then placed in 1.0% potassium hydroxide for one week and in 2.0% potassium hydroxide for another week; and stained for approximately four days in a solution of alizarin red S and 0.5% potassium hydroxide. The stain was extracted from the soft tissue for two days with one part benzyl alcohol, one part glycerin, and two parts 70% alcohol; and the pups were cleared with 50% glycerin for approximately 24 hours and stored in 75% glycerin. Lamps were kept over the containers about 12 hours per day during the maceration procedure. Each skeleton was evaluated for relative differences in size, location, normal or abnormal bone



structure, degree of ossification, and the presence or absence of bone structure. The number of pups examined are presented in the Results section of this report.

Analysis of Data

Indices of fertility, gestation, live birth, and weaning survival were derived as follows: fertility index, number of pregnancies observed divided by the number of females placed on study following observation of sperm X 100; gestation index, number of full-term litters born divided by the number of females observed to be pregnant X 100; live birth index, number of pups born alive divided by the number of pups born X 100; and weaning survival index, number of pups weaned divided by the number of pups left to nurse X 100.

Statistical analysis of the following parameters was performed by the t-test at the 5.0% probability level: group mean maternal body weights at Days 14 (initiation of test diet administration) and 21 of gestation and at Days 7, 14, and 21 postdelivery; total group mean food consumption values per week during the entire period of test diet administration; mean duration of the gestation period; mean litter size born; and group mean pup body weight data. (Reference: Wilfred J. Dixon and Frank J. Massey, Jr., Introduction to Statistical Analysis, 123-124, McGraw Hill, 1957.)

RESULTS

Maternal Data

There were no deaths among any of the parental females during the study (survival: 100% in each group).



There were no apparent compound-related effects with regard to the general appearance and behavior of the test animals. Observations on appearance and behavior of the pregnant females are summarized below in Figure No. 1. Numbers in parentheses indicate the number of pregnant animals per group.

Figure No. 1 - Appearance and behavior of parental females

| <u>Observations</u> | <u>Control</u> (20) | <u>Group No. 2</u> (17) | <u>Group No. 3</u> (18) | <u>Group No. 4</u> (19) |
|--|------------------------|----------------------------|----------------------------|----------------------------|
| Transient or Isolated Instances of: | | | | |
| Alopecia | 0 | 2 | 0 | 1 |
| Hunching | 4 | 2 | 2 | 2 |
| Soft feces | 0 | 0 | 1 | 0 |
| Wheezing | 0 | 0 | 1 | 0 |

One nonpregnant female in Group No. 2 and two nonpregnant females in Group No. 3 also exhibited hunching. Otherwise, the control and test females were normal in appearance and behavior throughout the study.

Individual and group mean body weight and food consumption data and standard deviations (\pm s.d.) for the parental females during the study are presented in appended Table No. 1. Data for the pregnant females only were included in calculation of group mean values.

A summary of the group mean body weights and standard deviations (\pm s.d.), in grams, and of the group mean body weight gains, in grams and in percent, for the females at selected intervals are presented on the following page in Figure No. 2.



Figure No. 2 - Body weight data for parental females

| | <u>Control</u> | | <u>Group No. 2</u> | | <u>Group No. 3</u> | | <u>Group No. 4</u> | |
|--------------------------------|----------------|--------------|--------------------|--------------|--------------------|--------------|--------------------|--------------|
| | <u>Wt.</u> | <u>±s.d.</u> | <u>Wt.</u> | <u>±s.d.</u> | <u>Wt.</u> | <u>±s.d.</u> | <u>Wt.</u> | <u>±s.d.</u> |
| | g. | g. | g. | g. | g. | g. | g. | g. |
| <u>Group Mean Body Weights</u> | | | | | | | | |
| Gestation Period: | | | | | | | | |
| Day 0 | 235 | 13.4 | 233 | 13.9 | 244 | 6.8 | 242 | 20.5 |
| 7 | 267 | 16.6 | 262 | 17.4 | 259 | 30.5 | 271 | 16.6 |
| 14* | 303 | 16.2 | 296 | 18.9 | 306 | 13.0 | 304 | 19.5 |
| 21 | 382 | 34.2 | 376 | 35.5 | 399 | 24.1 | 388 | 32.6 |
| Postdelivery Period: | | | | | | | | |
| Day 7 | 290 | 19.5 | 283 | 22.0 | 289 | 26.6 | 292 | 20.4 |
| 14 | 286 | 23.6 | 276 | 20.6 | 291 | 28.3 | 290 | 21.4 |
| 21 | 319 | 21.7 | 309 | 21.7 | 321 | 23.6 | 321 | 23.1 |
| | | | | | | | | |
| | <u>Control</u> | | <u>Group No. 2</u> | | <u>Group No. 3</u> | | <u>Group No. 4</u> | |
| | <u>±g.</u> | <u>±%</u> | <u>±g.</u> | <u>±%</u> | <u>±g.</u> | <u>±%</u> | <u>±g.</u> | <u>±%</u> |
| | | | | | | | | |
| <u>Group Mean Weight Gains</u> | | | | | | | | |
| Gestation Period: | | | | | | | | |
| Days 0 thru 21 | +147 | +63 | +143 | +61 | +155 | +64 | +146 | +60 |
| Days 14* thru 21 | +79 | +26 | +80 | +27 | +93 | +30 | +84 | +28 |
| Postdelivery Period: | | | | | | | | |
| Days 7 thru 21 | +29 | +10 | +26 | +9 | +32 | +11 | +29 | +10 |

* Initiation of test diet administration.



Statistical analysis of group mean body weights at Days 14 (initiation of test diet administration) and 21 of gestation and at Days 7, 14, and 21 post-delivery revealed no statistically significant differences between the mean body weight data for the control and test groups. Group mean body weight gains for the three test groups during the gestation and postdelivery periods were within $\pm 4\%$ of that for the control group.

A summary of the group mean weekly food consumption values and standard deviations (\pm s.d.), in grams, for the females throughout the study are presented in Figure No. 3. Total group mean values, \pm s.d., per week during the total period of test diet administration are also presented in Figure No. 3. Group mean compound consumption values per day, expressed as g/kg/day, for each week of test diet administration and for the total period of test diet administration are presented in Figure No. 4.

There were no meaningful differences between the food consumption data for the control and test females. Weekly mean food consumption values per week varied somewhat between the control and test groups. However, the total group mean values per week during the entire period of test diet administration (from Day 14 of gestation through Day 21 postdelivery) were comparable between the control and test animals. The total mean value per week for Group No. 3 was the same as for the controls, while that for Groups No. 2 and No. 4 were 3% and 4% less, respectively, than that for the control group. Statistical analysis of the total mean food consumption values showed no statistically significant differences between these control and test data.



Figure No. 3 - Food consumption data for parental females

| | <u>Control</u> | | <u>Group No. 2</u> | | <u>Group No. 3</u> | | <u>Group No. 4</u> | |
|---|----------------|-------|--------------------|-------|--------------------|-------|--------------------|-------|
| | Food | ±s.d. | Food | ±s.d. | Food | ±s.d. | Food | ±s.d. |
| <u>Group Mean Values/Week</u> | | | | | | | | |
| Gestation Period: | | | | | | | | |
| Days 0 to 7 | 146 | 18.5 | 139 | 15.6 | 138 | 31.8 | 147 | 13.4 |
| Days 7 to 14 | 160 | 15.6 | 151 | 10.2 | 167 | 17.1 | 159 | 17.1 |
| Days 14* to 21 | 177 | 18.4 | 179 | 20.4 | 195 | 31.2 | 185 | 12.8 |
| Postdelivery Period: | | | | | | | | |
| Days 0 to 7 | 182 | 36.4 | 187 | 35.7 | 199 | 36.6 | 191 | 44.5 |
| Days 7 to 14 | 242 | 48.6 | 233 | 55.1 | 231 | 23.1 | 222 | 38.8 |
| Days 14 to 21 | 294 | 81.9 | 275 | 52.9 | 270 | 30.7 | 260 | 36.3 |
| <u>Total Group Mean Values/Week**</u> | | | | | | | | |
| Gestation and Postdelivery Periods: | | | | | | | | |
| From Day 14* Gestation thru Day 21 Post- delivery | 224 | 36.0 | 218 | 32.8 | 224 | 20.8 | 215 | 27.1 |

* Initiation of test diet administration.

