

**SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE**

**Pathology-Toxicology  
Project No. 1218**

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SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

J. F. Vonduska, R. E. Schroeder,\* and A. Mitchell

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INTRODUCTION

The purpose of this study was to evaluate the embryotoxic and teratogenic potential of SC-18862 (aspartame) when administered by means of dietary incorporation to the pregnant albino mouse during the period of fetal organogenesis. Such a study is designated as a Segment II protocol of the Teratology-Reproduction profile. This study was conducted to provide additional safety data on SC-18862, a nutritive substance with intense sweetness.

METHODS

Material evaluated.

SC-18862 is a fine white powder with the chemical name of L-aspartyl-L-phenylalanine methyl ester. Lot No. 59687, Q.C. C0075, was employed in this study and was considered 100% pure for the purpose of dosage calculation. This lot contained 0.29% of SC-19192 (a diketopiperazine), a conversion product of SC-18862.

\* This author left Searle in June, 1975. He performed/supervised a significant portion of the study and therefore deserves recognition as an author, but was not available for final review of the report.

### Animals, housing and diet.

One hundred forty-four virgin female Charles River CD-1 mice were employed. These mice were  $70 \pm 5$  days of age when mating was initiated.

Thirty-six males of the same strain, taken from a breeding colony maintained in this laboratory, were used solely for breeding purposes.

During a two-week acclimatization period, females were housed in groups of four in suspended wire mesh cages. Animal quarters were air-conditioned, with thermostats set to maintain 72°F temperature continuously; fluorescent lighting was provided 12 hours daily.

Mated females were housed individually in suspended wire mesh cages. All cages were fitted with four-ounce glass jars which served as feeders. The basal diet employed was Purina Rat Diet (Ralston Purina Co., St. Louis, Mo.). This diet and chlorinated tap water were continuously available.

### Experimental design.

Prior to mating the 144 female mice were equally distributed among the four experimental groups by simple randomization procedures.<sup>1</sup> Daily dosage levels intended for the various test groups are presented below:

Treatment Group	No. of Females	Intended Daily Dose Level (g/kg)
Control	36	0
Low Dose	36	1.0
Medium Dose	36	2.0
High Dose	36	4.0

Compound was administered by incorporation in the diet. Treatment began on post-mating day 6 and continued through post-mating day 15. On post-mating day 18 the females were sacrificed and a hysterotomy performed. Fetuses were recovered for detailed anatomical examinations.

#### Mating procedure.

For mating purposes females were distributed into mating units. Each unit contained one male and four females, one from each experimental group, which were identified by tail painting. Each evening (4:30 p.m.) from Wednesday to Sunday inclusive, the appropriate male was placed into each mating unit. It was removed the following morning and females were examined for the presence of a copulatory plug, and that day was designated day 0 of gestation. Mated females were removed from the mating unit and housed individually.

This procedure continued until at least 32 females from each experimental group had mated. A four-week mating period was necessary.

#### Compound formulation, administration and dosage calculation.

Compound was administered by dietary incorporation in powdered Purina Rat Diet from gestation days 6 through 15 inclusive. The concentrations of SC-18862 in the diet were 0.75, 1.50 and 3.0% (w/w) which were intended to supply dosages of 1.0, 2.0 and 4.0 g/kg for the low, medium and high dose groups, respectively, to mice weighing 30 grams and consuming four grams of food daily.

#### Observations and records on mated females.

Females were examined daily for morbidity, mortality and behavioral irregularities. These observations were generally performed in conjunction with recording daily food consumption. Body weights were recorded on gestation days 0, 3, 6, 10, 13, 15 and 18.

#### Terminal observations.

On gestation day 18, all females were sacrificed by carbon dioxide inhalation. The abdominal cavity was opened, the uterine horns exposed and the number of fetuses and resorption sites recorded. Additionally, the relative position of each implantation along the uterine horns was recorded. Subsequently, fetuses were removed from the uterus and fetal viability was determined on the basis of respiratory movements, skin color and movements of the extremities and head.

Fetuses designated for visceral examination were preserved in Bouin's solution. Fetuses designated for skeletal examination were preserved in 95% aqueous ethyl alcohol, macerated with 2.5% aqueous potassium hydroxide, stained with a saturated aqueous solution of Alizarin Red S, which was differentiated with Mall's solution. The fetuses were then stored in glycerin.

Fetal external examination. Sex, weight and crown-rump distance (CRD) were recorded for each fetus. Fetuses were then given a thorough gross external examination prior to being euthanized and preserved intact in a fixative solution.

Fetal soft-tissue examination. Approximately one-third of the fetuses from each litter were fixed in Bouin's solution for subsequent examination by the free-hand sectioning technique of Wilson,<sup>2</sup> as follows:

Head: Four parallel tissue slices, approximately 1 mm thick, were prepared in a transverse plane and were examined for malformations of the palate, nasal cavities, eyes and brain.

Thorax: Two parallel slices, somewhat thinner than 1 mm, were made in a transverse plane starting at the shoulders and proceeding caudally to the diaphragm. These slices were examined for malformations of the thymus, heart, lungs, esophagus, trachea, diaphragm and major blood vessels.

Abdomen: One slice was made approximately 2 mm caudal to the diaphragm and was examined for malformations of the liver, aorta, spinal cord and stomach. A second slice was made at the level of the renal pelvis and was examined for malformations of the spinal cord, aorta, intestinal tract and kidneys. Structures found in the pelvic cavity (i.e., ureters, bladder and reproductive tract) were examined in situ after removal of the intestines.

Tissue slices were examined under a dissecting microscope (7X). All tissue slices from control and treated fetuses were then transferred to glass vials filled with 70% ethanol for temporary storage.

Fetal skeletal examination. The remaining fetuses (approximately two-thirds of each litter) were preserved in 95% ethanol for subsequent skeletal staining by the Alizarin Red S staining technique.<sup>3</sup> Following gross examination of the internal organs, these fetuses were eviscerated, and the soft-tissues macerated and cleared in 2.5% aqueous potassium hydroxide solution.

Skeletal structures were then stained with Alizarin Red S and the stained preparations were stored in 100% glycerin (to which several crystals of thymol were added to reduce microbial growth). Such preparations were examined under a dissecting microscope (7X) for malformations. The number and size of sternebrae, degree of closure of cranial ossifications, number of metacarpals, metatarsals and corresponding phalanges, etc., were recorded. All treated and control skeletal preparations were then placed in temporary storage.

#### Statistical procedures employed.

The means and standard errors (S.E.) of the various measured parameters were calculated for each experimental group.

The two-tailed Student's t-test<sup>4</sup> ( $p < 0.05$ ) was used to analyze mean maternal body weight data at each measurement interval, daily mean food consumption data, mean litter size and resorption data and mean fetal body weight and CRD data.

The following parameters were analyzed by the Chi-Square Test<sup>5</sup> ( $p < 0.05$ ): maternal survival and conception rates, the incidences of litters containing fetuses only, both fetuses and resorption sites, or resorption sites only, and fetal sex ratios.

The litter and fetal incidence of major malformations and certain skeletal variants was analyzed by the Fisher Exact test<sup>6</sup> ( $p < 0.05$ ).

## RESULTS

### Maternal observations.

Survival and conception data. Survival and conception rates for the control, low, medium and high dose groups are shown in the following table. The conception rate of the treated groups did not differ significantly from that of the control group.

	Treatment Group			
	Control	Low	Medium	High
<u>No. of Females</u>				
Mated:	35	33	32	32
Surviving to post-mating day 18:	35	33	32	32
Pregnant:	27	25	27	21
Non-pregnant:	8	8	5	11
Maternal Survival Rate (%):	100	100	100	100
Conception Rate* (%):	77.1	75.8	84.4	65.6

$$* \text{ Conception Rate} = \frac{\text{No. of Females Pregnant}}{\text{No. of Females Mated}} \times 100.$$

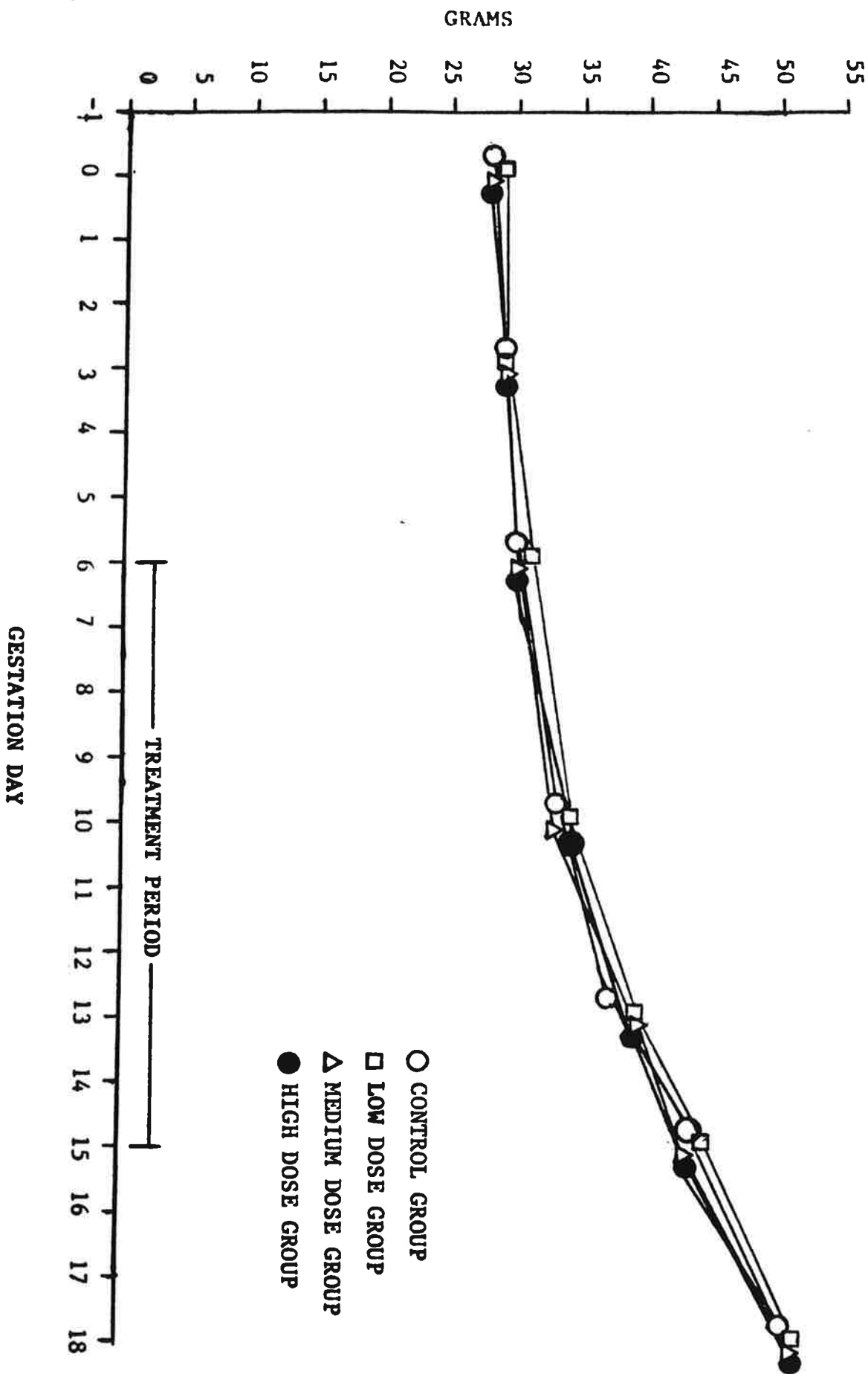
Daily observations of the mated females for physical or behavioral irregularities revealed no unusual findings.

Body weight data. Group mean body weight data for the pregnant females during representative days of the gestation period are summarized in Figure 1. Individual and group mean body weights are presented in Appendix I, Table 1. No significant differences were found between the control and each of the treated groups at any measurement interval using the Student's t-test.

