

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

Pathology-Toxicology
Project No. 1201

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INTRODUCTION

The purpose of this study was to determine the embryotoxic and teratogenic potential of SC-18862 (aspartame) when administered by gavage to the pregnant rabbit during the period of fetal organogenesis. L-phenylalanine and L-aspartic acid, dietary amino acids which are the principal constituents of SC-18862, were administered to two additional groups of pregnant rabbits. The doses of L-phenylalanine and L-aspartic acid were 75% and 134%, respectively, of the amounts present in the highest dose of SC-18862. Such a study is commonly referred to as a Segment II study of the Teratology-Reproduction profile. This study was conducted to provide additional rabbit teratology data with SC-18862 and to compare the embryotoxic and teratogenic impact of the two amino acids which are the products of hydrolysis of SC-18862.

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 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.

this study and was considered 100% pure for the purposes of dosage calculation. This lot actually did contain 0.29% of SC-19192 (a diketopiperazine), which is a conversion product of SC-18862. L-phenylalanine, Lot No. 79190, and L-aspartic acid, Lot No. 98040, were both obtained from Ajinomoto Company, Inc., Tokyo, Japan. Both products were considered to be 100% pure for purposes of dosage calculation.

Animals, housing and diet.

Three hundred two mature nulliparous female New Zealand White rabbits of the Leuenberg strain, obtained from Pel-Freez Biological, Inc., Rogers, Arkansas, were employed in this study. These rabbits had a mean body weight of 3.97 kg and were approximately eight months old at insemination. Twenty proven males of the same strain were used as semen donors for artificial insemination.

Animals were housed individually in stainless steel cages and acclimatized to the laboratory environment for at least one month prior to being placed on study. The animal quarters were air-conditioned, with thermostats set to maintain 72°F temperature continuously; fluorescent lighting was provided daily as a 12 hour dark/light photoperiod.

Basal diet (Rabbit Chow Special No. 5430, Ralston Purina Co., St. Louis, Mo.) and chlorinated tap water were continuously available.

Experimental design.

Prior to insemination the 302 female rabbits were distributed among six experimental groups by a simple randomization procedure.¹ Daily dosage levels administered are presented on the following page.

Treatment Group	Compound Administered	Dose Level (g/kg)	No. of Females Inseminated	Female Identification Nos.
Control	None	--	50	101-150
Low Dose	SC-18862	0.5	50	201-250
Medium Dose	SC-18862	1.0	52	301-350
High Dose	SC-18862	2.0	50	401-450
L-Phe	L-phenylalanine	0.82	50	251-299,201R
L-Asp	L-aspartic acid	1.10	50	351-399,301R

Compound and/or vehicle was administered intragastrically twice daily in two divided doses, separated by an interval of at least three hours. Treatment began on gestation day 6 and continued through gestation day 18, a thirteen-day period. The females were sacrificed and autopsied on gestation day 28.

Compound formulation, administration and dosage calculation.

Compound was suspended in a solution of 0.5% carboxymethyl cellulose (w/v) and 1% Tween-80 (v/v) in the low, medium, and high dose groups at concentrations (w/v) of 2.5%, 5% and 10%, respectively. L-phenylalanine and L-aspartic acid were prepared at concentrations of 4.0% and 5.5% respectively, in the same vehicle. Solutions were prepared fresh daily. Control animals received vehicle only in comparable volumes (20 ml/kg body weight daily). Compound and/or vehicle was administered by gastric intubation in two equally divided daily doses, separated by a three-hour interval. Treatment began on gestation day 6 and continued through gestation day 18, a thirteen-day period. Individual dosages were adjusted to body weights on post-insemination day 13.

Insemination procedures.

Artificial insemination procedures were employed and the day of insemination considered day 0 of gestation. Semen was collected from proven males by using an artificial vagina. First and second ejaculates were collected when possible. A small amount of each ejaculate was placed on a slide, coverslipped, examined microscopically, and rated qualitatively on the basis of apparent sperm motility and density. Semen collections with high ratings were then pooled and diluted with nine parts of Sodium Chloride Injection, U.S.P. Females were inseminated with 0.7-1.0 ml of diluted pooled semen containing not less than 20 million sperm.

Ovulation was induced by a 2.0 mg dose of pituitary luteinizing hormone (PLH, Armour-Baldwin Labs., Omaha, Neb.) administered intravenously via the marginal ear vein. Each female received PLH immediately following insemination.

Insemination procedures were performed on seventeen separate days. Usually three females from each experimental group were inseminated on each day, though in exceptional cases additional replacement animals were inseminated. On the last insemination day, only two animals from each group were inseminated.

Observations and records on inseminated females.

Females were examined daily for morbidity, mortality and behavioral irregularities. These observations were generally performed in conjunction with recording food consumption and handling the animal to administer compound. Food consumption was recorded daily during gestation by weighing the food containers at the beginning and end of each 24 hour period. The difference in weight represented the food consumed during that interval.

Due to the construction of the food containers, the amount of food spillage was negligible. Body weights were recorded on gestation days 0, 3, 6, 10, 13, 15, 18, 22 and 28.