** Total mean values/week from initiation of test diet administration.



Figure No. 4 - Compound consumption data for test parental females

| | <u>Group No. 2</u> g/kg/day | <u>Group No. 3</u> g/kg/day | <u>Group No. 4</u> g/kg/day |
|---|--------------------------------|--------------------------------|--------------------------------|
| <u>Group Mean Values/Day</u> | | | |
| Gestation Period: | | | |
| Days 14 to 21 | 0.50 | 1.04 | 2.01 |
| Postdelivery Period: | | | |
| Days 0 to 7 | 0.53 | 1.09 | 2.11 |
| Days 7 to 14 | 0.78 | 1.50 | 2.87 |
| Days 14 to 21 | 0.89 | 1.70 | 3.20 |
| Total Treatment Period: | | | |
| From Day 14 Gestation thru Day 21 Postdelivery | 0.67 | 1.31 | 2.54 |

Evaluation of food consumption data within time periods indicates an increase in consumption during Days 7 to 21 postdelivery with a parallel increase in compound consumption among the test groups during this time. It is noted that while there is undoubtedly an increase in food consumption by the parental animals, the possibility that this increase is also due in part to consumption by the neonatal animals cannot be discounted.

Perinatal and Postnatal Data

Evaluation of perinatal and postnatal data revealed no apparent compound-related effects among the test groups. A summary of the breeding data is presented in Figure No. 5 and graphic presentation of mean pup body weights and standard deviations (\pm s.d.) is presented in Figure No. 6. Individual litter mean body weights, group mean body weights, and standard deviations are presented in appended Table No. 2.



All of the control and test females observed to be pregnant completed the gestation period with natural deliveries. No instances of abortion, dystocia, or delayed or prolonged labor were observed (Gestation index: 100% for all groups).

The mean duration of the gestation period was very slightly increased for each of the test groups, as compared to the control (to a statistically significant degree for Group No. 4); however, this finding is considered of minor biological significance. Mean values and standard deviations for this parameter were as follows: control - 21.9, ± 0.52 days; Group No. 2 - 22.4, ± 1.00 days; Group No. 3 - 22.2, ± 0.88 days; and Group No. 4 - 22.3, ± 0.67 days. The cumulative mean duration of gestation, \pm standard deviation, obtained from historical laboratory data for eight studies of similar design is 21.9, ± 0.19 days; and the range in values for these eight control groups was from 21.7 to 22.2 days.

There was no indication of a compound-related effect with regard to live birth and weaning survival indices (Live birth indices: control, 97.8%, Group No. 2, 98.4%, Group No. 3, 99.1%, and Group No. 4, 98.6%. Weaning survival indices: control, 84.4%; Group No. 2, 89.7%; Group No. 3, 91.5%; and Group No. 4, 90.2%). Postmortem data for stillbirths and for pups found dead during lactation are presented on Page No. 18.

Statistical analysis of mean litter size born and of mean pup body weights at 24 hours and four days postpartum and at weaning showed no statistically significant differences between the control and test groups and these parameters were comparable between control and test litters.



Figure No. 5 - Summary of breeding data for female albino rats serving as controls or receiving SC-19192

SEGMENT III

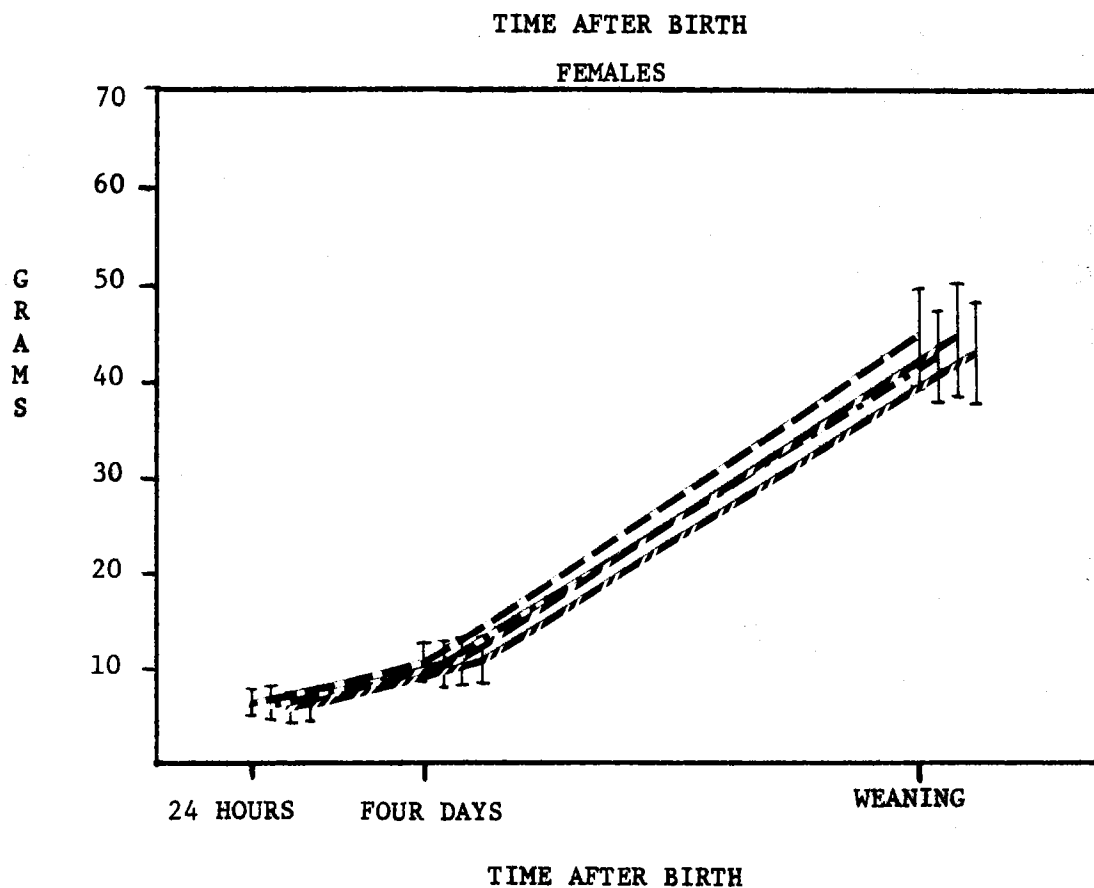
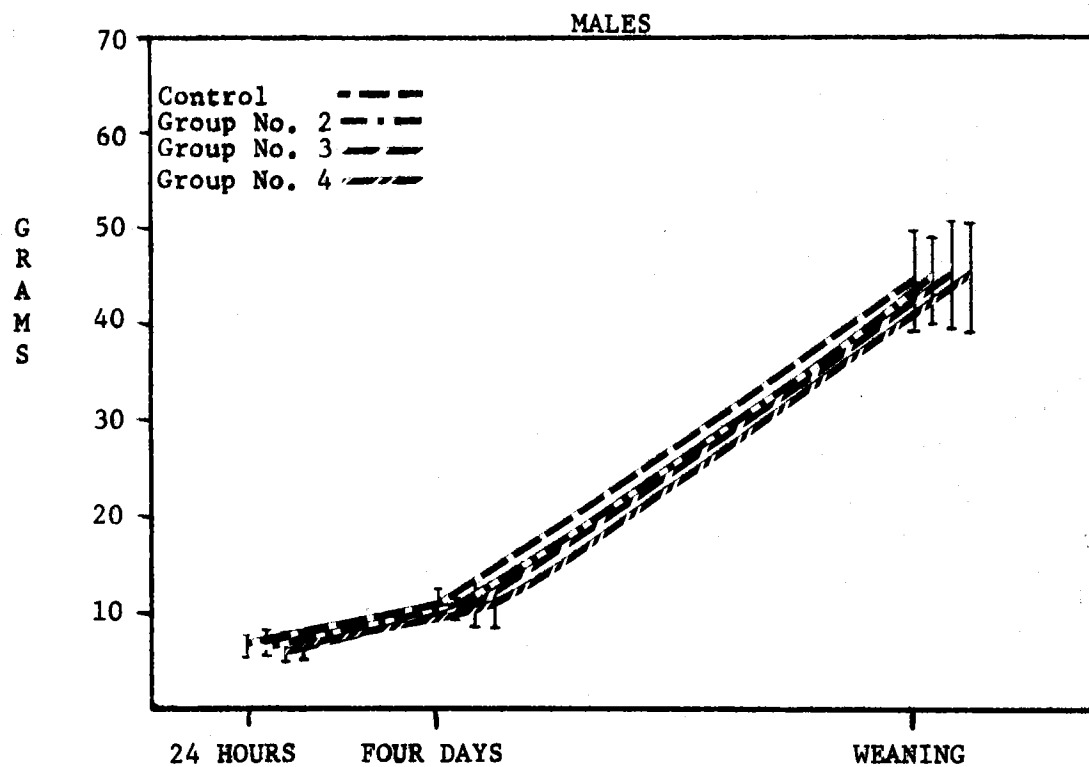
| | <u>Control</u> | <u>Group No. 2</u> | <u>Group No. 3</u> | <u>Group No. 4</u> |
|--------------------------------|----------------|--------------------|--------------------|--------------------|
| No. of Females Placed on Study | 20 | 20 | 20 | 20 |
| No. of Pregnancies Observed | 20 | 17 | 18 | 19 |
| Fertility Index* | 100% | 85.0% | 90.0% | 95.0% |
| No. of Pregnant Females | 20 | 17 | 18 | 19 |
| No. of Full-term Litters Born | 20 | 17 | 18 | 19 |
| Gestation Index | 100% | 100% | 100% | 100% |
| No. of Pups Observed at Birth | 224 | 189 | 232 | 222 |
| No. of Pups Born Alive | 219 | 186 | 230 | 219 |
| Live Birth Index | 97.8% | 98.4% | 99.1% | 98.6% |
| No. of Pups Left to Nurse | 147 | 126 | 141 | 143 |
| No. of Pups Weaned | 124 | 113 | 129 | 129 |
| Weaning Survival Index | 84.4% | 89.7% | 91.5% | 90.2% |
| Mean Litter Size Born | | | | |
| No. of Male Pups | 6 | 5 | 6 | 6 |
| No. of Female Pups | 6 | 6 | 7 | 6 |
| Pup Body Weight Data, Grams: | | | | |
| Males at 24 Hours | | | | |
| Mean | 6.3 | 6.6 | 6.3 | 6.4 |
| ±s.d. | 0.56 | 0.77 | 0.78 | 0.60 |
| Females at 24 Hours | | | | |
| Mean | 6.2 | 6.3 | 6.0 | 6.0 |
| ±s.d. | 0.72 | 0.84 | 0.78 | 0.62 |
| Males at Four Days | | | | |
| Mean | 11.0 | 10.8 | 11.4 | 11.4 |
| ±s.d. | 1.68 | 1.22 | 2.08 | 2.08 |
| Females at Four Days | | | | |
| Mean | 10.2 | 10.2 | 10.9 | 11.1 |
| ±s.d. | 1.59 | 1.50 | 1.69 | 1.58 |
| Males at Weaning | | | | |
| Mean | 44.8 | 44.8 | 45.8 | 44.5 |
| ±s.d. | 5.67 | 4.68 | 5.68 | 5.38 |
| Females at Weaning | | | | |
| Mean | 44.2 | 42.2 | 44.2 | 43.2 |
| ±s.d. | 5.63 | 4.16 | 5.92 | 5.30 |