Figure 1

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
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MEAN MATERNAL BODY WEIGHT DATA



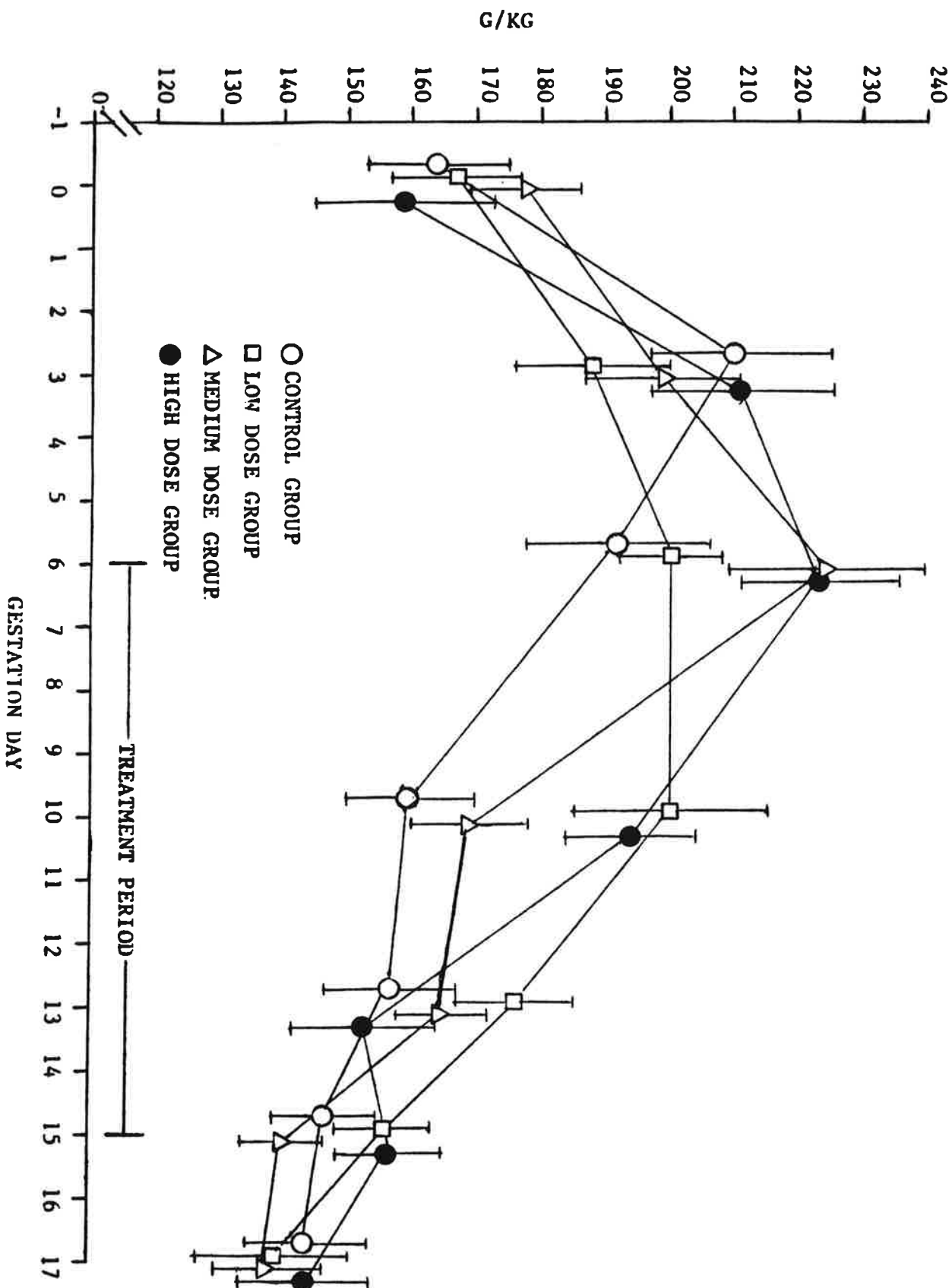
Food consumption data. Group mean food consumption data for the pregnant females on those representative days during gestation when maternal body weights were recorded are summarized in Figure 2. Appendix I, Table 2 contains individual daily maternal food consumption data and group mean food consumption data on each day during the treatment period and on representative days before and after the treatment period. Significant differences as detected by the Student's t-test are indicated in Appendix I, Table 2. On gestation day 7, food consumption for the low dose group was significantly greater than that of the control group and was attributed to random variation. On gestation day 10, there was a transitory drop in food consumption of the control group. No additional significant differences in food consumption were detected.

Test compound consumption. Individual and mean consumption of SC-18862 by the pregnant females during each day of gestation and over the entire treatment period is presented in Appendix I, Table 3. The pregnant animals actually consumed dose levels of 1.4, 2.7 and 5.7 g/kg for the low, medium and high dose groups, respectively, which are approximately 40% more than the originally intended doses of 1.0, 2.0 and 4.0 g/kg.

Figure 2

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
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MATERNAL FOOD CONSUMPTION DATA  
(Mean  $\pm$  S.E.)



Abortions and premature deliveries. An aborted pregnancy, as indicated by the presence of vaginal bleeding on post-mating day 13, was observed in control female 117. At autopsy on post-mating day 18, the left uterine horn contained what appeared to be three resorption sites or sites of former placental attachment, and the right horn contained seven.

Premature delivery is indicated by the presence of delivered live or dead pups prior to but near the time of anticipated delivery. Low dose female 236 delivered one dead and three live pups on gestation day 18. At autopsy, each uterine horn was noted to contain five sites of placental attachment. Medium dose female 308 delivered one partially cannibalized and nine live pups on gestation day 18. At autopsy, the left uterine horn was found to contain four sites of placental attachment and the right horn six. The prematurely delivered pups were examined grossly and discarded. Data derived from pregnant females delivering their litters prematurely or aborting was not included in calculations of means or in statistical comparisons which involved litter size, fetal size or malformation incidence.

Hysterotomy data. A total of 35 control, 33 low, 32 medium and 32 high dose females were sacrificed near term on post-mating day 18. Gross examination of the contents of the thoracic and abdominal cavities of each of these females revealed no unusual findings.

A summary of the uterine implantation data is presented in Table 1; implantation data for individual females are presented in Appendix I, Table 4. No significant differences existed in the proportions

of females whose litters contained fetuses only, both fetuses and resorption sites, or resorption sites only, when the control group was compared to each of the treated groups. The mean litter size and mean number of resorption sites per litter did not differ significantly between the control group and each of the treated groups.

Five dead fetuses, one each from the control and low dose groups and three from the medium dose group, were recovered from females sacrificed near term. Females whose in utero litter contained a dead fetus are indicated in Appendix I, Table 4.

Fetal body weight and crown-rump distance (CRD) data are summarized in Table 2. Fetal body weight and CRD data reported as means per individual litter are presented in Appendix I, Table 4. No significant differences in male and female fetal body weight or CRD data were present between the control group and each of the treated groups.

Table 1

SC-18362: AN EVALUATION OF EMBRYOTOXIC AND  
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Treatment Group	No. of Pregnant Females <sup>1</sup>	No. of Litters <sup>2</sup>	Pregnant Females With			Premature Deliveries	Litter Size <sup>3</sup> (Mean $\pm$ S.E.)	No. of Resorption Sites Per Litter (Mean $\pm$ S.E.)
			Fetuses Only	Fetuses and Resorption Sites	Resorption Sites Only			
Control	27	25	6	19	2 <sup>†</sup>	0	10.0 $\pm$ 0.6	1.4 $\pm$ 0.2
Low Dose	25	24	6	18	0	1	10.5 $\pm$ 0.5	1.2 $\pm$ 0.2
Medium Dose	27	25	6	19	1	1	10.4 $\pm$ 0.4	1.6 $\pm$ 0.3
High Dose	21	20	8	12	1	0	10.2 $\pm$ 0.4	1.2 $\pm$ 0.5

\* Differs significantly from the control group ( $p < 0.05$ ).<sup>1</sup> Females were considered pregnant if their uteri contained one or more sites of placental attachment at autopsy on post-mating day 18.<sup>2</sup> Litter - at least one fetus, viable or nonviable, was necessary to constitute an in utero litter.<sup>3</sup> Number of fetuses per litter (viable and nonviable).<sup>†</sup> One control litter was aborted on gestation day 13. Data from this litter were not included in the calculation of means and statistical comparisons.

Table 2

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
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Fetal Sex Distribution, Body Weight and Crown-Rump Distance (CRD) Data

Treatment Group	No. of Fetuses		Fetal Body Weight (g)		Fetal CRD (cm)	
			Male	Female	Male	Female
	Male	Female	(Mean $\pm$ S.E.)	(Mean $\pm$ S.E.)	(Mean $\pm$ S.E.)	(Mean $\pm$ S.E.)
Control	135	115	1.25 $\pm$ 0.034	1.16 $\pm$ 0.040	2.43 $\pm$ 0.019	2.37 $\pm$ 0.024
Low Dose	113	138	1.28 $\pm$ 0.029	1.22 $\pm$ 0.023	2.43 $\pm$ 0.029	2.38 $\pm$ 0.027
Medium Dose	138	123	1.25 $\pm$ 0.028	1.21 $\pm$ 0.027	2.42 $\pm$ 0.017	2.37 $\pm$ 0.021
High Dose	100	104	1.27 $\pm$ 0.031	1.23 $\pm$ 0.032	2.42 $\pm$ 0.030	2.39 $\pm$ 0.020

\* Mean differs significantly from control ( $p < 0.05$ ).

Fetal examination.

Fetal abnormalities have been categorized into major malformations and skeletal variants, using the Glossary in Appendix II as a guide. All fetuses were examined for externally evident abnormalities. Approximately one-third of the fetuses of each litter were further examined for soft tissue abnormalities<sup>2</sup> and two-thirds for skeletal abnormalities.<sup>3</sup> The number of fetuses and litters examined for external, soft tissue and skeletal abnormalities are presented in Appendix I, Table 5. In addition to the fetuses listed in this table, several pups delivered prematurely were recovered. The condition of the pups dictated that only an external examination could be performed, after which the pups were discarded. No unusual findings were noted in these pups.

The incidences of major malformations which were detected in fetuses recovered at hysterotomy were as follows:

Control group - one of 250 fetuses (one of 25 litters)

Low dose group - none of 251 fetuses (24 litters)

Medium dose group - one of 261 fetuses (one of 25 litters)

High dose group - none of 204 fetuses (20 litters)

Control group fetus 10803 (viable male) was one of eight fetuses in a litter of 13 of control female 108 examined for skeletal malformations and was found to have a hypoplastic 4th thoracic vertebral centrum, a major malformation. No other major malformations were detected in this group. Major malformations of the vertebrae and ribs are noted to occur with an incidence of 0.07% in the Charles River CD-1 mouse.<sup>7</sup>

Medium dose group fetus 32703 (viable female) was one of a litter of eight fetuses of medium dose female 327, and was noted to have exencephaly, cleft palate and bilaterally open eyes, which are major malformations. These malformations are not unusual in this strain of mouse and occur with a combined incidence of slightly less than 1%.<sup>7</sup> This malformed fetus is therefore considered to be a spontaneous occurrence. No other major malformations were detected in this group.

Normal anatomical variants detected at skeletal examination are presented in Appendix I; Table 6. This table includes only those fetuses examined for skeletal malformations and in which no major malformations of any type were detected. The purpose of this tabulation of ossification data is to assess the degree of skeletal maturation among the various groups, and it is appropriate that seriously malformed fetuses be excluded since it is known that their development has been seriously affected.

Statistical analysis of malformation and skeletal variant data.

The incidence and types of major malformations detected in this study were not unusual for the Charles River CD-1 mouse and were not representative of a teratogenic response. Analysis of the major malformation incidence data using the Fisher Exact Test<sup>6</sup> indicates that the incidence of malformations in the treated groups was not significantly different from that of the control group when compared on both a litter and an individual basis.