A necropsy was performed on the maternal animals that died or were sacrificed during the study. Each female that completed the study was sacrificed by air embolism and the following tissues examined grossly in situ: heart, lungs, liver, kidneys, stomach, small intestine, large intestine, uterus and ovaries.

Terminal observations.

On gestation day 28 all females were sacrificed and the abdominal cavity opened. The ovaries and uterine horns were exposed, and the number of corpora lutea, 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 by respiratory movements, skin color, and movements of the extremities and head.

Fetal external examination. The weight and length (crown-rump distance, CRD) of each fetus were recorded. Each fetus was then given a thorough gross examination for external malformations prior to being euthanized and preserved intact in a fixative solution. Fetuses designated for soft-tissue examination were preserved in Bouin's solution. Fetuses designated for skeletal examination were preserved in 95% (v/v) aqueous ethyl alcohol.

Fetal soft tissue examination. Approximately one-half of the fetuses from each litter were fixed in Bouin's solution for subsequent examination by the free hand sectioning technique of Wilson² as follows:

Head: Five parallel tissue slices, approximately 5 mm thick, were prepared in a transverse plane and were examined for malformations of the palate, nasal cavities, eyes and brain.

Thorax: Five parallel slices, approximately 2 mm thick, 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 8 mm caudal to the diaphragm and was examined for malformations of the liver, stomach and spinal cord. The next slice was made at the level of the right kidney and was examined for malformations of the kidney, liver, stomach, spleen and spinal cord. A final slice was made at the level of the left kidney and was examined for malformations of the spinal cord, aorta and renal pelvis. Structures found in the pelvic cavity (i.e., ureters, bladder and reproductive tract) were examined in situ after removal of the intestine.

Tissue slices were examined under a dissecting microscope (7X). All tissue slices from control and treated fetuses were then transferred to amber glass bottles filled with 70% (v/v) aqueous ethyl alcohol for temporary storage.

Fetal skeletal examination. The remaining fetuses (approximately one-half of each litter) were preserved in 95% (v/v) aqueous ethyl alcohol for subsequent skeletal staining by the Alizarin Red S staining technique.³

Following gross examination of the internal organs, these fetuses were eviscerated, and the remaining soft tissues macerated and cleared in 5.0% 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. Additionally, 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 measured parameters were calculated for each experimental group.

The two-tailed Student's t-test⁴ was used to compare maternal body weight, maternal food consumption, litter size, fetal body weight and fetal CRD data.

The following parameters were compared by the Chi-Square Test⁵: maternal survival and conception rates, the incidences of litters consisting of fetuses only, of both fetuses and resorption sites, or of resorption sites only, the incidences of abortions and premature deliveries, the fetal sex ratios, and the incidence of certain anatomical variants. The univariate Wilcoxon Rank Sum Test⁶ was employed to compare the mean number of fetal resorptions in the control and each treated group. The Permutation Test⁷ was used to evaluate the distribution of litters containing one or more fetal resorptions.

The incidences of major and minor malformations were compared on a litter incidence and fetal incidence basis using the two-tailed Fisher Exact

Test.⁸ The level of significance in all tests was set at $p < 0.05$, except in the case of the Fisher Exact Test, in which $p < 0.01$ was also used.

RESULTS

Maternal observations.

Survival and conception data. Survival rates during the period from insemination to post-insemination day 28 did not differ significantly between the control and each treated group. Survival data are summarized below:

Number of Females	Treatment Group					
	Control	Low Dose	Medium Dose	High Dose	L-Phe	L-Asp
Inseminated:	50	50	52 ⁺	50	50	50
Surviving to post-insemination day 28:	46	46	49	46	45	48
Dying:	4	4	1	4	5	2
Removed from study:	0	0	2	0	0	0
Maternal Survival Rate* (%):	92	92	98	92	90	96

*Maternal Survival Rate = $\frac{\text{No. of females alive at post-insemination day 28}}{\text{No. of females inseminated} - \text{No. of females removed from study}} \times 100.$

⁺Includes two females subsequently removed from the study.

During the first two days of treatment (post-insemination days 6 and 7) two females from the medium dose group suffered broken backs and were sacrificed and removed from the study. Both of these females were pregnant. Two additional females were inseminated and added to the medium dose group as replacements for the two females which were removed. No data were recorded for those two females removed from the study and they are not included in any of the subsequent tables.

The causes of death for those females dying spontaneously during the study are summarized on the following page.

Cause of Death	Treatment Group					
	Control	Low Dose	Medium Dose	High Dose	L-Phe	L-Asp
Pneumonia:	1	0	0	2	1	1
Pneumonia and pyothorax:	1	2	0	0	2	0
Pneumonia, pyothorax and peritonitis:	0	0	0	1	0	0
Tracheal obstruction:	0	0	0	0	0	1
Faulty administration of test compound:	1	2	1	0	2	0
Undetermined:	1	0	0	1	0	0
Total:	4	4	1	4	5	2

Detailed gross autopsy reports for those females dying during the study are presented in Appendix II. All of these animals had been pregnant with the exception of female No. 397 of the L-aspartic acid group, which died of pneumonia.