* = Included only as reference to number of pregnancies obtained.

±s.d. = Standard deviation.

Figure No. 6 - Graphic presentation of mean pup body weights and standard deviations

SC-19192





Appearance and behavior of the test offspring revealed no evidence of a compound-related effect. Observations at delivery, during nursing, and at weaning are summarized in Figure No. 7. Incidence is expressed as number and percent.

Figure No. 7 - Appearance and behavior of offspring

| <u>Observations</u> | <u>Control</u> | <u>Group No. 2</u> | <u>Group No. 3</u> | <u>Group No. 4</u> |
|---|----------------|--------------------|--------------------|--------------------|
| At Delivery: (Number of pups born) | (224) | (189) | (232) | (222) |
| Appeared pale | 0 - | 0 - | 1 1% | 2 1% |
| Appeared small | 1 1% | 0 - | 0 - | 0 - |
| Appeared thin | 0 - | 1 1% | 0 - | 3 1% |
| Red spot present on tail | 0 - | 0 - | 0 - | 1 1% |
| Sore present on head | 0 - | 0 - | 0 - | 1 1% |
| Blue marks or areas present on head, torso, and/or Limbs* | 13 6% | 29 15% | 34 15% | 21 9% |
| Head appeared short** | 0 - | 4 2% | 0 - | 3 1% |

* Further identification as to the etiology of this observation was not possible; however, it is assumed that this finding is due to postnatal bruising and is considered of minor significance.

** For Group No. 2 - litter incidence, two live fetuses from one litter and one dead fetus each from two litters; this external observation was not confirmed by subsequent skeletal examination of these two dead fetuses both of which exhibited 100% staining of the skull surface and normal development of all head bones. For Group No. 4 - litter incidence, three live fetuses from one litter.



Figure No. 7 - Continued

| <u>Observations</u> | <u>Control</u> | <u>Group No. 2</u> | <u>Group No. 3</u> | <u>Group No. 4</u> |
|--|----------------|--------------------|--------------------|--------------------|
| During Nursing: (Number of pups left to nurse) | (147) | (126) | (141) | (143) |
| Appeared small | 9 6% | 11 9% | 1 1% | 5 3% |
| Appeared thin | 1 1% | 0 - | 0 - | 0 - |
| Appeared hunched | 0 - | 1 1% | 0 - | 0 - |
| Cold to the touch | 0 - | 1 1% | 0 - | 0 - |
| At Weaning: (Number of pups Weaned) | (124) | (112) | (129) | (129) |
| Appeared small | 8 6% | 8 7% | 6 5% | 13 10% |
| Tail appeared short | 0 - | 1 1% | 0 - | 0 - |

Otherwise, all control and test pups were normal in appearance and behavior throughout the study.

Ophthalmoscopic Examination

No apparent compound-related effects were evident at the ophthalmoscopic examinations performed on the Group No. 4 weanling rats. Ocular changes were observed among pups of two litters involving one or more, frequently, both eyes. These changes consisted of a swollen and reddened conjunctiva, purulent conjunctival discharge, and diffuse corneal opacity in about 50% of the affected eyes. Subsequent examination of the control weanling rats revealed



ocular lesions among pups of four litters which were comparable with those seen in Group No. 4, although incidence within the litters was lower among the controls. The ratios of the affected rats versus the number of weanling rats per litter are as follows.

| <u>Control</u> | | <u>Group No. 4</u> | |
|-----------------------------------|--------------|-----------------------------------|--------------|
| <u>Maternal</u> <u>Rat No.</u> | <u>Ratio</u> | <u>Maternal</u> <u>Rat No.</u> | <u>Ratio</u> |
| 4560 | 1/8 | 4625 | 3/8 |
| 4568 | 2/8 | 4632 | 6/8 |
| 4569 | 1/4 | | |
| 4572 | 2/7 | | |

The presence of comparable lesions in control, as well as Group No. 4 weanling rats, and the pattern of distribution among the litters indicate that the above described ocular changes were not compound related, and the probable cause for these findings was an infectious conjunctivitis with secondary corneal involvement.

Other incidental changes noted during examination included circumscribed corneal opacity in the left eye of one rat each in the control group and Group No. 4, and focal retinal atrophy in two Group No. 4 rats.

Postmortem Data for Offspring

A summary of litter and sex distribution and postmortem weight data for stillbirths is presented in Figure No. 8. Litter distribution of deaths is expressed as number of litters with deaths per total number of full-term litters born (data given in parentheses); and litters are identified by maternal rat numbers.



Figure No. 8 - Summary of data for stillbirths

| Group | Litter Distribution and No. of Stillbirths per Litter | Sex Distribution and Weight Data | | | |
|---------|--|----------------------------------|-----------|---------|-----------|
| | | Males | | Females | |
| | | No. | Wt. g. | No. | Wt. g. |
| Control | (4/20 Litters) Maternal Rats: | | | | |
| | No. 4556 - one pup | - | - | 1** | 6.0 |
| | No. 4557 - two pups | 1** | 6.0 | 1** | 5.0 |
| | No. 4573 - one pup | 1 | 5.0 | - | - |
| | No. 4574 - one pup | 1 | 4.0 | - | - |
| No. 2 | (3/17 Litters) Maternal Rats: | | | | |
| | No. 4588 - one pup | 1** | 8.0 | - | - |
| | No. 4589 - one pup | 1** | 6.0 | - | - |
| | No. 4591 - one pup | 1** | 6.0 | - | - |
| No. 3 | (2/18 Litters) Maternal Rats: | | | | |
| | No. 4598 - one pup | 1** | 6.0 | - | - |
| | No. 4602 - one pup | - | - | 1* | 5.0 |
| No. 4 | (3/19 Litters) Maternal Rats: | | | | |
| | No. 4615 - one pup | - | - | 1* | 7.0 |
| | No. 4616 - one pup | 1* | 7.0 | - | - |
| | No. 4630 - one pup | 1** | 6.0 | - | - |

* Indicates pups which could be evaluated for visceral anomalies only.