The incidence of certain skeletal variants, including reduced skull closure, poorly ossified supraoccipital bones, the presence of 14 pairs of ribs, a split 5th sternebra, a split 6th sternebra, two split sternebrae, more than two split sternebrae, one or more split sternebrae, the presence of an additional sternebra, the presence of any sternebra variant, and the presence of any vertebral variant were compared on a fetal incidence and litter incidence basis, using the Fisher Exact Test<sup>6</sup>. An increased incidence of poorly ossified occipital bones was detected in the medium dose group when the data were compared on a fetal incidence basis. Since this difference is not dose-related, it is attributed to random variation. Significantly lesser numbers of fetuses with additional sternebrae were detected in both the low and high dose groups. These commonly observed variants are attributed to random variation. The number of litters in the high dose group which contained one or more fetuses with one or more split sternebrae was significantly less than observed in the control group and is a random effect as a result of combination of data. No other statistically significant differences in the incidences of skeletal variants were detected.

## SUMMARY AND CONCLUSIONS

This study was conducted to assess the embryotoxic and/or teratogenic potential of SC-18862 (aspartame), a nutritive substance with intense sweetness, in the Charles River CD-1 mouse. Compound was mixed in commercial pulverized rodent diet which was offered to the mated mice from post-mating day 6 through 15, a ten day period. The dose levels consumed were 1.4 (low dose), 2.7 (medium dose) and 5.7 (high dose) g/kg of body weight. The concurrent control group received pulverized rodent diet only. On post-copulation day 18, all females were sacrificed and autopsied. Fetuses were recovered and examined for external, soft tissue and skeletal abnormalities.

Administration of SC-18862 to the Charles River CD-1 mouse by dietary incorporation at levels of up to 5.7 g/kg of body weight from gestation days 6 through 15 was without effect upon maternal survival and conception rates, maternal body weight changes, food consumption, the incidence of abortions and premature deliveries, the proportions of litters that consisted of fetuses only, of both fetuses and resorption sites, or of resorption sites only, mean litter size, mean number of resorptions per litter, mean male and female fetal body weights and crown-rump distances, and the number of major malformations and skeletal variants, when compared on a fetal incidence and a litter incidence basis. All comparisons were made between the control group and each treated group with the level of significance at  $p < 0.05$ .

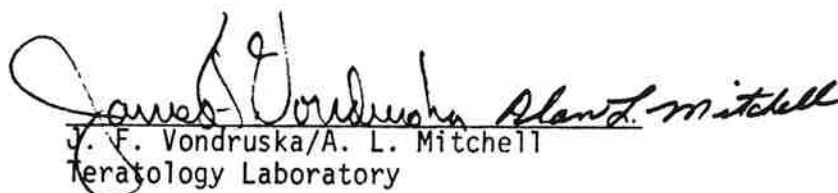
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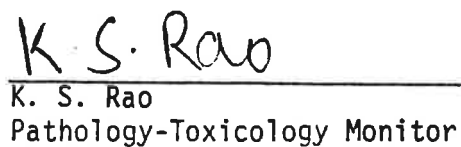
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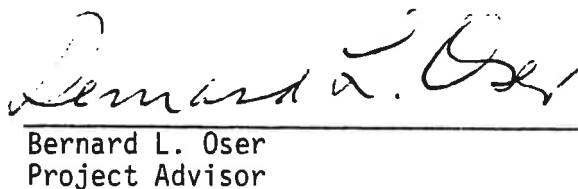
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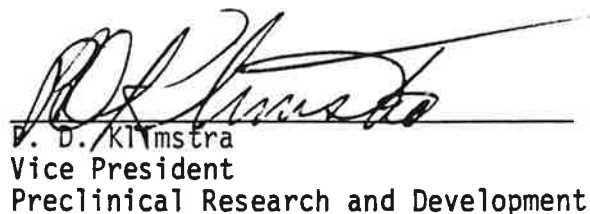
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October 23, 1975


Dr. W. Joseph Potts, Assoc. Director,  
PreClinical Research & Development  
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Box 5110  
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Dear Dr. Potts:

As requested, I have reviewed the protocol and the report of your Path-Tox Project No. 1218S75 entitled "SC-18862: An Evaluation of the Teratogenic Potential in the Mouse".

The protocol appears to have been followed as described and in my opinion the results of the study support the conclusion reached by the authors, viz. that Aspartame was neither teratogenic nor embryotoxic to mice under the test conditions employed.

BLO:b

Cordially,  
  
Bernard L. Oser, Ph.D.

## APPENDIX I

### Individual Maternal and Fetal Data

# APPENDIX I; Table 1

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

## MATERNAL BODY WEIGHT DATA ( G ) (ARITHMETIC MEANS WITH STANDARD ERRORS)

TREATMENT GROUP	NO. OF PREGNANT FEMALES	0	3	6	10	13	15	18
CONTROL	27	28. 0.4	29. 0.4	30. 0.4	33. 0.5	37. 0.9	43. 1.2	50. 1.7
LOW	25	29. 0.5	29. 0.5	31. 0.4	34. 0.5	39. 0.6	44. 0.9	51. 1.2
MEDIUM	27	28. 0.5	29. 0.4	30. 0.4	33. 0.4	39. 0.5	43. 0.9	51. 1.3
HIGH	21	28. 0.3	29. 0.4	30. 0.4	34. 0.7	39. 0.7	43. 0.7	51. 1.3

\* DIFFERENCE STATISTICALLY SIGNIFICANT FROM CONTROL (P < 0.05).

<sup>a</sup>Female Nos. 236 and 308 delivered prematurely on gestation day 18. Data for this day is not included in this table.

## Appendix I; Table 1 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
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## MATERNAL BODY WEIGHT DATA FOR THE CONTROL GROUP (G)

ANIMAL NUMBER	0	3	6	GESTATION DAY			
				10	13	15	18
101	28.	28.	31.	32.	39.	51.	53.
102	27.	28.	30.	32.	39.	45.	54.
104	29.	30.	30.	30.	31.	33.	37.
105	26.	27.	28.	29.	33.	38.	43.
106	29.	30.	31.	34.	39.	46.	54.
107	23.	25.	25.	29.	33.	38.	46.
108	25.	25.	29.	30.	41.	53.	55.
109	27.	28.	29.	30.	35.	40.	49.
111	31.	31.	31.	33.	40.	44.	50.
112	30.	32.	32.	36.	39.	44.	49.
113	26.	29.	32.	34.	39.	44.	54.
114	33.	33.	36.	38.	46.	53.	64.
115	29.	30.	30.	34.	41.	47.	58.
117	28.	28.	29.	28.	23.	34.	34.
118	26.	29.	29.	34.	27.	25.	21.
121	26.	28.	29.	32.	37.	40.	48.
122	28.	30.	31.	35.	39.	43.	45.
123	25.	26.	27.	29.	32.	35.	38.
124	28.	29.	29.	32.	38.	44.	55.
126	29.	30.	34.	36.	42.	49.	60.
128	29.	30.	31.	34.	39.	45.	52.
129	28.	29.	31.	34.	40.	45.	55.
130	29.	29.	30.	33.	40.	44.	53.
132	31.	30.	31.	34.	38.	40.	49.
134	28.	29.	30.	34.	40.	46.	56.

Appendix I; Table 1 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
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ANIMAL NUMBER	MATERNAL BODY WEIGHT DATA FOR THE CONTROL GROUP (G)					
	0	3	6	10	13	15
135	29.	28.	30.	35.	41.	45.
136	28.	26.	27.	32.	36.	41.
MEANS	28.	29.	30.	33.	37.	43.
						50.
						55.
						53.

## Appendix I; Table 1 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

## MATERNAL BODY WEIGHT DATA FOR THE LOW DOSE GROUP (G)

ANIMAL NUMBER	0	3	6	GESTATION DAY				
				10	13	15	18	
201	32.	34.	33.	37.	41.	48.	55.	
202	23.	27.	29.	31.	35.	39.	44.	
203	30.	30.	30.	34.	38.	45.	53.	
204	30.	31.	33.	36.	40.	45.	54.	
205	30.	30.	31.	33.	38.	41.	50.	
206	30.	29.	31.	35.	41.	45.	53.	
208	26.	29.	30.	32.	38.	42.	52.	
210	29.	31.	31.	34.	40.	46.	54.	
211	28.	30.	31.	33.	38.	42.	48.	
213	30.	31.	31.	34.	40.	45.	51.	
214	32.	32.	32.	35.	41.	47.	55.	
218	29.	29.	30.	34.	39.	43.	51.	
221	27.	28.	29.	32.	38.	43.	52.	
222	27.	28.	29.	31.	37.	42.	52.	
223	32.	34.	37.	42.	47.	51.	61.	
225	28.	N.D.	30.	31.	35.	37.	43.	
226	30.	33.	32.	34.	42.	48.	54.	
227	32.	32.	33.	35.	40.	44.	55.	
228	28.	28.	30.	33.	37.	42.	49.	
229	28.	27.	30.	34.	41.	43.	61.	
232	25.	27.	30.	33.	42.	54.	54.	
233	28.	27.	30.	32.	38.	44.	53.	
234	30.	29.	31.	35.	38.	42.	47.	
235	26.	25.	28.	28.	32.	35.	41.	
236	27.	27.	28.	30.	34.	35.	32.	
MEANS	29.	30.	31.	34.	39.	44.	51.	

N.D. = No Data.

## Appendix I; Table 1 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

## MATERNAL BODY WEIGHT DATA FOR THE MEDIUM DOSE GROUP (G)

ANIMAL NUMBER	GESTATION DAY						
	0	3	6	10	13	15	18
301	30.	29.	31.	33.	38.	40.	46.
302	28.	30.	30.	33.	39.	45.	53.
304	27.	28.	29.	30.	33.	35.	38.
305	26.	25.	28.	30.	38.	51.	51.
306	28.	28.	29.	32.	36.	43.	50.
307	36.	33.	32.	37.	41.	49.	52.
308	27.	30.	29.	33.	39.	45.	N.D.
309	29.	31.	32.	35.	39.	45.	54.
312	26.	27.	28.	31.	36.	40.	48.
313	24.	27.	28.	31.	38.	43.	53.
314	29.	29.	30.	33.	41.	46.	57.
315	29.	30.	32.	37.	42.	49.	58.
316	25.	25.	26.	30.	34.	38.	45.
317	27.	27.	30.	33.	39.	45.	55.
319	28.	30.	31.	34.	40.	44.	52.
320	28.	30.	30.	34.	39.	44.	52.
323	33.	N.D.	35.	39.	45.	51.	61.
324	30.	N.D.	33.	35.	41.	44.	53.
327	25.	25.	25.	31.	36.	41.	49.
329	27.	29.	29.	34.	38.	43.	50.
330	27.	29.	30.	34.	39.	43.	53.
331	27.	28.	30.	33.	39.	43.	53.
332	30.	31.	31.	35.	38.	42.	49.
333	29.	29.	31.	34.	39.	42.	52.
334	27.	28.	31.	34.	40.	45.	54.

N.D. = No Data.

## Appendix I; Table 1 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

ANIMAL NUMBER	0	MATERNAL BODY WEIGHT DATA FOR THE MEDIUM DOSE GROUP (G)					
		3	6	10	GESTATION DAY		
				13	15	18	
335	30.	30.	30.	35.	38.	42.	51.
336	28.	28.	29.	31.	37.	28.	28.
MEANS	28.	29.	30.	33.	39.	43.	51.