Conception rates did not differ significantly between the control and each of the treated groups. Conception data are summarized below:

Number of Females	Treatment Group					
	Control	Low Dose	Medium Dose	High Dose	L-Phe	L-Asp
Inseminated:	50	50	52 ⁺	50	50	50
Ovulating*:	48	50	51	49	46	47
Pregnant:	42	46	48	37	39	44
Not pregnant:	8	4	4	13	11	6
Conception Rate(%)**:	87.5	92.0	94.1	75.5	84.8	93.6

*As indicated by the presence of corpora lutea in at least one ovary.

**Conception Rate = $\frac{\text{No. of pregnant females}}{\text{No. of females ovulating}} \times 100$.

+Includes two females subsequently removed from the study.

Aborted pregnancies and premature deliveries. Aborted pregnancies were diagnosed by the presence of fetal-placental remnants and/or blood spots in the cage or the sub-floor cage pan prior to gestation day 26. Occurrence of an abortion was confirmed at sacrifice on post-insemination day 28 or following a spontaneous death, by the presence of sites of former placental attachment visible to the naked eye. No abortions were detected in the control, medium dose or L-aspartic acid groups. Two abortions were detected in the low dose group, 24 in the high dose group and four in the L-phenylalanine group. Two of the high dose and one of the L-phenylalanine animals that aborted subsequently died. The proportion of pregnancies which terminated in abortion was significantly greater in the high dose group than in the control group ($p < 0.01$). The abortion incidence of the remaining treated groups did not differ significantly from that of the control group.

Premature delivery is defined as the delivery of viable and/or nonviable fetuses between gestation day 26 and sacrifice on gestation day 28. Premature delivery was observed in three control, one medium dose and two L-phenylalanine dose group animals. Premature delivery did not occur in the low dose, high dose and L-aspartic acid dose groups. The incidence of premature deliveries did not differ significantly between the control group and each of the treated groups.

The combined incidence of abortions and premature deliveries was significantly greater in the high dose group than in the control group ($p < 0.01$). The combined incidence of abortions and premature deliveries in the remaining treated groups did not differ significantly from that of the control group.

Data for all pregnant females which aborted or delivered their litters prematurely are presented in Appendix I, Table 3. This table also includes pertinent observations made during the gestation period and at autopsy. Autopsy reports for those females which aborted and then died spontaneously prior to sacrifice on post-insemination day 28 are presented in Appendix II. The term hemorrhage as used in Appendix I, Table 3, as evidence of loss of a litter, includes the finding of blood in the cage, the sub-floor cage pan or in the perineal area of the animal.

Body weight and food consumption data are being presented and discussed in the following sections in detail. The purpose of this expanded presentation is to demonstrate the relationship of the decreased food consumption to the body weight losses and abortions and subsequent effects observed in the fetuses.

Body weight data. Group mean body weight data for the pregnant rabbits are summarized in Figure 1. Individual and group mean female body weight data, including statistical analyses, are presented in Appendix I, Table 1. Only body weights of females determined to have been pregnant are included in the mean and individual values. The number of pregnant females in each group at gestation day 28 is less than at day 0 due to spontaneous mortality, though data for females which aborted are included through day 28. Mean body weights for the low, medium, L-phenylalanine and L-aspartic acid dose groups did not differ significantly from those of the control group at any of the intervals at which they were measured. In the high dose group, a notable decrease in the mean body weight of the pregnant females was noted on gestation day 10, compared to the control and other treated groups. The mean body weight of the high dose group further decreased on gestation day 13 and was significantly less than that of the control group on gestation days 13, 15, 18, 22 and 28. A similar pattern of weight loss was noted in the L-phenylalanine group, though the weight losses were not as large and the mean weights did not differ significantly from those of the control group.

Because of the statistically significant decrease in mean body weight of the high dose group beginning on gestation day 13, and the significantly high number of abortions occurring in that group, the high dose group animals were divided into those surviving until sacrifice on gestation day 28 with pregnancy intact, and those surviving until post-insemination day 28 without pregnancy intact (post-abortion). Those high dose animals not pregnant or dying prior to post-insemination day 28 were not included in this tabulation. These data are summarized in Figure 2, along with the data for the control and L-phenylalanine groups from Figure 1. Group mean female

FIGURE 1

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TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