** Indicates pups evaluated for visceral anomalies and skeletal development.
(Other pups not footnoted could not be evaluated.)

A summary of litter and sex distribution for pups found dead or missing during lactation or at weaning due to apparent cannibalization and postmortem weight data for dead pups is presented in Figure No. 9. As in the preceding figure, litter distribution is expressed as number of litters involved per total number of full-term litters (data given in parentheses); and litters are identified by maternal rat numbers. Body weight data are expressed as mean weights when given for more than one pup per sex.



Figure No. 9 - Summary of data for pups found dead or missing during lactation

| Group | Litter of Distribution and No. of Dead or Missing Pups per Litter | Sex Distribution and Weight Data | | | |
|---------|---|----------------------------------|-----------|---------|-----------|
| | | Males | | Females | |
| | | No. | Wt. g. | No. | Wt. g. |
| Control | (8/20 Litters) Maternal Rats: | | | | |
| | No. 4555 - Day 15, one pup found dead | 1 | 20.0 | - | - |
| | No. 4557 - Day 21, one pup missing | - | - | 1 | - |
| | No. 4563 - Day 10, one pup found dead | - | - | 1 | 8.0 |
| | and Day 12, one pup missing | - | - | 1 | - |
| | No. 4569 - Day 4, four pups missing | 1 | - | 3 | - |
| | No. 4570 - Day 21, two pups missing | - | - | 2 | - |
| | No. 4572 - Day 21, one pup missing | 1 | - | - | - |
| | No. 4573 - Day 3, one pup found dead | 1* | 2.0 | - | - |
| | and seven pups missing (entire litter) | 3 | - | 4 | - |
| | No. 4574 - Day 9, two pups found dead | - | - | 2 | 9.0 |
| | and Day 21, two pups missing | 2 | - | - | - |
| No. 2 | (5/18 Litters) Maternal Rats: | | | | |
| | No. 4578 - Day 4, one pup missing | - | - | 1 | - |
| | and Day 21, four pups missing | 1 | - | 3 | - |
| | No. 4579 - Day 10, one pup found dead | - | - | 1** | 7.0 |
| | and Day 21, two pups missing | 1 | - | 1 | - |
| | No. 4580 - Day 21, two pups missing | 2 | - | - | - |
| | No. 4587 - Day 4, one pup missing | - | - | 1 | - |
| | and Day 21, one pup missing | - | - | 1 | - |
| | No. 4589 - Day 21, one pup missing | - | - | 1 | - |
| No. 3 | (5/18 Litters) Maternal Rats: | | | | |
| | No. 4598 - Day 7, one pup found dead | 1** | 7.0 | - | - |
| | No. 4599 - Day 12, eight pups found dead (entire litter) | 2♂ | 11.0♂♂ | 6** | 10.5 |
| | No. 4607 - Day 3, one pup found dead | 1** | 5.0 | - | - |
| | No. 4610 - Day 17, one pup found dead | - | - | 1** | 23.0 |
| | No. 4613 - Day 21, one pup missing | - | - | 1 | - |

* Indicates pups which could be evaluated for visceral anomalies only.

** Indicates pups evaluated for visceral anomalies and skeletal development. (Other pups not footnoted could not be evaluated.)

♂ One male processed for visceral and skeletal evaluations; other male discarded due to mutilation.

♂♂ Weight for one male only.



Figure No. 9 - Continued

| Group | Litter of Distribution and No. of Dead or Missing Pups per Litter | Sex Distribution and Weight Data | | | |
|-------|--|----------------------------------|-----------|---------|-----------|
| | | Males | | Females | |
| | | No. | Wt. g. | No. | Wt. g. |
| No. 4 | (5/19 Litters) Maternal Rats: | | | | |
| | No. 4615 - Day 2, one pup found dead; | - | - | 1* | 4.0 |
| | Day 4, one pup missing; | - | - | 1 | - |
| | and Day 21, one pup missing | 1 | - | - | - |
| | No. 4616 - Day 21, six pups missing | 1 | - | 5 | - |
| | No. 4626 - Day 4, one pup missing | - | - | 1 | - |
| | No. 4629 - Day 4, two pups missing | | | | |
| | (entire litter) | 2 | - | - | - |
| | No. 4630 - Day 21, two pups missing | - | - | 2 | - |

* Indicates pups which could be evaluated for visceral anomalies only.

Results of visceral examinations of the stillbirths and of pups found dead during lactation revealed no evidence of a compound-related effect.

Findings are summarized in Figure No. 10. Number in parentheses indicates the number of pups evaluated per group.



Figure No. 10 - Visceral data

| | Incidence as Number | | | |
|--|---------------------|-------------|-------------|-------------|
| | Control | Group No. 2 | Group No. 3 | Group No. 4 |
| | (3) | (3) | (2) | (3) |
| <u>Data for Pups Dead at Delivery</u> | | | | |
| All viscera appeared normal | 3 | 2 | 1 | 3 |
| Stomach filled with soft white material | 0 | 1 | 1 | 0 |
| <u>Data for Pups Found Dead During Lactation</u> | | | | |
| | (1) | (1) | (10) | (1) |
| All viscera appeared normal | 1 | 1 | 9 | 0 |
| Dark areas on lung | | | | |
| All Lobes | 0 | 0 | 1 | 0 |
| Left lobe only | 0 | 0 | 0 | 1 |

Results of skeletal examination of pups found dead at delivery or during lactation revealed no evidence of a compound-related effect. Findings are presented in Figure No. 11. The skull, ribs, sternum, vertebrae, pelvic girdle, longbones, forepaws, and hindpaws of the animals were evaluated. Included in Figure No. 11 are those bone structures which are consistently indicative of developmental variations. Number in parentheses indicates the

EXPLANATION FOR FOOTNOTES

Figure No. 11

* Grading of development of skull:

4 = Approximately 100% of skull surface stained.

** Variation in number of pups examined reflects inability to evaluate development of both hindpaws due to damage during processing.

Figure No. 11 - Skeletal development of pups found dead at delivery or during lactation.
Numbers in parentheses indicate the number of pups evaluated.

| | INCIDENCE AS NUMBER | | | |
|---|---------------------|--------------------|--------------------|--------------------|
| | CONTROL (3) | GROUP NO. 2 (3) | GROUP NO. 3 (1) | GROUP NO. 4 (1) |
| <u>Data for Pups Found Dead at Delivery</u> | | | | |
| Skull | | | | |
| Closure Grading*: 4 | 3 | 3 | 1 | 1 |
| Ribs | | | | |
| Pairs 13 | 3 | 3 | 1 | 1 |
| Vertebrae | | | | |
| Total Number Nonossified: | | | | |
| Cervical | | | | |
| Centra 1 | 0 | 1 | 1 | 0 |
| 2 | 0 | 1 | 0 | 0 |
| 4 | 0 | 1 | 0 | 0 |
| Caudal | | | | |
| Centra 14 | 0 | 0 | 0 | 1 |
| 16 | 3 | 0 | 0 | 0 |
| 17 | 0 | 1 | 0 | 0 |
| 19 | 0 | 2 | 0 | 0 |
| 20 | 0 | 0 | 1 | 0 |
| Dorsal Arches 23 | 3 | 1 | 1 | 1 |
| 24 | 0 | 2 | 0 | 0 |
| Total Number Small: | | | | |
| Cervical | | | | |
| Centra 2 | 1 | 0 | 0 | 0 |
| 3 | 2 | 1 | 0 | 0 |
| 4 | 0 | 1 | 0 | 0 |
| 5 | 0 | 1 | 1 | 0 |
| Total Number Dumbbell Shaped: | | | | |
| Cervical | | | | |
| Centra 1 | 2 | 1 | 1 | 1 |
| Total Number Split: | | | | |
| Cervical | | | | |
| Centra 1 | 1 | 0 | 0 | 0 |