## Appendix I; Table 1 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

## MATERNAL BODY WEIGHT DATA FOR THE HIGH DOSE GROUP (G)

ANIMAL NUMBER	0	3	6	GESTATION DAY			
				10	13	15	18
401	27.	28.	26.	30.	33.	37.	42.
402	26.	26.	27.	30.	36.	36.	47.
403	N.D.	30.	31.	41.	38.	42.	51.
405	27.	28.	29.	32.	36.	40.	48.
407	29.	28.	29.	33.	48.	45.	53.
408	28.	29.	30.	33.	37.	43.	52.
411	26.	24.	27.	30.	35.	47.	45.
412	27.	26.	27.	31.	35.	41.	47.
414	29.	29.	30.	34.	41.	48.	56.
415	29.	30.	30.	33.	37.	42.	52.
416	30.	28.	32.	36.	40.	46.	56.
417	27.	28.	30.	34.	40.	40.	54.
419	29.	29.	32.	36.	43.	44.	57.
420	29.	31.	33.	35.	41.	46.	55.
422	N.D.	30.	31.	43.	38.	43.	50.
424	29.	30.	33.	37.	42.	47.	56.
426	29.	28.	28.	33.	38.	42.	53.
428	27.	28.	30.	33.	38.	42.	33.
430	28.	28.	29.	31.	36.	39.	46.
432	29.	30.	30.	34.	40.	44.	54.
436	29.	31.	32.	35.	42.	48.	59.
MEANS	28.	29.	30.	34.	39.	43.	51.

N.D. = No Data.

# APPENDIX 1 TABLE 2.

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

MATERNAL FOOD CONSUMPTION DATA (G/KG/DAY)  
(ARITHMETIC MEANS WITH STANDARD ERRORS)

TREATMENT GROUP	NO. OF PREGNANT FEMALES	GESTATION DAY									
		0	3	6	7	8	9	10	11	12	13
CONTROL	27	164.1 10.9	210.7 13.6	192.4 14.1	197.8 12.6	199.7 11.4	189.9 15.3	159.8 10.1	195.5 10.0	183.2 9.6	157.1 9.8
		167.3 9.6	188.0 11.7	199.9 8.3	239.1* 9.2	205.2 11.3	180.5 10.8	200.0* 14.6	196.3 6.9	195.3 9.6	176.4 9.2
MEDIUM	27	177.6 7.6	199.7 11.7	224.1 15.4	203.9 12.4	208.8 8.3	199.6 12.1	168.8 9.1	191.1 7.7	183.2 8.9	164.7 7.3
		159.0 14.1	211.1 13.6	223.0 12.2	218.1 13.5	201.5 11.0	208.4 16.9	194.2* 10.9	176.4 13.2	200.2 9.3	152.5 10.9
HIGH	21	14.1	13.6	12.2	13.5	11.0	16.9	10.9	13.2	9.3	10.9
		159.0 14.1	211.1 13.6	223.0 12.2	218.1 13.5	201.5 11.0	208.4 16.9	194.2* 10.9	176.4 13.2	200.2 9.3	152.5 10.9
TREATMENT GROUP	NO. OF PREGNANT FEMALES	GESTATION DAY									
		14	15	17							
CONTROL	27	154.4 10.5	146.6 8.3	144.2 8.9							
		168.9 10.2	155.9 7.2	138.8 <sup>a</sup> 11.5							
MEDIUM	27	154.1 6.9	140.8 5.5	138.4 <sup>a</sup> 8.2							
		181.3 9.4	156.6 7.9	144.1 10.3							
HIGH	21	181.3 9.4	156.6 7.9	144.1 10.3							
		181.3 9.4	156.6 7.9	144.1 10.3							

\* DIFFERENCE STATISTICALLY SIGNIFICANT FROM CONTROL ( $P < 0.05$ ).

<sup>a</sup>Female Nos. 236 and 308 delivered prematurely on gestation day 18. Data for this day is not included in this table.

## Appendix I; Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

MATERNAL FOOD CONSUMPTION DATA FOR THE CONTROL GROUP  
(G/KG)

ANIMAL NUMBER	0	1	2	GESTATION DAY					7	8	9
				3	4	5	6				
101	175.0	257.1	235.7	253.6	175.0	242.9	319.4		132.3	125.8	274.2
102	N.D.	263.0	N.D.	267.9	N.D.	N.D.	N.D.		N.D.	143.3	80.0
104	182.8	231.0	172.4	203.3	176.7	180.0	N.D.		183.3	N.D.	N.D.
105	92.3	153.8	173.1	163.0	151.9	163.0	160.7		214.3	178.6	128.6
106	155.2	179.3	237.9	173.3	176.7	240.0	193.5		203.2	171.0	187.1
107	269.6	182.6	273.9	384.0	148.0	N.D.	192.0		212.0	220.0	N.D.
108	108.0	200.0	272.0	312.0	184.0	296.0	179.3		86.2	210.3	300.0
109	137.0	192.6	122.2	185.7	171.4	160.7	141.4		144.8	165.5	196.6
111	100.0	206.5	296.8	129.0	238.7	264.5	N.D.		N.D.	312.9	154.8
112	120.0	206.7	206.7	N.D.	231.3	128.1	181.3		215.6	N.D.	187.5
113	200.0	192.3	207.7	255.2	158.6	224.1	N.D.		209.4	N.D.	209.4
114	124.2	187.9	N.D.	N.D.	N.D.	224.2	183.3		169.4	191.7	N.D.
115	N.D.	179.3	251.7	183.3	130.0	N.D.	163.3		203.3	N.D.	N.D.
117	171.4	235.7	260.7	189.3	228.6	285.7	217.2		224.1	244.8	48.3
118	142.3	219.2	188.5	131.0	82.8	148.3	131.0		75.9	151.7	148.3
121	173.1	180.8	192.3	250.0	182.1	192.9	172.4		317.2	306.9	N.D.
122	192.9	235.7	239.3	153.3	223.3	150.0	309.7		245.2	200.0	254.8
123	N.D.	164.0	264.0	N.D.	188.5	N.D.	N.D.		N.D.	N.D.	N.D.
124	N.D.	164.3	200.0	165.5	165.5	210.3	248.3		255.2	234.5	203.4
125	269.0	151.7	220.7	156.7	166.7	233.3	167.6		255.9	252.9	N.D.
128	N.D.	13.8	10.3	N.D.	236.7	163.3	258.1		254.8	200.0	141.9
129	164.3	200.0	110.7	293.1	200.0	175.9	258.1		N.D.	196.8	148.4
130	N.D.	206.9	155.2	206.9	193.1	217.2	200.0		193.3	210.0	223.3
132	N.D.	N.D.	N.D.	160.0	N.D.	N.D.	29.0		219.4	135.5	N.D.
134	153.6	150.0	142.9	N.D.	N.D.	172.4	N.D.		213.3	106.7	193.3

N.D. = No Data.

Appendix I; Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

MATERNAL FOOD CONSUMPTION DATA FOR THE CONTROL GROUP  
(G/KG)

ANIMAL NUMBER	0	1	2	GESTATION DAY					8	9
				3	4	5	6	7		
135	137.9	158.6	220.7	200.0	182.1	N.D.	123.3	80.0	253.3	286.7
136	214.3	142.9	150.0	219.2	169.2	N.D.	211.1	240.7	181.5	240.7
MEANS	164.1	186.8	200.2	210.7	180.9	203.6	192.4	197.8	199.7	189.9

N.D. = No Data.

## Appendix I; Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

MATERNAL FOOD CONSUMPTION DATA FOR THE CONTROL GROUP  
(G/KG)

ANIMAL NUMBER	10	11	12	GESTATION DAY					16	17
				13	14	15				
101	146.9	N.D.	N.D.	217.9	128.2	145.1			100.0	182.4
102	40.6	96.9	109.4	94.9	92.3	86.7			104.4	97.8
104	90.0	190.0	180.0	196.8	219.4	242.4			184.8	218.2
105	120.7	182.8	231.0	190.9	181.8	110.5			N.D.	123.7
106	211.8	211.8	244.1	138.5	210.3	189.1			137.0	110.9
107	175.9	158.6	203.4	187.9	193.9	126.3			139.5	155.3
108	196.7	213.3	N.D.	209.8	90.2	143.4			113.2	N.D.
109	116.7	153.3	166.7	162.9	180.0	160.0			167.5	155.0
111	233.3	145.5	93.9	145.0	N.D.	145.5			N.D.	N.D.
112	133.3	177.8	205.6	148.7	164.1	193.2			163.6	168.2
113	226.5	211.8	276.5	192.3	128.2	165.9			134.1	106.8
114	N.D.	N.D.	N.D.	N.D.	184.8	156.6			171.7	134.0
115	111.8	217.6	N.D.	N.D.	192.7	138.3			189.4	N.D.
117	N.D.	N.D.	232.1	N.D.	34.8	167.6			279.4	214.7
118	91.2	67.6	132.4	25.9	155.6	180.0			108.0	108.0
121	N.D.	243.8	196.9	232.4	240.5	197.5			120.0	N.D.
122	194.3	182.9	202.9	194.9	210.3	N.D.			141.9	148.8
123	182.8	279.3	N.D.	187.5	225.0	162.9			160.0	217.1
124	196.9	178.1	168.7	157.9	189.5	143.2			159.1	154.5
126	166.7	250.0	163.9	90.5	59.5	55.1			100.0	138.8
128	214.7	252.9	208.8	87.2	159.0	53.3			104.4	53.3
129	129.4	185.3	105.9	125.0	67.5	100.0			106.7	71.1
130	166.7	212.1	175.8	160.0	150.0	159.1			200.0	150.0
132	214.7	220.6	167.6	136.8	144.7	162.5			147.5	145.0
134	188.2	200.0	185.3	150.0	155.0	178.3			180.4	137.0

N.D. = No Data.

Appendix I; Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

MATERNAL FOOD CONSUMPTION DATA FOR THE CONTROL GROUP (G/KG)								
ANIMAL NUMBER	GESTATION DAY							
	10	11	12	13	14	15	16	17
135	142.9	228.6	185.7	182.9	114.6	124.4	151.1	142.2
136	143.7	256.3	193.8	152.8	141.7	124.4	151.2	182.9
MEANS	159.9	196.5	183.2	157.1	154.4	146.6	148.6	144.2

N.D. = No Data.

Appendix I; Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

MATERNAL FOOD CONSUMPTION DATA FOR THE LOW DOSE GROUP  
(G/KG)

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9
201	168.7	218.8	N.D.	N.D.	N.D.	179.4	178.8	260.6	N.D.	239.4
202	95.7	160.9	195.7	200.0	170.4	159.3	137.9	172.4	172.4	N.D.
203	230.0	220.0	186.7	210.0	240.0	293.3	N.D.	206.7	283.3	103.3
204	203.3	173.3	136.7	154.8	N.D.	N.D.	N.D.	N.D.	169.7	169.7
205	116.7	143.3	200.0	140.0	123.3	N.D.	203.2	200.0	167.7	154.8
206	N.D.	146.7	183.3	117.2	158.6	234.5	222.6	193.5	209.7	190.3
208	176.9	238.5	188.5	151.7	141.4	N.D.	196.7	203.3	280.0	160.0
210	179.3	200.0	200.0	151.6	225.8	245.2	164.5	293.5	N.D.	200.0
211	264.3	245.4	196.4	136.7	166.7	N.D.	193.5	254.8	251.6	171.0
213	173.3	166.7	220.0	180.6	248.4	296.8	229.0	280.6	N.D.	271.0
214	137.5	190.6	N.D.	231.2	293.7	N.D.	275.0	265.6	N.D.	N.D.
218	175.9	141.4	106.9	144.8	141.4	210.3	N.D.	203.3	160.0	166.7
221	151.9	177.8	174.1	225.0	207.1	N.D.	N.D.	N.D.	N.D.	N.D.
222	111.1	203.7	185.2	232.1	192.9	178.6	172.4	N.D.	N.D.	N.D.
223	109.4	190.6	162.5	138.2	138.2	N.D.	178.4	237.8	173.0	170.3
225	171.4	339.3	203.6	N.D.	N.D.	N.D.	216.7	176.7	N.D.	N.D.
226	190.0	160.0	223.3	N.D.	281.8	N.D.	200.0	271.9	303.1	N.D.
227	134.4	156.3	146.9	134.4	143.8	221.9	215.2	218.2	215.2	127.3
228	N.D.	N.D.	N.D.	285.7	N.D.	N.D.	N.D.	N.D.	216.7	N.D.
229	142.9	264.3	303.6	311.1	277.8	211.1	N.D.	293.3	170.0	N.D.
232	268.0	328.0	376.0	251.9	333.3	207.4	N.D.	N.D.	150.0	236.7
233	167.9	167.9	28.6	185.2	159.3	N.D.	N.D.	260.0	203.3	213.3
234	206.7	146.7	113.3	151.7	200.0	N.D.	N.D.	N.D.	232.3	N.D.
235	138.5	134.6	188.5	N.D.	148.0	N.D.	N.D.	275.0	189.3	164.3
236	133.3	148.1	218.5	214.8	251.9	174.1	214.3	275.0	146.4	150.0
MEANS	167.3	194.3	188.1	188.0	202.1	217.7	199.9	239.1	205.2	180.5

N.D. = No Data.