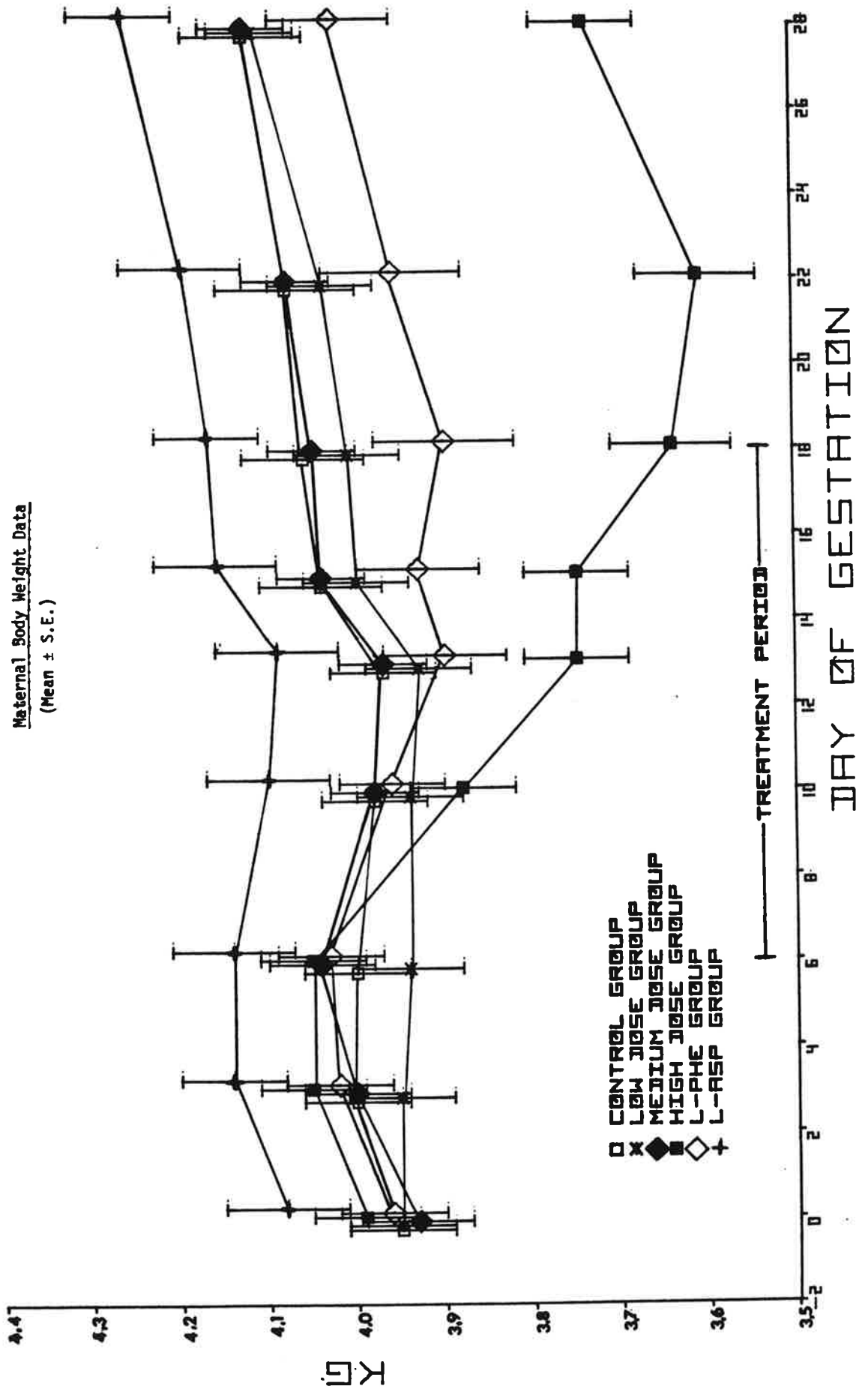