Figure No. 11 - Continued

| | INCIDENCE AS NUMBER | | | |
|--|---------------------|--------------------|--------------------|--------------------|
| | CONTROL (3) | GROUP NO. 2 (3) | GROUP NO. 3 (1) | GROUP NO. 4 (1) |
| <u>Data for Pups Found Dead at Delivery</u> | | | | |
| Forepaws | | | | |
| Ossification Centers | | | | |
| Total Number Absent: | | | | |
| Carpus 16 | 3 | 3 | 1 | 1 |
| Metacarpus 2 | 3 | 3 | 1 | 1 |
| Phalanges 10 | 1 | 3 | 1 | 1 |
| 12 | 1 | 0 | 0 | 0 |
| 16 | 1 | 0 | 0 | 0 |
| Hindpaws | | | | |
| Ossification Centers | (3) | (2)** | (1) | (1) |
| Total Number Absent: | | | | |
| Tarsus 14 | 1 | 0 | 0 | 1 |
| 16 | 2 | 2 | 1 | 0 |
| Phalanges 10 | 2 | 2 | 1 | 1 |
| 11 | 1 | 0 | 0 | 0 |
| <u>Data for Pups Found Dead During Lactation</u> | | | | |
| Skull | (0) | (1) | (10) | (0) |
| Closure Grading*: 4 | | 1 | 10 | |
| Ribs | | | | |
| Pairs 13 | | 1 | 10 | |
| Vertebrae | | | | |
| Total Number Nonossified: | | | | |
| Caudal | | | | |
| Centra 1 | | 0 | 2 | 1 |
| 2 | | 1 | 0 | 0 |
| 3 | | 0 | 1 | 1 |
| 8 | | 0 | 1 | 1 |

Figure No. 11 - Continued

| | INCIDENCE AS NUMBER | | | |
|--|---------------------|--------------------|---------------------|--------------------|
| | CONTROL (0) | GROUP NO. 2 (1) | GROUP NO. 3 (10) | GROUP NO. 4 (0) |
| <u>Data for Pups Found Dead During Lactation</u> | | | | |
| Vertebrae (Cont'd) | | | | |
| Dorsal Arches 22 | | 0 | 8 | |
| 23 | | 1 | 2 | |
| Total Number Dumbbell Shaped: | | | | |
| Cervical | | | | |
| Centra 1 | | 1 | 2 | |
| Sternebrae | | | | |
| Extra Ossification Center Present | | 0 | 2 | |
| Forepaws | | | | |
| Ossification Centers | | | | |
| Total Number Absent: | | | | |
| Carpus 2 | | 0 | 2 | |
| 4 | | 0 | 5 | |
| 12 | | 1 | 0 | |
| 16 | | 0 | 2 | |
| Metacarpus 2 | | 1 | 2 | |
| Phalanges 2 | | 0 | 2 | |
| Hindpaws | | | | |
| Ossification Centers | | (1) | (9)** | |
| Total Number Absent: | | | | |
| Tarsus 8 | | 0 | 1 | |
| 10 | | 0 | 5 | |
| 12 | | 0 | 2 | |
| Phalanges 4 | | 1 | 1 | |



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number of pups evaluated per group. The skeletal evaluations are presented as combined data for stillbirths and combined data for pups found dead during lactation.

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NOTE: The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

Table No. 1 - Individual and group mean body weight and food consumption data and standard deviations (\pm s.d.) expressed in grams for parental females serving as controls or receiving SC-19192

| MATERNAL RAT NUMBER | DAY OF DELIVERY* | DAY OF GESTATION | | | | DAY POSTDELIVERY | | | | | | | | |
|------------------------|---------------------|------------------|------|-----|------|------------------|------|-----|------|-----|-----|-----|-----|-----|
| | | 0 | | 7 | | 14 | | 21 | | | | | | |
| | | WT. | FOOD | WT. | FOOD | WT. | FOOD | WT. | FOOD | | | | | |
| GROUP NO. 1 - CONTROL | | | | | | | | | | | | | | |
| 4555 | 22 | 236 | 280 | 165 | 306 | 174 | 392 | 170 | 316 | 185 | 289 | 245 | 323 | 373 |
| 4556 | 22 | 226 | 271 | 161 | 305 | 185 | 406 | 197 | 281 | 216 | 311 | 289 | 343 | 343 |
| 4557 | 21 | 235 | 272 | 152 | 288 | 153 | 409 | 183 | 293 | 171 | 298 | 287 | 315 | 542 |
| 4558 | 22 | 216 | 258 | 164 | 286 | 173 | 371 | 171 | 279 | 205 | 263 | 226 | 289 | 321 |
| 4559 | 22 | 253 | 282 | 134 | 308 | 146 | 378 | 165 | 294 | 174 | 334 | 216 | 342 | 246 |
| 4560 | 22 | 234 | 276 | 121 | 315 | 171 | 408 | 205 | 308 | 244 | 297 | 266 | 341 | 318 |
| 4561 | 22 | 211 | 230 | 127 | 270 | 130 | 340 | 155 | 248 | 195 | 266 | 209 | 321 | 254 |
| 4562 | 21 | 256 | 306 | 178 | 335 | 167 | 447 | 201 | 333 | 184 | 312 | 213 | 333 | 245 |
| 4563 | 22 | 230 | 261 | 129 | 290 | 140 | 371 | 169 | 281 | 176 | 277 | 212 | 331 | 271 |
| 4564 | 22 | 250 | 274 | 101 | 295 | 160 | 348 | 186 | 258 | 210 | 302 | 260 | 347 | 263 |
| 4565 | 22 | 224 | 262 | 149 | 309 | 162 | 405 | 179 | 291 | 210 | 267 | 210 | 293 | 229 |
| 4566 | 23 | 232 | 252 | 140 | 289 | 150 | 302 | 141 | 285 | 145 | 308 | 225 | 322 | 245 |
| 4567 | 23 | 248 | 268 | 165 | 306 | 167 | 389 | 180 | 304 | 170 | 253 | 221 | 279 | 247 |
| 4568 | 21 | 235 | 263 | 155 | 304 | 153 | 410 | 180 | 295 | 179 | 264 | 299 | 291 | 341 |
| 4569 | 22 | 229 | 252 | 135 | 293 | 139 | NR | NR | 305 | 131 | 305 | 210 | 339 | 241 |
| 4570 | 22 | 220 | 244 | 139 | 328 | 147 | NR | NR | 289 | 105 | 238 | 219 | 299 | 248 |
| 4571 | 22 | 245 | 273 | 149 | 301 | 176 | 350 | 175 | 278 | 118 | 269 | 215 | 311 | 247 |
| 4572 | 22 | 257 | 284 | 154 | 328 | 185 | 399 | 205 | 310 | 195 | 292 | 354 | 321 | 405 |
| 4573 | 14** | 259 | 291 | 175 | 358 | 175 | 280 | NR | 283 | 190 | 287 | 140 | 341 | 169 |
| 4574 | 22 | 228 | 259 | 150 | 295 | 160 | 371 | 151 | 275 | 240 | 282 | 318 | 290 | 341 |

Mean (Pregnant

only)

±s.d.

* = Day of gestation.

** = Day of mating apparently occurred prior to observation of sperm; therefore, body weight and food consumption data during gestation and duration of gestation were excluded from group mean calculations.

NR = Not recorded.

Table No. 1 - Continued

| MATERNAL RAT NUMBER | DAY OF DELIVERY* | DAY OF GESTATION | | | | | | DAY POSTDELIVERY | | | | | | |
|------------------------|---------------------|------------------|-----|-----|------|-----|------|------------------|------|-----|------|-----|------|-----|
| | | 0 | | 7 | | 14 | | 7 | | 14 | | 21 | | |
| | | WT. | WT. | WT. | FOOD | WT. | FOOD | WT. | FOOD | WT. | FOOD | WT. | FOOD | |
| GROUP NO. 2 | | | | | | | | | | | | | | |
| 4575 | 22 | 224 | 265 | 131 | 293 | 146 | 380 | 174 | 261 | 210 | 267 | 210 | 299 | 250 |
| 4576 | 22 | 226 | 259 | 137 | 295 | 152 | 389 | 179 | 270 | 206 | 289 | 297 | 344 | 341 |
| 4577 | 22 | 237 | 261 | 116 | 285 | 147 | 346 | 172 | 298 | 215 | 272 | 287 | 305 | 323 |
| 4578 | 25 | 231 | 254 | 125 | 292 | 160 | 376 | 165 | 243 | 220 | 284 | 261 | 299 | 265 |
| 4579 | 22 | 229 | 275 | 142 | 308 | 151 | 416 | 180 | 293 | 231 | 262 | 365 | 281 | 415 |
| 4580 | 21 | 232 | 269 | 148 | 303 | 155 | 399 | 205 | 321 | 190 | 300 | 228 | 316 | 310 |
| 4581 | 24 | 230 | 263 | 141 | 280 | 136 | 318 | 175 | 290 | 155 | 303 | 189 | 305 | 220 |
| 4582 | 22 | 232 | 257 | 140 | 290 | 148 | 370 | 189 | 272 | 124 | 261 | 206 | 310 | 251 |
| 4583 | 22 | 270 | 309 | 178 | 341 | 171 | 446 | 210 | 301 | 147 | 261 | 211 | 342 | 273 |
| 4584 | 21 | 234 | 261 | 133 | 293 | 137 | 368 | 161 | 283 | 183 | 286 | 211 | 297 | 245 |
| 4585 | NP | 234 | 242 | 125 | 253 | 117 | 256 | 126 | - | - | - | - | - | - |
| 4586 | NP | 233 | 251 | 101 | 270 | 151 | 256 | 119 | - | - | - | - | - | - |
| 4587 | 23 | 242 | 265 | 141 | 302 | 155 | 329 | 176 | 285 | 102 | 317 | 190 | 338 | 245 |
| 4588 | 22 | 226 | 255 | 140 | 299 | 150 | 373 | 190 | 289 | 180 | 241 | 220 | 299 | 269 |
| 4589 | 22 | 257 | 288 | 170 | 334 | 174 | 437 | 225 | 328 | 220 | 281 | 219 | 320 | 239 |
| 4590 | 23 | 211 | 242 | 135 | 283 | 149 | 347 | 153 | 269 | 191 | 262 | 175 | 299 | 227 |
| 4591 | 22 | 218 | 234 | 140 | 262 | 141 | 352 | 155 | 255 | 195 | 249 | 143 | 282 | 220 |
| 4592 | 22 | 236 | 256 | 129 | 292 | 147 | 394 | 180 | 289 | 205 | 295 | 307 | 338 | 335 |
| 4593 | 23 | 222 | 243 | 120 | 282 | 146 | 345 | 150 | 271 | 205 | 263 | 238 | 273 | 245 |
| 4594 | NP | 246 | 270 | 130 | 271 | 126 | 268 | 85 | - | - | - | - | - | - |