Appendix I; Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

MATERNAL FOOD CONSUMPTION DATA FOR THE LOW DOSE GROUP  
(G/KG)

ANIMAL NUMBER	10	11	12	GESTATION DAY				16	17
				13	14	15	16		
201	202.7	N.D.	170.3	217.1	N.D.	154.2	195.8	N.D.	
202	225.8	180.6	180.6	182.9	188.6	146.2	74.4	189.7	
203	252.9	N.D.	267.6	147.4	89.5	162.2	N.D.	155.6	
204	125.0	130.6	152.8	135.0	80.0	140.0	88.9	86.7	
205	133.3	203.0	184.8	123.7	131.6	170.7	163.4	153.7	
206	240.0	205.7	182.9	N.D.	224.4	N.D.	173.3	N.D.	
208	125.0	250.0	203.1	178.9	152.6	183.3	166.7	142.9	
210	102.9	167.6	135.3	105.0	N.D.	158.7	210.9	N.D.	
211	387.9	218.2	N.D.	N.D.	134.2	138.1	161.9	173.8	
213	167.6	170.6	132.4	N.D.	N.D.	188.9	206.7	6.7	
214	231.4	N.D.	228.6	248.8	N.D.	174.5	N.D.	25.5	
218	282.4	170.6	182.4	151.3	146.2	165.1	146.5	127.9	
221	159.4	200.0	193.8	150.0	176.3	127.9	127.9	134.9	
222	N.D.	135.5	238.7	202.7	197.3	152.4	150.0	150.0	
223	140.5	164.3	214.3	157.4	155.3	154.9	147.1	156.9	
225	N.D.	203.2	251.6	237.1	268.6	245.9	183.8	N.D.	
226	194.1	N.D.	176.5	161.9	N.D.	135.4	150.0	N.D.	
227	142.9	162.9	231.4	122.5	185.0	152.3	163.6	115.9	
228	239.4	221.2	236.4	210.8	213.5	133.3	145.2	166.7	
229	N.D.	188.2	167.6	N.D.	N.D.	N.D.	N.D.	195.3	
232	130.3	184.8	N.D.	211.9	171.4	127.8	105.6	N.D.	
233	218.8	153.1	140.6	134.2	168.4	145.5	104.5	150.0	
234	225.7	217.1	274.3	200.0	192.1	214.3	178.6	157.1	
235	182.1	232.1	242.9	184.4	184.4	154.3	180.0	171.4	
236	290.0	153.3	103.3	241.2	150.0	60.0	128.6	177.1	
MEANS	200.0	186.3	195.3	176.4	168.9	155.9	152.4	138.8	

N.D. = No Data.

## Appendix I; Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218MATERNAL FOOD CONSUMPTION DATA FOR THE MEDIUM DOSE GROUP  
(G/KG)

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9
301	210.0	220.0	103.3	293.1	N.D.	N.D.	N.D.	N.D.	225.8	177.4
302	N.D.	164.3	196.4	143.3	140.0	N.D.	N.D.	N.D.	203.3	193.3
304	N.D.	244.4	155.6	160.7	128.6	N.D.	231.0	196.6	127.6	144.8
305	157.7	188.5	215.4	212.0	152.0	260.0	350.0	92.9	235.7	228.6
306	110.7	110.7	171.4	135.7	153.6	167.9	317.2	N.D.	293.1	165.5
307	194.4	172.2	202.8	157.6	190.9	248.5	159.4	184.4	250.0	153.1
308	181.5	185.2	N.D.	286.7	N.D.	N.D.	N.D.	N.D.	169.0	217.2
309	165.5	148.3	134.5	122.6	N.D.	N.D.	N.D.	240.6	181.2	21.9
312	180.8	234.6	215.4	N.D.	N.D.	N.D.	246.4	N.D.	253.6	192.9
313	183.3	212.5	233.3	N.D.	211.1	N.D.	N.D.	N.D.	N.D.	N.D.
314	141.4	137.9	N.D.	N.D.	193.1	234.5	250.0	226.7	166.7	240.0
315	203.4	134.5	N.D.	N.D.	N.D.	210.0	181.2	203.1	246.9	221.9
316	188.0	168.0	160.0	236.0	196.0	N.D.	188.5	165.4	200.0	265.4
317	207.4	92.6	222.2	188.9	155.6	44.4	153.3	N.D.	N.D.	N.D.
319	185.7	217.9	196.4	156.7	N.D.	N.D.	283.9	N.D.	N.D.	193.5
320	210.7	167.9	221.4	166.7	140.0	N.D.	170.0	236.7	210.0	260.0
323	124.2	181.8	169.7	254.5	181.8	197.0	171.4	154.3	200.0	251.4
324	196.7	180.0	173.3	270.0	173.3	N.D.	N.D.	169.7	N.D.	N.D.
327	280.0	156.0	212.0	204.0	164.0	N.D.	216.0	N.D.	N.D.	N.D.
329	125.9	214.8	229.6	179.3	117.2	N.D.	N.D.	N.D.	220.7	206.9
330	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	263.3	213.3	280.0
331	148.1	240.7	192.6	153.6	150.0	N.D.	256.7	253.3	183.3	180.0
332	206.7	183.3	176.7	148.4	206.5	209.7	N.D.	267.7	219.4	174.2
333	137.9	189.7	106.9	241.4	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
334	196.3	211.1	177.8	271.4	214.3	182.1	187.1	174.2	193.5	190.3

N.D. = No Data.

Appendix I; Table 2 (cont.)

SC-13862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

MATERNAL FOOD CONSUMPTION DATA FOR THE MEDIUM DOSE GROUP  
(G/KG)

ANIMAL NUMBER	0	1	2	GESTATION DAY					8	9
				3	4	5	6	7		
335	183.3	183.3	236.7	190.0	206.7	N.D.	N.D.	230.0	183.3	233.3
336	142.9	203.6	132.1	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
MEANS	177.6	182.5	184.2	198.7	170.8	194.9	224.1	203.9	208.8	199.6

N.D. = No Data.

## Appendix I, Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218MATERNAL FOOD CONSUMPTION DATA FOR THE MEDIUM DOSE GROUP  
(G/KG)

ANIMAL NUMBER	10	11	12	GESTATION DAY				16	17
				13	14	15	16		
301	197.0	187.9	227.3	155.3	173.7	185.0	177.5	135.0	
302	178.8	187.9	163.6	117.9	117.9	128.9	124.4	102.2	
304	150.0	180.0	173.3	148.5	160.6	162.9	162.9	94.3	
305	156.7	206.7	N.D.	168.4	107.9	133.3	111.8	174.5	
306	187.5	190.6	193.8	227.8	225.0	216.3	223.3	181.4	
307	164.9	N.D.	200.0	234.1	N.D.	106.1	134.7	77.6	
308	206.1	139.4	187.9	128.2	151.3	122.2	184.4	11.1	
309	100.0	85.7	28.6	92.3	94.9	106.7	135.6	84.4	
312	219.4	241.9	193.5	141.7	163.9	152.5	182.5	122.5	
313	254.8	190.3	174.2	152.6	126.3	132.6	134.9	151.2	
314	190.9	197.0	157.6	165.9	100.0	106.5	110.9	150.0	
315	208.1	237.8	148.6	202.4	166.7	93.9	89.8	98.0	
316	163.3	196.7	156.7	217.6	185.3	139.5	176.3	160.5	
317	54.5	175.8	248.5	166.7	184.6	113.3	146.7	142.2	
319	194.1	185.3	152.9	127.5	152.5	143.2	165.9	N.D.	
320	158.8	176.5	185.3	174.4	156.4	145.5	181.8	154.5	
323	151.3	192.3	151.3	177.8	180.0	145.1	131.4	166.7	
324	151.4	200.0	234.3	134.1	187.8	127.3	129.5	165.9	
327	64.5	241.9	209.7	172.2	197.2	151.2	146.3	202.4	
329	158.8	150.0	158.8	136.8	142.1	130.2	120.9	130.2	
330	182.4	152.9	211.8	192.3	102.6	141.9	176.7	118.6	
331	190.9	209.1	224.2	202.6	207.7	172.1	172.1	169.8	
332	185.7	205.7	131.4	136.8	160.5	152.4	159.5	147.8	
333	217.6	226.5	223.5	205.1	174.4	152.4	157.1	185.7	
334	N.D.	179.6	179.4	185.0	135.0	126.7	144.4	131.1	

N.D. = No Data.

Appendix I, Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

MATERNAL FOOD CONSUMPTION DATA FOR THE MEDIUM DOSE GROUP  
(G/KG)

ANIMAL NUMBER	10	11	12	13	14	15	16	17
335	131.4	154.3	191.4	192.1	152.6	116.7	152.4	183.3
336	N.D.	287.1	254.8	91.9	100.0	196.4	185.7	157.1
MEANS	168.8	191.1	183.2	164.7	154.1	140.8	152.6	138.4

N.D. = No Data.

## Appendix I; Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218MATERNAL FOOD CONSUMPTION DATA FOR THE HIGH DOSE GROUP  
(G/KG)

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9
401	288.9	118.5	N.D.	N.D.	157.1	200.0	288.5	192.3	146.2	238.5
402	88.5	N.D.	161.5	257.7	246.2	126.9	318.5	N.D.	296.3	92.6
403	N.D.	N.D.	N.D.	216.7	216.7	76.7	245.2	N.D.	206.5	N.D.
405	N.D.	N.D.	N.D.	178.6	103.6	N.D.	258.6	210.3	179.3	151.7
407	N.D.	231.0	148.3	271.4	207.1	N.D.	189.7	224.1	279.3	N.D.
408	178.6	182.1	142.9	151.7	196.6	193.1	143.3	173.3	136.7	250.0
411	161.5	223.1	265.4	341.7	212.5	266.7	N.D.	118.5	240.7	366.7
412	148.1	137.0	148.1	173.1	173.1	188.5	166.7	192.6	185.2	159.3
414	58.6	289.7	341.4	169.0	175.9	169.0	226.7	256.7	170.0	140.0
415	158.6	137.9	148.3	160.0	180.0	203.3	213.3	293.3	153.3	170.0
416	183.3	176.7	123.3	214.3	157.1	217.9	N.D.	290.6	200.0	237.5
417	151.9	248.1	122.2	257.1	342.9	178.6	300.0	303.3	223.3	N.D.
419	237.9	220.7	265.5	319.3	N.D.	200.0	275.0	281.3	159.4	221.9
420	158.6	196.6	203.4	238.7	193.5	N.D.	157.6	172.7	297.0	N.D.
422	N.D.	N.D.	N.D.	216.7	250.0	123.3	187.1	N.D.	203.2	N.D.
424	162.1	127.6	N.D.	N.D.	N.D.	240.0	178.8	209.1	184.8	190.9
426	124.1	144.8	203.4	146.4	160.7	N.D.	175.0	192.9	200.0	242.9
428	N.D.	N.D.	159.3	171.4	N.D.	N.D.	280.0	N.D.	183.3	N.D.
430	121.4	167.9	171.4	167.9	292.9	175.0	182.8	172.4	275.9	196.6
432	162.1	182.8	148.3	156.7	160.0	200.0	250.0	273.3	180.0	273.3
435	N.D.	N.D.	151.7	N.D.	N.D.	N.D.	200.0	150.0	131.3	193.8
MEANS	158.9	185.6	181.5	211.1	201.5	183.9	223.0	218.0	201.5	208.4

N.D. = No Data.