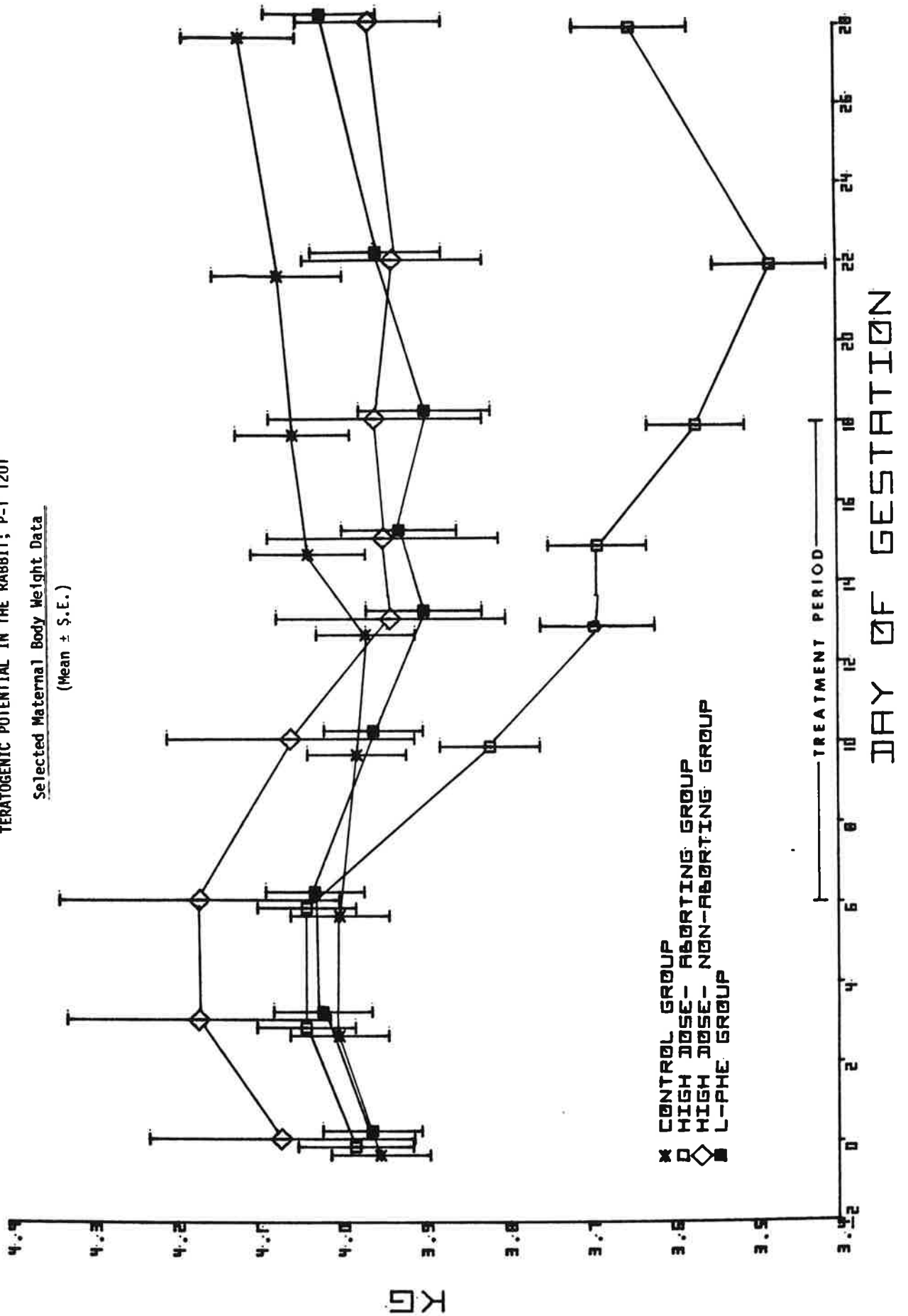