Mean (Pregnant

Only)

±s.d.

| | | | | | | | | | | | | | |
|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| 22.4 | 233 | 262 | 139 | 296 | 151 | 376 | 179 | 283 | 187 | 276 | 233 | 309 | 275 |
| 1.00 | 13.9 | 17.4 | 15.6 | 18.9 | 10.2 | 35.5 | 20.4 | 22.0 | 35.7 | 20.6 | 55.1 | 21.7 | 52.9 |

* = Day of gestation.

NP = Not pregnant; data excluded from calculation of mean.

Table No. 1 - Continued

| MATERNAL RAT NUMBER | DAY OF DELIVERY* | DAY OF GESTATION | | | | | | DAY POSTDELIVERY | | | | | | | | | |
|------------------------|---------------------|------------------|-----|-----|------|-----|------|------------------|------|-----|------|-----|------|-----|------|--|--|
| | | 0 | | 7 | | 14 | | 21 | | 7 | | 14 | | 21 | | | |
| | | WT. | WT. | WT. | FOOD | WT. | FOOD | WT. | FOOD | WT. | FOOD | WT. | FOOD | WT. | FOOD | | |
| GROUP NO. 3 | | | | | | | | | | | | | | | | | |
| 4595 | 22 | 245 | 205 | 60 | 296 | 187 | 403 | 284 | 275 | 219 | 290 | 235 | 325 | 288 | | | |
| 4596 | 22 | 246 | 204 | 80 | 302 | 180 | 418 | 190 | 275 | 218 | 289 | 200 | 308 | 233 | | | |
| 4597 | 22 | 233 | 269 | 140 | 303 | 163 | 366 | 195 | 319 | 205 | 314 | 262 | 321 | 293 | | | |
| 4598 | 21 | 248 | 288 | 147 | 325 | 172 | 446 | 210 | 343 | 90 | 275 | 210 | 323 | 263 | | | |
| 4599 | 22 | 253 | 280 | 150 | 304 | 174 | 399 | 193 | 238 | 140 | 227 | 220 | 257 | 288 | | | |
| 4600 | 22 | 245 | 248 | 173 | 295 | 176 | 403 | 194 | 306 | 200 | 304 | 260 | 321 | 310 | | | |
| 4601 | 22 | 237 | 272 | 173 | 307 | 176 | 410 | 225 | 300 | 220 | 321 | 285 | 333 | 318 | | | |
| 4602 | 21 | 240 | 269 | 156 | 304 | 150 | 419 | 207 | 307 | 235 | 308 | 233 | 329 | 258 | | | |
| 4603 | 22 | 232 | 254 | 131 | 290 | 130 | 380 | 173 | 287 | 248 | 296 | 264 | 342 | 318 | | | |
| 4604 | 23 | 254 | 261 | 170 | 312 | 192 | 403 | 195 | 294 | 210 | 304 | 199 | 338 | 233 | | | |
| 4605 | 22 | 246 | 277 | 146 | 319 | 157 | 428 | 214 | 310 | 215 | 323 | 230 | 349 | 254 | | | |
| 4606 | 23 | 240 | 262 | 140 | 304 | 161 | 352 | 125 | 287 | 160 | 297 | 225 | 330 | 272 | | | |
| 4607 | 23 | 242 | 185 | 90 | 273 | 174 | 360 | 179 | 258 | 210 | 247 | 227 | 290 | 258 | | | |
| 4608 | 25 | 256 | 285 | 155 | 320 | 190 | 411 | 205 | 246 | 210 | 325 | 227 | 344 | 310 | | | |
| 4609 | 22 | 239 | 263 | 133 | 302 | 139 | 383 | 170 | 273 | 200 | 249 | 217 | 283 | 230 | | | |
| 4610 | 22 | 246 | 270 | 124 | 304 | 150 | 405 | 173 | 294 | 198 | 268 | 214 | 321 | 241 | | | |
| 4611 | NP | 230 | 243 | 110 | 237 | 121 | 240 | 120 | - | - | - | - | - | - | | | |
| 4612 | NP | 206 | 218 | 104 | 244 | 131 | 230 | 127 | - | - | - | - | - | - | | | |
| 4613 | 22 | 251 | 290 | 165 | 325 | 165 | 388 | 190 | 317 | 216 | 285 | 220 | 321 | 244 | | | |
| 4614 | 22 | 248 | 280 | 145 | 317 | 175 | 412 | 185 | 276 | 189 | 318 | 225 | 343 | 245 | | | |

* = Day of gestation.

NP = Not pregnant; data excluded from calculation of mean.

Table No. 1 - Continued

| MATERNAL RAT NUMBER | DAY OF DELIVERY* | DAY OF GESTATION | | | | | | DAY POSTDELIVERY | | | | | | | |
|------------------------|---------------------|------------------|-----|------|-----|------|-----|------------------|-----|------|-----|------|-----|-----|-----|
| | | 0 | | 7 | | 14 | | 21 | | 7 | | 14 | | | |
| | | WT. | WT. | FOOD | WT. | FOOD | WT. | FOOD | WT. | FOOD | WT. | FOOD | | | |
| GROUP NO. 4 | | | | | | | | | | | | | | | |
| 4615 | 22 | 226 | 253 | 135 | 280 | 143 | 356 | 155 | 179 | 272 | 179 | 280 | 221 | 339 | 255 |
| 4616 | 22 | 221 | 254 | 143 | 277 | 145 | 360 | 185 | 190 | 287 | 190 | 292 | 200 | 341 | 259 |
| 4617 | 23 | 220 | 251 | 135 | 287 | 146 | 372 | 165 | 182 | 258 | 182 | 316 | 207 | 341 | 249 |
| 4618 | 22 | 242 | 281 | 157 | 316 | 176 | 407 | 190 | 136 | 290 | 136 | 290 | 204 | 320 | 221 |
| 4619 | 22 | 228 | 266 | 141 | 305 | 141 | 411 | 185 | 200 | 304 | 200 | 284 | 260 | 308 | 310 |
| 4620 | 22 | 258 | 306 | 166 | 341 | 190 | 443 | 202 | 170 | 344 | 170 | 342 | 262 | 358 | 319 |
| 4621 | 22 | 244 | 273 | 130 | 296 | 136 | 413 | 174 | 262 | 296 | 262 | 295 | 262 | 331 | 301 |
| 4622 | 22 | 244 | 292 | 163 | 331 | 175 | 442 | 200 | 260 | 298 | 260 | 276 | 258 | 330 | 298 |
| 4623 | 22 | 233 | 267 | 144 | 299 | 141 | 390 | 182 | 223 | 289 | 223 | 270 | 260 | 261 | 310 |
| 4624 | 22 | 238 | 275 | 132 | 304 | 155 | 392 | 179 | 211 | 262 | 211 | 263 | 211 | 312 | 231 |
| 4625 | 21 | 230 | 266 | 144 | 291 | 162 | 354 | 187 | 200 | 287 | 200 | 312 | 251 | 291 | 247 |
| 4626 | 22 | 236 | 265 | 150 | 300 | 175 | 389 | 190 | 218 | 307 | 218 | 278 | 229 | 328 | 240 |
| 4627 | 23 | 312 | 238 | 127 | 278 | 143 | 342 | 189 | 149 | 290 | 149 | 281 | 220 | 334 | 224 |
| 4628 | 22 | 243 | 279 | 179 | 316 | 167 | 421 | 209 | 220 | 306 | 220 | 253 | 216 | 291 | 240 |
| 4629 | 23 | 235 | 262 | 155 | 295 | 155 | 338 | 191 | 90 | 281 | 90 | 297 | 115 | 318 | 199 |
| 4630 | 23 | 230 | 265 | 143 | 298 | 140 | 378 | 181 | 205 | 297 | 205 | 285 | 178 | 326 | 244 |
| 4631 | 24 | 245 | 276 | 155 | 299 | 170 | 346 | 170 | 220 | 261 | 220 | 314 | 257 | 338 | 300 |
| 4632 | 22 | 258 | 283 | 143 | 328 | 179 | 411 | 190 | 115 | 315 | 115 | 311 | 170 | 340 | 218 |
| 4633 | 23 | 260 | 296 | 155 | 339 | 180 | 405 | 191 | 205 | 295 | 205 | 277 | 241 | 301 | 266 |
| 4634 | NP | 252 | 262 | 117 | 272 | 145 | 285 | 127 | - | - | - | - | - | - | - |