## Appendix I; Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

MATERNAL FOOD CONSUMPTION DATA FOR THE HIGH DOSE GROUP  
(G/KG)

ANIMAL NUMBER	10	11	12	13	14	15	16	17
401	220.0	166.7	143.3	157.6	221.2	N.D.	N.D.	221.6
402	190.0	13.3	243.3	N.D.	272.2	138.9	N.D.	138.9
403	N.D.	136.6	239.0	160.5	176.3	N.D.	7.1	128.6
405	146.9	187.5	146.9	125.0	175.0	N.D.	177.5	177.5
407	N.D.	221.2	257.6	N.D.	91.7	184.4	135.6	37.8
408	193.9	203.0	218.2	110.8	235.1	186.0	127.9	134.9
411	230.0	276.7	N.D.	237.1	148.6	180.9	119.1	183.0
412	171.0	183.9	254.8	168.6	174.3	209.8	95.1	122.0
414	132.4	202.9	220.6	136.6	175.6	112.5	183.3	118.8
415	160.6	172.7	218.2	154.1	173.0	142.9	197.6	121.4
416	163.9	180.6	216.7	135.0	157.5	145.7	N.D.	160.9
417	200.0	108.8	191.2	N.D.	N.D.	95.0	N.D.	175.0
419	255.6	155.6	141.7	N.D.	218.6	202.3	4.5	168.2
420	202.9	231.4	205.7	N.D.	195.1	171.7	134.8	130.4
422	N.D.	123.3	200.0	65.8	181.6	N.D.	2.3	100.0
424	175.7	143.2	145.9	135.7	166.7	134.0	119.1	170.2
426	139.4	209.1	212.1	165.8	178.9	128.6	190.5	195.2
428	N.D.	200.0	230.3	231.6	218.4	188.1	23.8	138.1
430	309.7	N.D.	180.6	N.D.	N.D.	146.2	212.8	233.3
432	223.5	270.6	223.5	160.0	180.0	163.6	N.D.	97.7
436	185.7	140.0	114.3	142.9	114.3	131.3	114.6	72.9
MEANS	194.2	176.4	200.2	152.5	181.8	156.6	115.4	144.1

N.D. = No Data.

## APPENDIX I; TABLE 3

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC PCTENTIAL IN THE MOUSE; P-T 1218Maternal Consumption of SC-18862 for the Low Dose Group  
(g/kg)

Animal Number	Gestation Day										Mean Intake Each Mouse
	6	7	8	9	10	11	12	13	14	15	
201	1.3	2.0	N.D.	1.8	1.5	N.D.	1.3	1.6	N.D.	1.2	1.53
202	1.0	1.3	1.3	N.D.	1.7	1.4	1.4	1.4	1.4	1.1	1.33
203	N.D.	1.6	2.1	0.8	1.9	N.D.	2.0	1.1	0.7	1.2	1.43
204	N.D.	N.D.	1.3	1.3	0.9	1.0	1.1	1.0	0.6	1.1	1.04
205	1.5	1.5	1.3	1.2	1.0	1.5	1.4	0.9	1.0	1.3	1.26
206	1.7	1.5	1.6	1.4	1.8	1.5	1.4	N.D.	1.7	N.D.	1.58
208	1.5	1.5	2.1	1.2	0.9	1.9	1.5	1.3	1.1	1.4	1.44
210	1.2	2.2	N.D.	1.5	0.8	1.3	1.0	0.8	N.D.	1.2	1.25
211	1.5	1.9	1.9	1.3	2.9	1.6	N.D.	N.D.	1.0	1.0	1.64
213	1.7	2.1	N.D.	2.0	1.3	1.3	1.0	N.D.	N.D.	1.4	1.54
214	2.1	2.0	N.D.	N.D.	1.7	N.D.	1.7	1.9	N.D.	1.3	1.78
218	N.D.	1.5	1.2	1.3	2.1	1.3	1.4	1.1	1.1	1.2	1.36
221	N.D.	N.D.	N.D.	N.D.	1.2	1.5	1.5	1.1	1.3	1.0	1.27
222	1.3	N.D.	N.D.	N.D.	N.D.	1.0	1.8	1.5	1.5	1.1	1.37
223	1.3	1.8	1.3	1.3	1.1	1.2	1.6	1.2	1.2	1.2	1.32
225	1.6	1.3	N.D.	N.D.	N.D.	1.5	1.9	1.8	2.0	1.8	1.70
226	1.5	2.0	2.3	N.D.	1.5	N.D.	1.3	1.2	N.D.	1.0	1.54
227	1.6	1.6	1.6	1.0	1.1	1.2	1.7	0.9	1.4	1.1	1.32
228	N.D.	N.D.	1.6	N.D.	1.8	1.7	1.8	1.6	1.6	1.0	1.59
229	N.D.	2.2	1.3	N.D.	N.D.	1.4	1.3	N.D.	N.D.	N.D.	1.55
232	N.D.	N.D.	1.1	1.8	1.0	1.4	N.D.	1.6	1.3	1.0	1.31
233	N.D.	2.0	1.5	1.6	1.6	1.1	1.1	1.0	1.3	1.1	1.37
234	N.D.	N.D.	1.7	N.D.	1.7	1.6	2.1	1.5	1.4	1.6	1.66
235	N.D.	2.1	1.4	1.2	1.4	1.7	1.8	1.4	1.4	1.2	1.51
236	1.6	2.1	1.1	1.1	2.2	1.1	0.8	1.8	1.1	0.5	1.34
Mean Intake, Each Day	1.5	1.8	1.5	1.4	1.5	1.4	1.5	1.3	1.3	1.2	1.4

N.D. = Data not available.

## APPENDIX I; Table 3 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Maternal Consumption of SC-18862 for the Medium Dose Group  
(g/kg)

Animal Number	Gestation Day										Mean Intake Each Mouse
	6	7	8	9	10	11	12	13	14	15	
301	N.D.	N.D.	3.4	2.7	3.0	2.8	3.4	2.3	2.6	2.8	2.88
302	N.D.	N.D.	3.0	2.9	2.7	2.8	2.5	1.8	1.8	1.9	2.43
304	3.5	2.9	1.9	2.2	2.3	2.7	2.6	2.2	2.4	2.4	2.51
305	5.3	1.4	3.5	3.4	2.4	3.1	N.D.	2.5	1.6	2.0	2.80
306	4.8	N.D.	4.4	2.5	2.8	2.9	2.9	3.4	3.4	3.2	3.37
307	2.4	2.8	3.8	2.3	2.5	N.D.	3.0	3.5	N.D.	1.6	2.74
308	N.D.	N.D.	2.5	3.3	3.1	2.1	2.8	1.9	2.3	1.8	2.48
309	N.D.	3.6	2.7	0.3	1.5	1.3	0.4	1.4	1.4	1.6	1.58
312	3.7	N.D.	3.8	2.9	3.3	3.6	2.9	2.1	2.5	2.3	3.01
313	N.D.	N.D.	N.D.	N.D.	3.8	2.9	2.6	2.3	1.9	2.0	2.58
314	3.8	3.4	2.5	3.6	2.9	3.0	2.4	2.5	1.5	1.6	2.72
315	2.7	3.0	3.7	3.3	3.1	3.6	2.2	3.0	2.5	1.4	2.85
316	2.8	2.5	3.0	4.0	2.4	3.0	2.4	3.3	2.8	2.1	2.83
317	2.3	N.D.	N.D.	N.D.	0.8	2.6	3.7	2.5	2.8	1.7	2.34
319	4.3	N.D.	N.D.	2.9	2.9	2.8	2.3	1.9	2.3	2.1	2.69
320	2.6	3.6	3.2	3.9	2.4	2.6	2.8	2.6	2.3	2.2	2.82
323	2.6	2.3	3.0	3.8	2.3	2.9	2.3	2.7	2.7	2.2	2.68
324	N.D.	2.5	N.D.	N.D.	2.3	3.0	3.5	2.0	2.8	1.9	2.57
327	3.2	N.D.	N.D.	N.D.	1.0	3.6	3.1	2.6	3.0	2.3	2.69
329	N.D.	N.D.	3.3	3.1	2.4	2.3	2.4	2.1	2.1	2.0	2.46
330	N.D.	3.9	3.2	4.2	2.7	2.3	3.2	2.9	1.5	2.1	2.89
331	3.9	3.8	2.7	2.7	2.9	3.1	3.4	3.0	3.1	2.6	3.12
332	N.D.	4.0	3.3	2.6	2.8	3.1	2.0	2.1	2.4	2.3	2.73
333	N.D.	N.D.	N.D.	N.D.	3.3	3.4	3.4	3.1	2.6	2.3	2.45
334	2.8	2.6	2.9	2.9	N.D.	2.6	2.7	2.3	2.0	1.9	2.58
335	N.D.	3.5	2.7	3.5	2.0	2.3	2.9	2.9	2.3	1.8	2.66
336	N.D.	N.D.	N.D.	N.D.	N.D.	4.3	3.8	1.4	1.5	2.9	2.78
Mean Intake, Each Day	3.4	3.1	3.1	3.0	2.5	2.9	2.8	2.4	2.3	2.1	2.7

N.D. = Data not available.

## APPENDIX I; Table 3 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Maternal Consumption of SC-18862 for the High Dose Group  
(g/kg)

Animal Number	Gestation Day										Mean Intake Each Mouse
	6	7	8	9	10	11	12	13	14	15	
401	8.7	5.8	4.4	7.2	6.6	5.0	4.3	4.7	6.6	N.D.	5.92
402	9.6	N.D.	8.9	2.8	5.7	0.4	7.3	N.D.	8.2	4.2	5.89
403	7.4	N.D.	6.2	N.D.	N.D.	4.1	7.2	4.8	5.3	N.D.	5.83
405	7.8	6.3	5.4	4.6	4.4	5.6	4.4	3.8	5.3	N.D.	5.29
407	5.7	6.7	8.4	N.D.	N.D.	6.6	7.7	N.D.	2.8	5.5	6.20
408	4.3	5.2	4.1	7.5	5.8	6.1	6.5	3.3	7.1	5.6	5.55
411	N.D.	3.6	7.2	11.0	6.9	8.3	N.D.	7.1	4.5	5.4	6.75
412	5.0	5.8	5.6	4.8	5.1	5.5	7.6	5.1	5.2	6.3	5.60
414	6.8	7.7	5.1	4.2	4.0	6.1	6.6	4.1	5.3	3.4	5.33
415	6.4	8.8	4.6	5.1	4.8	5.2	6.5	4.6	5.2	4.3	5.55
416	N.D.	8.7	6.0	7.1	4.9	5.4	6.5	4.1	4.7	4.4	5.76
417	9.0	9.1	6.7	N.D.	6.0	3.3	5.7	N.D.	N.D.	2.9	6.10
419	8.3	8.4	4.8	6.7	7.7	4.7	4.3	N.D.	6.6	6.1	6.40
420	4.7	5.2	8.9	N.D.	6.1	6.9	6.2	N.D.	5.9	5.2	4.84
422	5.6	N.D.	6.1	N.D.	N.D.	3.7	6.0	2.0	5.4	N.D.	4.80
424	5.4	6.3	5.5	5.7	5.3	4.3	4.4	4.1	5.0	4.0	5.00
426	5.3	5.8	6.0	7.3	4.2	6.3	6.4	5.0	5.4	3.9	5.56
428	8.4	N.D.	5.5	N.D.	N.D.	6.0	6.9	6.9	6.6	5.6	6.56
430	5.5	5.2	8.3	5.9	9.3	N.D.	5.4	N.D.	N.D.	4.4	6.29
432	7.5	8.2	5.4	8.2	6.7	8.1	6.7	4.8	5.4	4.9	6.59
436	6.0	4.5	3.9	5.8	5.6	4.2	3.4	4.3	3.4	3.9	4.50
Mean Intake, Each Day	6.7	6.5	6.1	6.3	5.8	5.3	6.0	4.6	5.5	4.7	5.7

N.D. = Data not available.