FIGURE 2

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

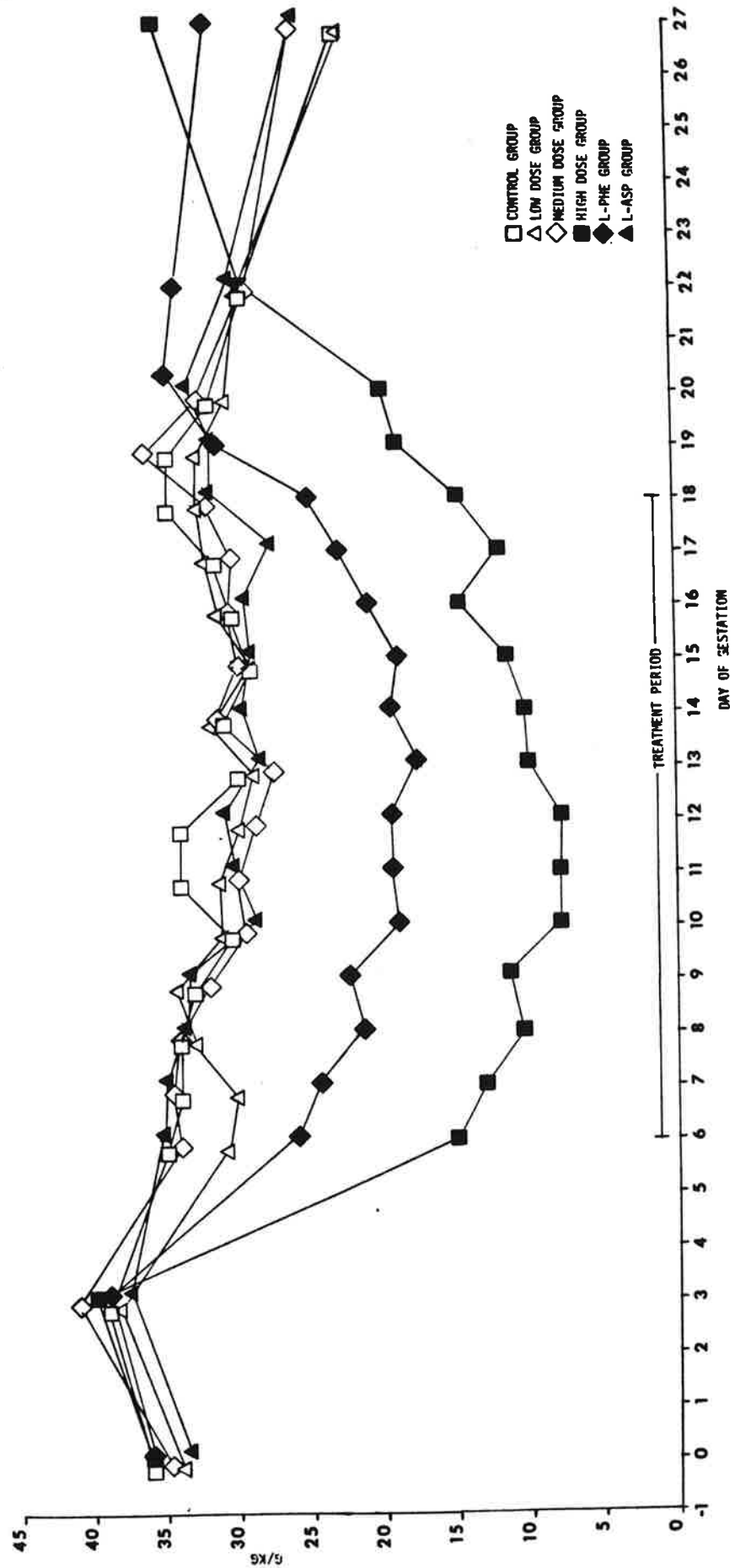


body weight data, including statistical analyses, are presented in Appendix I, Table 1. Those high dose pregnant females that did not abort their litters lost a slight amount of weight in the early portion of the dosing period, but the mean body weights for this group did not differ significantly from those of the controls at any of the measurement intervals. Mean body weights for these non-aborting high dose females also did not differ significantly from those of the control group at any of the measurement intervals. Those high dose pregnant females that survived until post-insemination day 28 but aborted their litters weighed significantly less than the control group animals from post-insemination days 13 to 28 and significantly less than the non-aborting high dose females from post-insemination days 18 to 28. Since the decrease in body weight in those females subsequently aborting occurred several days before the actual evidence of abortions was detected, the maternal body weight losses are not a result of the abortions. Instead, the losses of maternal body weight and the abortions are both manifestations of the same insult to the maternal rabbit during a critical phase of gestation, and abortion is contingent upon significant and rapid body weight loss.⁹

Food consumption data. Group mean food consumption data for the pregnant rabbits are summarized in Figure 3. Appendix I, Table 2 contains daily mean food consumption data during the treatment period from gestation days 6 through 18 and representative data before and after the treatment period, plus all individual daily food consumption data. Statistical analyses are also reported with the mean food consumption data. Only food consumption data of females determined to have been pregnant are included in the mean and individual values. The number of pregnant females in each group at gestation day 28 is less than at day 0 due to spontaneous mortality, though data for females which aborted are included. Mean food consumption for the low, medium and L-aspartic acid dose groups did not differ significantly from that of the control group at any of the measurement periods. Food consumption for the control, low, medium and L-aspartic acid dose groups did decrease to approximately 75 to 90% of their respective pretreatment values as a result of the twice daily gastric intubation procedures. Food consumption for the high dose group females from gestation days 6 through 18 was decreased to about 25 to 35% of their pretreatment mean values and was significantly less than that of the control group on each day of treatment. Similarly, food consumption for the L-phenylalanine group females from gestation days 6 through 18 was decreased to between 50 to 60% of their pretreatment mean and was significantly less than that of the control group on each day of treatment, though their food consumption was generally greater than that of the high dose group.

After the treatment period, the food consumption of the high dose group gradually increased and was normal by gestation day 22. Food consumption for the L-phenylalanine group returned to normal on gestation

FIGURE 3
SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201
Mean Maternal Food Consumption Data