| | | | | | | | | | | | | | |
|----------------------|--------------------|------|------|------|------|------|------|------|------|------|------|------|------|
| Mean (Pregnant Only) | 22.3 ^{S+} | 242 | 271 | 147 | 159 | 304 | 185 | 388 | 191 | 292 | 191 | 290 | 222 |
| ±s.d. | 0.67 | 20.5 | 16.6 | 13.4 | 17.1 | 19.5 | 12.8 | 32.6 | 44.5 | 20.4 | 44.5 | 21.4 | 38.8 |
| | | | | | | | | | | | | 23.1 | 36.3 |

* = Day of gestation.

NP = Not pregnant; data excluded from calculation of mean.

S+ = Significantly higher than control at $p < 0.05$.

Table No. 2 - Individual litter mean body weights, group mean pup body weights, and standard deviations (\pm s.d.) by sex expressed in grams

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| MATERNAL RAT NUMBER | AT 24 HOURS | | | | AT FOUR DAYS | | | | AT WEANING | | | |
|------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | MALES | | FEMALES | | MALES | | FEMALES | | MALES | | FEMALES | |
| | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT |
| GROUP NO. 1 - CONTROL | | | | | | | | | | | | |
| 4555 | 7 | 6.1 | 6 | 5.8 | 4 | 11.0 | 4 | 11.5 | 3 | 41.3 | 4 | 40.5 |
| 4556 | 5 | 6.4 | 9 | 6.3 | 4 | 12.0 | 4 | 10.8 | 4 | 40.2 | 4 | 40.5 |
| 4557 | 8 | 6.6 | 5 | 5.8 | 4 | 9.8 | 4 | 9.5 | 4 | 38.0 | 3 | 43.7 |
| 4558 | 6 | 6.3 | 6 | 6.2 | 4 | 11.8 | 4 | 11.5 | 4 | 44.2 | 4 | 43.8 |
| 4559 | 6 | 6.5 | 6 | 6.2 | 4 | 11.0 | 4 | 10.5 | 4 | 44.5 | 4 | 45.2 |
| 4560 | 8 | 7.2 | 5 | 6.8 | 4 | 11.8 | 4 | 10.8 | 4 | 45.0 | 4 | 44.0 |
| 4561 | 3 | 7.0 | 8 | 5.9 | 3 | 11.0 | 5 | 9.4 | 3 | 44.0 | 5 | 43.4 |
| 4562 | 7 | 5.9 | 7 | 6.0 | 4 | 8.5 | 4 | 9.2 | 4 | 41.8 | 4 | 41.2 |
| 4563 | 5 | 6.2 | 6 | 5.8 | 4 | 6.8 | 4 | 6.0 | 4 | 37.0 | 2 | 31.5 |
| 4564 | 2 | 6.5 | 3 | 6.7 | 2 | 11.5 | 3 | 11.7 | 2 | 52.5 | 3 | 51.7 |
| 4565 | 5 | 7.0 | 8 | 7.2 | 4 | 12.8 | 4 | 11.0 | 4 | 46.8 | 4 | 48.0 |
| 4566 | 0 | - | 1 | 8.0 | - | - | 1 | 8.0 | - | - | 1 | 49.0 |
| 4567 | 5 | 7.2 | 5 | 7.0 | 4 | 13.0 | 4 | 11.8 | 4 | 48.2 | 4 | 49.5 |
| 4568 | 9 | 6.0 | 5 | 6.0 | 4 | 11.2 | 4 | 11.5 | 4 | 40.5 | 4 | 38.5 |
| 4569 | 9 | 5.9 | 6 | 6.0 | 3 | 8.7 | 1 | 8.0 | 3 | 40.0 | 1 | 40.0 |
| 4570 | 2 | 7.0 | 6 | 6.5 | 2 | 12.5 | 6 | 10.3 | 2 | 48.5 | 4 | 45.2 |
| 4571 | 1 | 6.0 | 4 | 6.2 | 1 | 13.0 | 4 | 12.2 | 1 | 58.0 | 4 | 54.2 |
| 4572 | 10 | 5.7 | 2 | 5.0 | 6 | 10.7 | 2 | 9.5 | 5 | 42.0 | 2 | 37.5 |
| 4573 | 6 | 5.2 | 7 | 5.1 | 0 | - | 0 | - | - | - | - | - |
| 4574 | 5 | 5.8 | 5 | 5.2 | 4 | 10.0 | 4 | 10.2 | 2 | 54.0 | 2 | 51.5 |
| Mean | 6 | 6.3 | 6 | 6.2 | 4 | 11.0 | 4 | 10.2 | 3 | 44.8 | 3 | 44.2 |
| \pm s.d. | | 0.56 | | 0.72 | | 1.68 | | 1.59 | | 5.67 | | 5.63 |

Table No. 2 - Continued

SC-19192

| MATERNAL RAT NUMBER | AT 24 HOURS | | | | AT FOUR DAYS | | | | AT WEANING | | | |
|------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | MALES | | FEMALES | | MALES | | FEMALES | | MALES | | FEMALES | |
| | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT |
| GROUP NO. 2 | | | | | | | | | | | | |
| 4575 | 6 | 6.2 | 6 | 5.8 | 4 | 10.2 | 4 | 9.2 | 4 | 44.2 | 4 | 40.2 |
| 4576 | 5 | 6.8 | 8 | 6.2 | 4 | 11.0 | 4 | 11.2 | 4 | 42.2 | 4 | 40.8 |
| 4577 | 2 | 6.5 | 6 | 6.2 | 2 | 12.0 | 6 | 11.8 | 2 | 49.0 | 6 | 49.8 |
| 4578 | 9 | 6.0 | 6 | 6.8 | 4 | 12.0 | 3 | 10.0 | 3 | 55.3 | 0 | - |
| 4579 | 8 | 6.4 | 6 | 5.8 | 4 | 8.5 | 4 | 8.8 | 3 | 44.0 | 2 | 41.0 |
| 4580 | 8 | 5.9 | 4 | 5.5 | 4 | 10.8 | 4 | 10.5 | 2 | 43.0 | 4 | 44.2 |
| 4581 | 1 | 9.0 | 1 | 9.0 | 1 | 12.0 | 1 | 13.0 | 1 | 52.0 | 1 | 52.0 |
| 4582 | 5 | 6.8 | 5 | 6.8 | 4 | 11.0 | 4 | 11.2 | 4 | 42.8 | 4 | 42.0 |
| 4583 | 5 | 6.6 | 10 | 6.1 | 4 | 10.5 | 4 | 9.2 | 4 | 35.0 | 4 | 37.0 |
| 4584 | 7 | 5.7 | 4 | 5.8 | 4 | 7.8 | 4 | 8.0 | 4 | 44.8 | 4 | 44.5 |
| 4587 | 0 | - | 4 | 6.5 | - | - | 3 | 7.3 | - | - | 2 | 36.0 |
| 4588 | 4 | 6.8 | 7 | 6.6 | 4 | 11.5 | 4 | 11.0 | 4 | 40.0 | 4 | 39.0 |
| 4589 | 4 | 6.2 | 9 | 6.1 | 4 | 11.8 | 4 | 11.5 | 4 | 41.8 | 3 | 40.7 |
| 4590 | 5 | 7.4 | 7 | 7.0 | 4 | 11.5 | 4 | 11.5 | 4 | 43.0 | 4 | 40.2 |
| 4591 | 7 | 6.3 | 6 | 6.0 | 4 | 10.0 | 4 | 8.8 | 4 | 43.0 | 4 | 44.5 |
| 4592 | 7 | 6.0 | 5 | 5.2 | 4 | 11.5 | 4 | 10.8 | 4 | 46.0 | 4 | 41.0 |
| 4593 | 5 | 6.6 | 4 | 6.0 | 4 | 11.2 | 4 | 10.2 | 4 | 44.0 | 4 | 42.5 |
| Mean | 5 | 6.6 | 6 | 6.3 | 4 | 10.8 | 4 | 10.2 | 3 | 44.8 | 3 | 42.2 |
| ± s.d. | | 0.77 | | 0.84 | | 1.22 | | 1.50 | | 4.68 | | 4.16 |