# Appendix I; Table 4

## SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

### Summary of Uterine Implantation Data - Control Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Wt. (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
101	5	4	2	2	5	4	1.3	1.2	2.5	2.4	3	6
102	10	3	1	0	9	4	1.2	1.2	2.3	2.3	5	8
103	N.P.											
104	0	2	0	0	1	1	1.6	1.3	2.6	2.4	1	1
105	5	4	0	0	4	5	1.3	1.2	2.4	2.3	3	6
106	4	6	1	0	5	5	1.5	1.4	2.5	2.4	4	6
107	7	5	1	0	1	11	1.1	1.0	2.4	2.3	4	8
108	5	8	1	0	10	3	1.3	1.3	2.4	2.6	5	8
109	4	4	1	2	4	4	1.3	1.2	2.4	2.4	3	5
110	N.P.											
111	3	5	1	1	2	6	1.3	1.2	2.4	2.4	3	5
112	1	6	0	1	2	5	1.2	1.1	2.3	2.3	3	4
113	1	9	3	0	5	5	1.4	1.4	2.5	2.5	4	6
114	8	4	0	1	7	5	1.3	1.2	2.4	2.4	4	8
115	6	6	2	0	10	2	1.2	1.0	2.5	2.4	4	8
116	N.P.											
117*	0	0	7	3	-	-	-	-	-	-	-	-
118†	0	0	6	7	-	-	-	-	-	-	-	-
119	N.P.											
121	8	1	1	2	3	6	1.2	1.1	2.5	2.4	3	6
122	2	7	0	0	5	4	1.1	1.1	2.4	2.3	3	6
123	2	3	0	0	4	1	1.0	0.6	2.3	2.0	2	3
124	5	9	0	0	8	6	1.0	0.9	2.3	2.3	5	9
125	N.P.											
126	5(1)	9	0	1	8	6	1.2	1.1	2.5	2.4	5	9

R = Right uterine horn.

L = Left uterine horn.

N.P. = Not pregnant.

CRD = Crown-rump distance.

( ) = Dead fetuses.

\* Excessive vaginal bleeding was noted on gestation day 13, consistent with abortion of a litter. The numbers in the resorption column are indicative of the sites of former placental attachment detected at autopsy on post-mating day 18. Data are not included in calculation of means.

†Not included in calculations for mean litter size and mean number of resorptions per litter.

Appendix I; Table 4 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Uterine Implantation Data - Control Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Wt. (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
127	N.P.											
128	5	6	1	0	4	7	1.2	1.1	2.4	2.3	4	7
129	8	5	0	0	9	4	1.1	1.1	2.4	2.4	5	8
130	3	7	0	1	4	6	1.7	1.7	2.6	2.5	4	6
131	N.P.											
132	6	4	1	0	7	3	1.2	1.1	2.3	2.2	4	6
133	N.P.											
134	8	2	1	1	5	5	1.1	1.0	2.4	2.3	4	6
135	5	4	2	2	7	2	1.1	1.2	2.4	2.5	3	6
136	7	4	0	1	6	5	1.3	1.2	2.6	2.5	4	7
Total	123	127	19	15	135	115					92	158
Mean	10.00+		1.36+				1.25	1.16	2.43	2.37		

R = Right uterine horn.  
L = Left uterine horn.  
N.P. = Not pregnant.

CRD = Crown-rump distance.  
+ = Per pregnant female.

Appendix I; Table 4 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Uterine Implantation Data - Low Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Wt. (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue/Skeletal	
201	3	9	0	2	6	6	1.2	1.1	2.3	2.1	4	8
202	4	4	2	1	3	5	1.1	1.0	2.3	2.2	3	5
203	6	4	1	0	6	4	1.4	1.2	2.7	2.5	4	6
204	7	5	1	0	6	6	1.1	1.0	2.4	2.4	4	8
205	6	3	1	1	6	3	1.2	1.1	2.3	2.2	3	6
206	7	4	2	0	7	4	1.2	1.1	2.4	2.5	4	7
207	N.P.											
208	6	5	1	1	4	7	1.5	1.4	2.5	2.5	4	7
210	4	6	0	0	7	3	1.4	1.3	2.6	2.5	4	6
211	3	6	1	0	6	3	1.2	1.3	2.3	2.3	3	6
213	3	6	1	2	4	5	1.2	1.3	2.4	2.5	3	6
214	9	1	0	1	4	6	1.5	1.3	2.7	2.6	4	6
215	N.P.											
217	N.P.											
218	5	5	2	0	5	5	1.2	1.2	2.4	2.5	4	6
219	N.P.											
220	N.P.											
221	7	4	1	0	3	8	1.3	1.3	2.5	2.4	4	7
222	6	7	0	0	3	10	1.2	1.2	2.4	2.3	5	8
223	3	11	1	1	6	8	1.4	1.3	2.4	2.4	5	9
224	N.P.											
225	0	4	0	0	1	3	1.6	1.4	2.7	2.6	2	2

R = Right uterine horn.

L = Left uterine horn.

N.P. = Not pregnant.

CRD = Crown-rump distance.

Appendix I; Table 4 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Uterine Implantation Data - Low Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Wt. (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
226	9	4	0	0	7	6	1.2	1.1	2.2	2.3	5	8
227	6	4	0	0	3	7	1.2	1.2	2.5	2.4	4	6
228	3	7	1	1	2	8	1.4	1.3	2.4	2.4	4	6
229	7	9(1)	0	1	7	9	1.1	1.1	2.3	2.2	6	10
230	N.P.											
231	N.P.											
232	5	6	1	0	4	7	1.4	1.3	2.6	2.4	4	7
233	7	5	0	0	5	7	1.3	1.3	2.3	2.4	4	8
234	1	6	0	1	4	3	1.1	1.2	2.4	2.3	3	4
235	6	3	1	0	4	5	1.3	1.2	2.4	2.3	3	6
236 <sup>Δ</sup>			5	5		10						
Total	123	128	17	12	113	138	1.28	1.22	2.43	2.38	93	158
Mean	10.46+		1.21+									

R = Right uterine horn.  
L = Left uterine horn.  
N.P. = Not pregnant.  
CRD = Crown-rump distance.  
+ = Per pregnant female.  
( ) = Dead fetuses.

<sup>Δ</sup>Female delivered prematurely on gestation day 18. Four pups were found; 3 live, 1 dead. No pups were saved for examination. Numbers shown in resorption column are indicative of sites of former placental attachment. Data are not included in calculation of means.

Appendix I; Table 4 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Uterine Implantation Data - Medium Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Wt. (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue/Skeletal	
301	4	3	2	3	5	2	1.3	1.4	2.3	2.4	3	4
302	7	6	1	0	7	6	1.3	1.3	2.3	2.3	5	8
304	1	3	0	0	3	1	1.5	1.4	2.5	2.5	2	2
305	4	7	1	2	6	5	1.3	1.3	2.5	2.3	4	7
306	4	5	2	0	5	4	1.3	1.3	2.6	2.6	3	6
307	4	8	0	2	7	5	0.9	0.9	2.4	2.5	4	8
308 <sup>Δ</sup>			6	4	10							
309	7	2	2	1	6	3	1.3	1.0	2.5	2.3	3	6
312	4	6	0	1	9	1	1.3	1.3	2.3	2.0	4	6
313	6	5	0	0	6	5	1.2	1.3	2.3	2.4	4	7
314	5	8	1	1	7	6	1.2	1.2	2.4	2.3	5	8
315	4	6	2	2	6	4	1.4	1.2	2.4	2.4	4	6
316	1	8	0	1	4	5	1.3	1.3	2.5	2.4	3	6
317	8(1)	5	0	0	9	4	1.1	1.1	2.4	2.4	5	8
318	N.P.											
319	8	3	0	1	3	8	1.3	1.2	2.4	2.3	4	7
320	11	2	0	1	6	7	1.0	1.0	2.4	2.4	5	8
321	N.P.											
322	N.P.											
323	7(1)	6	0	1	5	8	1.2	1.2	2.4	2.3	4	9

R = Right uterine horn. CRD = Crown-rump distance.

L = Left uterine horn. ( ) = Dead fetuses.

N.P. = Not pregnant.

<sup>Δ</sup>Female No. 308 delivered 10 pups prematurely on gestation day 18. None were saved for examination. Numbers in resorption column indicate sites of former placental attachment. Data are not included in calculation of means.

Appendix I; Table 4 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Uterine Implantation Data - Medium Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Wt. (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue/Skeletal	
324	7	3	2	0	9	1	1.1	1.3	2.4	2.4	4	6
326	N.P.											
327	1	7	1	1	4	4	1.4	1.1	2.6	2.4	3	5
328	N.P.											
329	4	5	0	1	4	5	1.5	1.4	2.5	2.4	3	6
330	4	7	0	0	5	6	1.2	1.2	2.5	2.4	4	7
331	7	6	0	0	5	8	1.2	1.3	2.4	2.4	5	8
332	5	5	1	2	4	6	1.1	1.0	2.3	2.3	4	6
333	6	4	1	1	7	3	1.2	1.2	2.4	2.4	4	6
334	4	7(1)	0	2	1	10	1.4	1.2	2.4	2.4	4	7
335	6	5	0	0	5	6	1.3	1.2	2.4	2.4	4	7
336†	0	0	2	3	-	-	-	-	-	-	-	-
Total	129	132	16	23	138	123	1.25	1.21	2.42	2.37	97	164
Mean	10.44+		1.56+									

R = Right uterine horn.

L = Left uterine horn.

N.P. = Not pregnant.

CRD = Crown-rump distance.

+ = Per pregnant female.

( ) = Dead fetuses.

†Not included in calculations for mean litter size and mean number of resorptions per litter.

Appendix I; Table 4 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Uterine Implantation Data - High Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Wt. (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue/Skeletal	
401	6	4	0	0	6	4	1.3	1.3	2.4	2.4	4	6
402	3	5	1	2	3	5	1.1	1.1	2.0	2.3	5	3
403	7	4	1	0	5	6	1.1	1.0	2.3	2.4	4	7
404	N.P.											
405	4	6	1	0	3	7	1.3	1.3	2.4	2.3	4	6
406	N.P.											
407	7	6	0	0	4	9	1.2	1.1	2.4	2.4	5	8
408	4	7	0	0	6	5	1.4	1.4	2.4	2.4	4	7
411	6	0	1	1	2	4	1.2	1.2	2.3	2.3	2	4
412	4	4	0	1	5	3	1.4	1.3	2.4	2.2	5	3
413	N.P.											50
414	8	4	0	0	9	3	1.2	1.2	2.6	2.5	4	8
415	8	3	0	0	8	3	1.0	1.0	2.4	2.3	4	7
416	3	7	1	0	5	5	1.2	1.1	2.4	2.3	4	6
417	5	4	4	2	4	5	1.4	1.4	2.6	2.5	6	3
419	5	6	0	0	6	5	1.5	1.4	2.5	2.5	7	4
420	8	2	2	0	7	3	1.3	1.3	2.5	2.5	4	6
421	N.P.											
422	7	3	1	1	4	6	1.2	1.1	2.4	2.5	4	5
423	N.P.											

R = Right uterine horn.

L = Left uterine horn.

N.P. = Not pregnant.

CRD = Crown-rump distance.

\* One fetus was lost during the skeletal staining process.

Appendix I; Table 4 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Uterine Implantation Data - High Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Wt. (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue/Skeletal	
424	8	4	0	0	4	8	1.5	1.4	2.6	2.5	4	8
425	N.P.											
426	6	6	0	1	4	8	1.1	1.1	2.4	2.3	4	8
427	N.P.											
428 <sup>†</sup>	0	0	7	4		11						
429	N.P.											
430	4	4	0	2	4	4	1.3	1.3	2.5	2.4	3	5
431	N.P.											
432	4	5	1	0	4	5	1.2	1.1	2.4	2.4	3	6
433	N.P.											
435	N.P.											
436	4	9	0	0	7	6	1.4	1.4	2.5	2.4	5	8
Total	111	93	13	10	100	104					85	118
Mean	10.20 <sup>+</sup>		1.15 <sup>+</sup>				1.27	1.23	2.42	2.39		

R = Right uterine horn. CRD = Crown-rump distance

L = Left uterine horn. + = Per pregnant female.