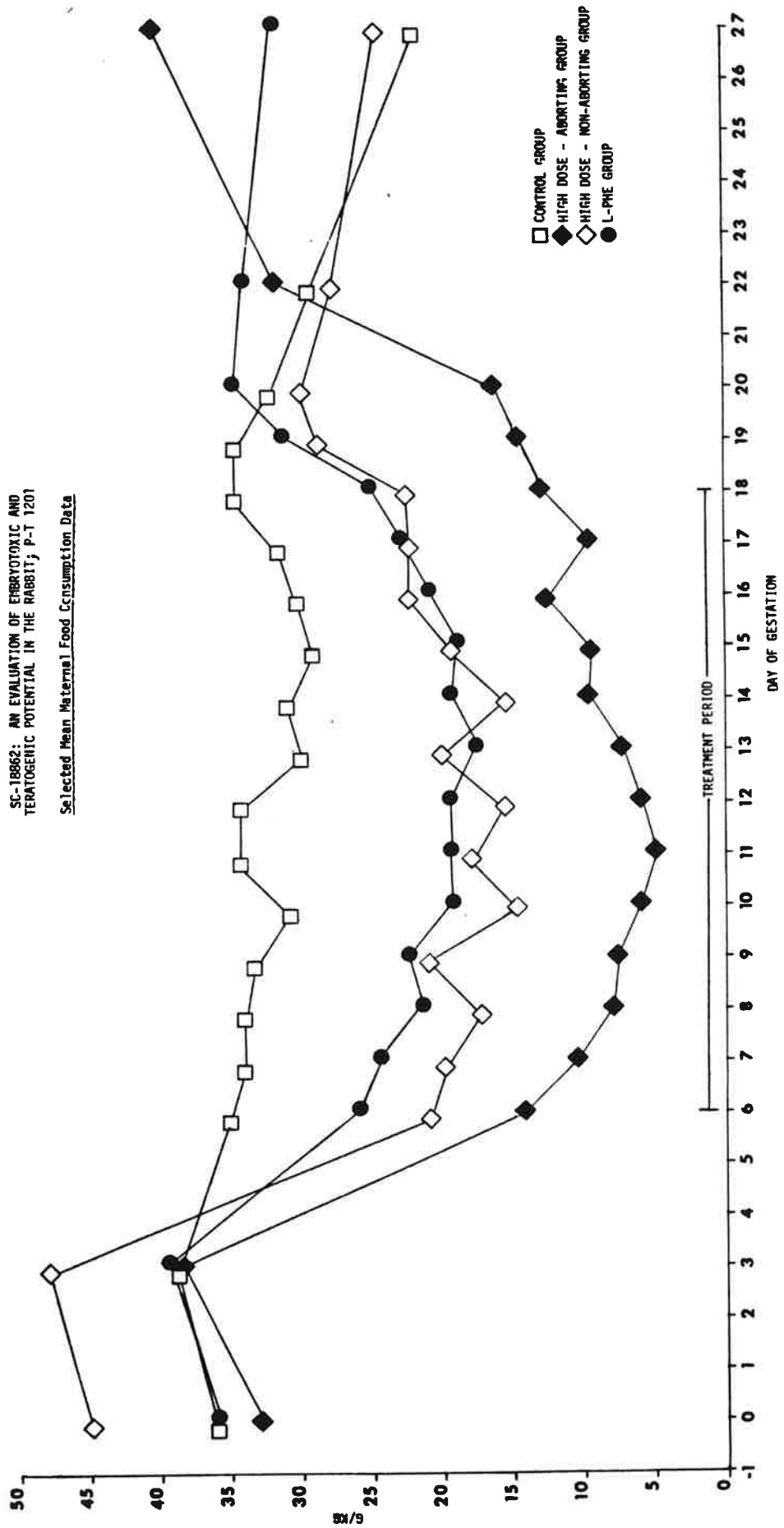


day 20. On gestation day 27 food consumption for both the high dose and L-phenylalanine groups was significantly increased compared to the control group. No other significant differences in food consumption were noted.

Because of the statistically significant decrease in food consumption and the high incidence of abortions in the high dose group, the high dose group animals were subdivided into two groups: those surviving until sacrificed on gestation day 28 and retaining their litter; and those surviving until post-insemination day 28 but aborting their pregnancies. Those high dose animals not pregnant or dying prior to post-insemination day 28 were not included in this tabulation. These data are summarized in Figure 4 accompanied by data for the control and L-phenylalanine groups representing all of the pregnant animals in these latter groups. The mean values and the statistical analyses are presented in Appendix I, Table 2. The data are presented on a daily basis over that period when significant decreases in food consumption for the entire high dose group were noted (gestation days 6 through 20). Before and after this period, only representative days are presented.

Examination of the data for gestation days 6 through 20, during which period food consumption for the entire high dose group was significantly less than for the control group, indicates that food consumption for the high dose aborting females was significantly less than for high dose non-aborting females on nearly one-half of these days. Similarly, while food consumption for the high dose non-aborting females was generally lower than that of the controls, it was significantly lower on only 69% of the days during this period, as compared to a significant reduction on 100% of the days for the high dose aborting females.

FIGURE 4
SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201
Selected Mean Maternal Food Consumption Data



Therefore, the conclusion to be drawn is that the body weight may be a result of decreased food consumption, which may be a result of gastric intubation of high levels of L-phenylalanine, either by itself or as part of the aspartame molecule. A decrease in food consumption, if severe enough, causes a reduction in body weight. If the reduced food consumption and body weight losses are of sufficient magnitude, they prompt the pregnant females to abort, and as a result only the in utero litters may be lost, and the females will have a better chance of survival.⁹ Decreased food consumption and reduced body weights were also present in the L-phenylalanine group, but these changes were not as severe as in the high dose group, and a significant number of abortions did not occur. The amount of L-phenylalanine received by this group was equivalent to only 75% of that received by the high dose group and less severe weight losses and a lower incidence of abortions would be expected.

Hysterotomy data. A total of 46 control, 46 low, 49 medium, 46 high, 45 L-phenylalanine and 48 L-aspartic acid rabbits were sacrificed near term (gestation day 28). Appendix I, Table 4 contains a summary of the maternal disease incidence in those animals sacrificed on post-insemination day 28 and identifies the affected animals. The incidence of maternal disease is not unusual for the laboratory rabbit and does not suggest treatment-related causation.¹⁰