Table No. 2 - Continued

SC-19192

| MATERNAL RAT NUMBER | AT 24 HOURS | | | | AT FOUR DAYS | | | | AT WEANING | | | |
|------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | MALES | | FEMALES | | MALES | | FEMALES | | MALES | | FEMALES | |
| | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT |
| GROUP NO. 3 | | | | | | | | | | | | |
| 4595 | 10 | 6.2 | 4 | 6.0 | 4 | 11.2 | 4 | 11.0 | 4 | 43.8 | 4 | 42.0 |
| 4596 | 8 | 7.0 | 8 | 6.8 | 4 | 12.5 | 4 | 12.0 | 4 | 46.2 | 4 | 42.8 |
| 4597 | 2 | 8.0 | 3 | 7.3 | 2 | 13.0 | 3 | 12.0 | 2 | 50.5 | 3 | 49.3 |
| 4598 | 8 | 5.4 | 7 | 5.1 | 4 | 9.2 | 4 | 8.5 | 3 | 40.3 | 4 | 37.2 |
| 4599 | 2 | 6.0 | 7 | 5.4 | 2 | 9.5 | 6 | 9.7 | 0 | - | 0 | - |
| 4600 | 5 | 5.8 | 7 | 5.1 | 4 | 10.5 | 4 | 11.0 | 4 | 46.8 | 4 | 45.0 |
| 4601 | 3 | 5.7 | 10 | 4.9 | 3 | 11.7 | 5 | 10.8 | 3 | 52.7 | 5 | 51.0 |
| 4602 | 7 | 6.0 | 7 | 5.7 | 4 | 10.5 | 4 | 10.0 | 4 | 43.2 | 4 | 40.2 |
| 4603 | 5 | 5.6 | 8 | 5.2 | 4 | 9.8 | 4 | 9.8 | 4 | 50.5 | 4 | 48.2 |
| 4604 | 4 | 7.8 | 7 | 7.4 | 4 | 15.2 | 4 | 14.0 | 4 | 42.8 | 4 | 42.2 |
| 4605 | 7 | 6.4 | 9 | 6.0 | 4 | 11.5 | 4 | 11.2 | 4 | 41.5 | 4 | 39.2 |
| 4606 | 7 | 7.1 | 4 | 6.8 | 4 | 14.5 | 4 | 12.2 | 4 | 48.8 | 4 | 46.8 |
| 4607 | 6 | 6.7 | 7 | 6.7 | 3 | 14.7 | 4 | 13.5 | 3 | 47.0 | 4 | 46.5 |
| 4608 | 7 | 6.6 | 6 | 6.5 | 4 | 13.5 | 4 | 13.5 | 4 | 53.8 | 4 | 52.8 |
| 4609 | 8 | 6.1 | 6 | 5.8 | 4 | 11.0 | 4 | 9.5 | 4 | 41.0 | 4 | 39.2 |
| 4610 | 6 | 6.2 | 8 | 6.4 | 4 | 9.5 | 4 | 9.2 | 4 | 44.2 | 3 | 44.7 |
| 4613 | 6 | 5.0 | 8 | 5.2 | 4 | 7.8 | 4 | 8.5 | 4 | 31.8 | 3 | 30.7 |
| 4614 | 9 | 6.4 | 4 | 5.8 | 4 | 10.5 | 4 | 9.8 | 4 | 53.5 | 4 | 53.0 |
| Mean | 6 | 6.3 | 7 | 6.0 | 4 | 11.4 | 4 | 10.9 | 4 | 45.8 | 4 | 44.2 |
| ±s.d. | | 0.78 | | 0.78 | | 2.08 | | 1.69 | | 5.68 | | 5.92 |

Table No. 2 - Continued

SC-19192

| MATERNAL RAT NUMBER | AT 24 HOURS | | | | AT FOUR DAYS | | | | AT WEANING | | | |
|------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | MALES | | FEMALES | | MALES | | FEMALES | | MALES | | FEMALES | |
| | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT | NO. OF PUPS | MEAN WEIGHT |
| GROUP NO. 4 | | | | | | | | | | | | |
| 4615 | 6 | 6.5 | 4 | 5.2 | 4 | 10.0 | 2 | 11.5 | 3 | 43.3 | 2 | 41.0 |
| 4616 | 1 | 7.0 | 8 | 6.9 | 1 | 6.0 | 7 | 7.4 | 0 | - | 2 | 38.5 |
| 4617 | 7 | 6.4 | 5 | 6.4 | 4 | 11.0 | 4 | 11.2 | 4 | 43.5 | 4 | 43.0 |
| 4618 | 5 | 5.8 | 9 | 5.4 | 4 | 11.0 | 4 | 10.5 | 4 | 38.8 | 4 | 37.5 |
| 4619 | 9 | 5.6 | 6 | 5.3 | 4 | 11.0 | 4 | 10.8 | 4 | 44.8 | 4 | 45.0 |
| 4620 | 7 | 6.7 | 7 | 5.9 | 4 | 12.5 | 4 | 10.8 | 4 | 45.0 | 4 | 44.5 |
| 4621 | 5 | 5.0 | 9 | 4.9 | 4 | 8.2 | 4 | 9.0 | 4 | 46.0 | 4 | 45.0 |
| 4622 | 9 | 6.0 | 6 | 5.8 | 4 | 12.0 | 4 | 11.0 | 4 | 47.8 | 4 | 47.5 |
| 4623 | 6 | 6.0 | 7 | 5.7 | 4 | 10.5 | 4 | 10.5 | 4 | 38.8 | 4 | 38.5 |
| 4624 | 10 | 6.0 | 4 | 5.8 | 4 | 11.0 | 4 | 10.2 | 4 | 38.8 | 4 | 39.0 |
| 4625 | 5 | 6.0 | 9 | 5.6 | 4 | 10.0 | 4 | 10.8 | 4 | 36.2 | 4 | 35.2 |
| 4626 | 4 | 7.0 | 7 | 6.3 | 4 | 12.8 | 3 | 11.3 | 4 | 43.0 | 3 | 42.0 |
| 4627 | 4 | 7.0 | 6 | 7.2 | 4 | 14.0 | 4 | 13.0 | 4 | 47.0 | 4 | 46.8 |
| 4628 | 11 | 6.5 | 2 | 6.5 | 6 | 12.0 | 2 | 11.0 | 6 | 42.8 | 2 | 39.0 |
| 4629 | 2 | 7.0 | 0 | - | 0 | - | - | - | - | - | - | - |
| 4630 | 2 | 7.5 | 8 | 6.5 | 2 | 14.5 | 6 | 11.2 | 2 | 56.0 | 4 | 52.5 |
| 4631 | 3 | 6.7 | 2 | 6.0 | 3 | 13.7 | 2 | 15.0 | 3 | 50.0 | 2 | 51.5 |
| 4632 | 6 | 6.7 | 6 | 6.7 | 4 | 12.2 | 4 | 12.0 | 4 | 54.2 | 4 | 52.0 |
| 4633 | 5 | 6.4 | 7 | 6.0 | 4 | 13.0 | 4 | 12.8 | 4 | 41.0 | 4 | 38.5 |
| Mean | 6 | 6.4 | 6 | 6.0 | 4 | 11.4 | 4 | 11.1 | 4 | 44.5 | 4 | 43.2 |
| ±s.d. | | 0.60 | | 0.62 | | 2.08 | | 1.58 | | 5.38 | | 5.30 |