N.P. = Not pregnant.

<sup>†</sup>Not included in calculations for mean litter size and mean number of resorptions per litter.

## Appendix I; Table 5

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Fetuses and Litters Examined For Abnormalities

Treatment Group	Examination Procedure		
	External Fetuses/Litters	Soft Tissue Fetuses/Litters	Skeletal Fetuses/Litters
Control	250/25	92/25	158/25
Low Dose	251/24	93/24	158/24
Medium Dose	261/25	97/25	164/25
High Dose	204/20	85/20	118/20 <sup>+</sup>

<sup>+</sup> The high dose group initially included 119 fetuses for skeletal examination; one was lost during the staining procedure.

# Appendix I; Table 6

## SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

### Summary of Fetal Skeletal Examination Data

No. of Fetuses Examined: (No. of Litters Examined):	Control Fetuses		Low Dose Fetuses		Medium Dose Fetuses		High Dose Fetuses	
	Number	% of Total	Number	% of Total	Number	% of Total	Number	% of Total
157 (25)	157	(25)	158	(24)	163	(25)	118 <sup>†</sup>	(20)
<b>Skull</b>								
Closure Grading*	0:	0	0	0	0	0	0	0
	1:	0	0	0	0	0	0	0
	2:	2	0	0	2	1	0	0
	3:	155	99	100	161	99	118	100
	4:	0	0	0	0	0	0	0
<b>Interparietal Bone</b>								
Poorly Ossified:	0	0	1	1	0	0	0	0
<b>Supraoccipital Bone</b>								
Poorly Ossified:	5	3	9	6	17 <sup>Δ</sup>	10	7	6
<b>Ribs</b>								
13 pair:	130	83	135	85	145	89	98	83
14 pair:	27	17	23	15	18	11	20	17
<b>Rudimentary structures**</b>								
unilateral:	25	16	25	16	17	9	20	17
bilateral:	9	6	6	4	7	4	4	3
Single ribs:	17	11	24	15	18	11	12	10
Wavy ribs (bilateral):	0	0	0	0	1	1	0	0

\*Closure Grading - 0 = 0% of skull ossified; 1 = 25% of skull ossified; 2 = 50% of skull ossified;  
3 = 75% of skull ossified; 4 = 100% of skull ossified.

\*\*Rudimentary structures: ossification centers positioned adjacent to the 14th thoracic or first lumbar vertebrae.  
† The high dose group initially included 119 fetuses for skeletal examination; one was lost during the staining procedure.

Δ A significantly greater number of fetuses with this variant were detected when compared to the control group incidence ( $p < 0.05$ ).

Appendix I; Table 6 (cont..)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Fetal Skeletal Examination Data

No. of Fetuses Examined: (No. of Litters Examined):	Control Fetuses		Low Dose Fetuses		Medium Dose Fetuses		High Dose Fetuses	
	Number	% of Total	Number	% of Total	Number	% of Total	Number	% of Total
	157 (25)		158 (24)		163 (25)		118 <sup>†</sup> (20)	
Sternebrae								
Centers small - No. 1:	0	0	0	0	0	0	0	0
2:	5	3	4	3	2	1	2	2
3:	3	2	2	1	1	1	0	0
4:	6	4	2	1	6	4	2	2
5:	38	24	43	27	52	32	28	24
6:	0	0	0	0	1	1	0	0
Centers absent - No. 1:	0	0	0	0	0	0	0	0
2:	0	0	0	0	0	0	0	0
3:	0	0	0	0	1	1	0	0
4:	1	1	0	0	1	1	0	0
5:	1	1	0	0	1	1	0	0
6:	0	0	1	1	0	0	0	0
Centers split* - No. 1:	0	0	0	0	0	0	0	0
2:	0	0	0	0	0	0	0	0
3:	0	0	0	0	0	0	0	0
4:	0	0	0	0	0	0	0	0
5:	21	13	21	13	21	13	14	12
6:	2	1	3	2	2	1	3	3
1 & 2:	0	0	0	0	1	1	0	0
1 & 5:	0	0	0	0	1	1	0	0
4 & 5:	3	2	2	1	2	1	0	0
4 & 6:	0	0	1	1	0	0	0	0

<sup>†</sup>The high dose group initially included 119 fetuses for skeletal examination; one was lost during the staining procedure.

\*The number of litters in the high dose group containing one or more fetuses with one or more split sternbrae was significantly less than the control group incidence ( $p < 0.05$ ).

Appendix I; Table 6 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Fetal Skeletal Examination Data

	Control Fetuses		Low Dose Fetuses		Medium Dose Fetuses		High Dose Fetuses	
	Number	% of Total	Number	% of Total	Number	% of Total	Number	% of Total
No. of Fetuses Examined:	157		158		163		118 <sup>†</sup>	
(No. of Litters Examined):	(25)		(24)		(25)		(20)	
Sternebrae (cont.)								
Centers split*-								
No. 5 & 6:	0	0	0	0	1	1	0	0
2,3 & 6:	1	1	0	0	0	0	0	0
2,5 & 6:	0	0	1	1	0	0	0	0
3,4 & 5:	0	0	1	1	0	0	0	0
2,3,4 & 5:	0	0	0	0	1	1	0	0
3,4,5 & 6:	0	0	1	1	0	0	0	0
Centers fused -								55
No. 1 & 2:	0	0	1	1	0	0	0	0
Additional Sternebra:	16	10	4 <sup>ΔΔ</sup>	3	9	6	5 <sup>Δ</sup>	4
Vertebrae								
Centra unossified:								
cervical:	14	9	14	9	14	9	7	6
thoracic:	0	0	0	0	0	0	0	0
lumbar:	0	0	0	0	0	0	0	0
sacral:	0	0	0	0	0	0	0	0
caudal (< 10):	149	95	143	91	161	99	108	92

<sup>†</sup>The high dose group initially included 119 fetuses for skeletal examination; one was lost during the staining procedure.

\*The number of litters in the high dose group containing one or more fetuses with one or more split sternebrae was significantly less than the control group incidence ( $p < 0.05$ ).

<sup>Δ</sup>A significantly lesser number of fetuses with this variant were detected when compared to the control group incidence ( $p < 0.05$ ).

<sup>ΔΔ</sup>A significantly lesser number of fetuses with this variant were detected when compared to the control group incidence ( $p < 0.01$ ).

Appendix I; Table 6 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Fetal Skeletal Examination Data

No. of Fetuses Examined: (No. of Litters Examined): Vertebrae (cont.)	Control Fetuses		Low Dose Fetuses		Medium Dose Fetuses		High Dose Fetuses	
	Number	% of Total	Number	% of Total	Number	% of Total	Number	% of Total
157 (25)			158 (24)		163 (25)		118 <sup>†</sup> (20)	
Transverse process 1st cervical vertebra (Unil. L.) split:	1	1	1	1	0	0	0	0
Transverse process 1st cervical vertebra (Bilat.) split:	0	0	0	0	0	0	1	1
Transverse process 2nd cervical vertebra (Unil. R.) split:	4	3	5	3	3	2	2	2
Transverse process 2nd cervical vertebra (Unil. L.) split:	1	1	4	3	1	1	0	0
Transverse process 2nd cervical vertebra (Bilat.) split:	0	0	1	1	0	0	1	1

<sup>†</sup>The high dose group initially included 119 fetuses for skeletal examination; one was lost during the staining procedure.

Appendix I; Table 6 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Fetal Skeletal Examination Data

No. of Fetuses Examined: (No. of Litters Examined):	Control Fetuses		Low Dose Fetuses		Medium Dose Fetuses		High Dose Fetuses	
	Number	% of Total	Number	% of Total	Number	% of Total	Number	% of Total
	157	(25)	158	(24)	163	(25)	118 <sup>†</sup>	(20)
Pelvic Girdle								
Elements unossified								
R. ischium:	0	0	0	0	0	0	0	0
L. ischium:	0	0	0	0	0	0	0	0
R. ilium:	0	0	0	0	0	0	0	0
L. ilium:	0	0	0	0	0	0	0	0
R. pubis:	0	0	0	0	0	0	0	0
L. pubis:	0	0	0	0	0	0	0	0
Axial Skeleton								
Forelimb (Bilat.)								
Carpals								
unossified:	157	100	158	100	163	100	118	100
Metacarpals								
unossified:	0	0	0	0	0	0	0	0
1-6 ossifications:	3	2	0	0	2	1	1	1
7-8 ossifications:	154	98	158	100	161	99	117	99
Phalanges								
unossified:	3	2	0	0	2	1	2	2
1-10 ossifications:	8	5	11	7	7	4	10	8
11-18 ossifications:	67	43	69	44	71	44	49	42
19-26 ossifications:	79	50	78	49	83	51	57	48

<sup>†</sup>The high dose group initially included 119 fetuses for skeletal examination; one was lost during the staining procedure.

Appendix I; Table 6 (cont.)

SC-18362: AN EVALUATION OF EMBRYOTOXIC AND  
TERATOGENIC POTENTIAL IN THE MOUSE; P-T 1218

Summary of Fetal Skeletal Examination Data

No. of Fetuses Examined: (No. of Litters Examined):	Control Fetuses		Low Dose Fetuses		Medium Dose Fetuses		High Dose Fetuses	
	Number	% of Total	Number	% of Total	Number	% of Total	Number	% of Total
	157		158		163		118†	
	(25)		(24)		(25)		(20)	
Axial Skeleton (cont.)								
Hindlimb (Bilat.)								
Tarsals								
unossified:	104	66	109	69	104	64	85	72
1-2 ossifications:	50	32	45	28	59	36	32	27
3-4 ossifications:	3	2	4	3	0	0	1	1
Metatarsals								
unossified:	0	0	0	0	0	0	0	0
1-6 ossifications:	1	1	0	0	0	0	0	0
7-8 ossifications:	6	4	6	4	11	7	3	3
9-10 ossifications:	150	96	152	96	152	93	115	97
Phalanges								
unossified:	4	3	4	3	4	2	3	3
1-10 ossifications:	8	5	9	6	11	7	0	0
11-18 ossifications:	81	51	89	56	96	59	72	61
19-26 ossifications:	64	41	56	35	52	32	43	36

†The high dose group initially included 119 fetuses for skeletal examination; one was lost during the staining procedure.

## APPENDIX II

### Glossary of Teratology Terminology

## GLOSSARY OF TERATOLOGY TERMINOLOGY

## Charles River (CD-1) Mouse

Morphological alterations of varied nature are known to occur in the Charles River CD-1 mouse. Such alterations may be "spontaneous", or of defined etiology. This list provides an operational approach toward categorizing most alterations, should they be encountered, into one of two categories, either major malformations or skeletal variants. It is thus of considerable value to the teratologist in summarizing data, since it facilitates prompt recognition of unusual alterations. Teratologic findings in various laboratory animal species, including 7,705 Charles River CD-1 mouse fetuses were summarized by Huntingdon Research Centre (Effects of Drugs on Reproductive Processes; HRC Proposals Based on FDA Recommendations; Huntingdon Research Centre; Huntingdon, England; October, 1968). This document was a primary source reference in devising the classification below.

MAJOR MALFORMATIONS

Encephalomeningocele

Exencephaly - alone  
- with open eye

Hydrocephaly - alone  
- with anophthalmia

Anophthalmia - alone  
- with cleft palate + meningocoele

Cyclopia - alone  
- with agnathia

Open eyes

Cleft palate

Renal agenesis

Segmented uterine horn (unilateral)

Agenesis of lumbar, sacral and caudal vertebrae

Fused ribs

Vertebral defects (i.e., fused centra, hypoplasia centra, fused transverse processes)

Umbilical hernia

SKELETAL VARIANTS

Two or more sternebrae bipartite and/or asymmetrical (scrambled)

14 rib pair

All sternebrae unossified

Additional sternebra (7th sternebra)

Fused sternebrae