Uterine implantation data for the control and treated groups are summarized in Table 1. Implantation data for individual females are presented in Appendix I, Table 5. There were no significant differences in the proportions of pregnant females having litters consisting of fetuses only, of both fetuses and resorption sites, or of resorption sites only, among those females that survived to sacrifice and remained pregnant to gestation day 28. Mean litter sizes of the treated groups did not differ significantly from that of the control group. The mean number of resorption sites in the high dose group was notably greater than that of the control group, but because of the small number of litters surviving to term in this group and the large amount of variability in these litters, the difference was not statistically significant. The number of resorption sites in the L-phenylalanine group was significantly greater than that of the control group. In addition, the L-phenylalanine group had a disproportionately high number of litters with large numbers of fetal resorption sites. The increased fetal resorption incidence in both the high dose and L-phenylalanine groups may be attributed to the reduced food consumption, and decreased body weights of the maternal animals. Depending upon the degree of reduction of food consumption, a maternal animal may continue to maintain her

Table 1

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Hysterotomy Data

Treatment Group	Number of Pregnant Females ¹	Number of Litters ²	Number of pregnant females with implantations comprised of:								Litter Size ³ (Mean \pm S.E.)	No. of Resorption Sites Per Litter (Mean \pm S.E.)
			Fetuses Only		Fetuses and Resorption Sites		Resorption Sites Only					
			No.	%	No.	%	No.	%				
Control	36	35	21	58	14	39	1	3	8.0 \pm 0.4	0.7 \pm 0.2		
Low Dose	41	40	23	56	17	42	1	2	8.5 \pm 0.3	0.8 \pm 0.2		
Medium Dose	44	44	20	45	24	55	0	0	7.8 \pm 0.4	1.0 \pm 0.2		
High Dose	11	9	3	27	6	55	2	18	8.3 \pm 1.1	1.4 \pm 0.6		
L-Phe	29	26	10	35	16	55	3	10	7.2 \pm 0.6	2.1 \pm 0.5*		
L-Asp	43	43	24	56	19	44	0	0	7.8 \pm 0.4	0.8 \pm 0.2		

*Difference statistically significant from control group ($p < 0.05$).¹Includes only females whose pregnancy was confirmed by the presence of uterine implantation sites at sacrifice on gestation day 28.²At least one fetus, viable or nonviable, was necessary to constitute an in utero litter.³Number of fetuses (viable or nonviable) per litter.

pregnancy intact, resorb some of the fetuses, or abort or resorb the entire litter. In this study abortion was the most likely outcome with the degree of reduced food consumption experienced by the high dose group, whereas the lesser degree of food consumption reduction experienced by the L-phenylalanine group more frequently caused the resorption of several fetuses, and preserved several until the time of sacrifice. The incidence of fetal resorption in the low dose, medium dose and L-aspartic acid groups did not differ significantly from that of the control group.

A total of eight nonviable fetuses were recovered at hysterotomy. The distribution of the nonviable fetuses was as follows: one control, four low dose (one litter), one L-phenylalanine and two L-aspartic acid (two litters). The individual females whose litters contained a nonviable fetus(es) are indicated in Appendix I, Table 5.

Fetal sex distribution, body weight and crown-rump distance data are presented in Table 2. Fetal sex distribution in all treated groups was similar to that of the control group except for the high dose group, which had a significantly greater proportion of female fetuses. This difference probably reflects the comparatively small number of litters at this level and thus is attributed to random variation. The mean male and female fetal body weights and crown-rump distances for the SC-18862 low and medium dose and L-aspartic acid groups did not differ significantly from those of the control group.

The mean male and female fetal body weights and crown-rump distances of the high dose and L-phenylalanine groups were significantly less than the corresponding values for the concurrent control group. In comparison with the L-phenylalanine group, the mean crown-rump distance measurements of the high dose group were not significantly reduced but the

Table 2

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

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 (Mean \pm S.E.)	Female (Mean \pm S.E.)	Male (Mean \pm S.E.)	Female (Mean \pm S.E.)
Control	136	143	33.2 \pm 1.0	32.0 \pm 0.9	7.9 \pm 0.09	7.7 \pm 0.08
Low Dose	175	164	32.4 \pm 0.7	31.3 \pm 0.6	7.7 \pm 0.07	7.6 \pm 0.07
Medium Dose	167	177	31.0 \pm 0.9	30.9 \pm 0.9	7.6 \pm 0.09	7.7 \pm 0.08
High Dose	32*	43*	23.5 \pm 1.0* Δ	23.3 \pm 1.2* Δ	7.2 \pm 0.12*	7.2 \pm 0.11*
L-Phe	89	97	28.2 \pm 1.1* Δ	27.1 \pm 1.1* Δ	7.5 \pm 0.11*	7.4 \pm 0.11*
L-Asp	176	160	31.7 \pm 1.1	32.4 \pm 1.5	7.7 \pm 0.11	7.6 \pm 0.13

*Difference statistically significant from control group ($p < 0.05$). Δ Difference statistically significant between the high dose and L-phenylalanine groups ($p < 0.05$).

mean body weights were. These differences may be attributed to a marked decrease in food consumption in these two groups, resulting from the forced ingestion of large amounts of L-phenylalanine, either alone or as part of the SC-18862 molecule. As a result of the decreased maternal food consumption, the fetuses which survived to term were smaller in length and lesser in weight than the control fetuses.¹¹

Fetal examination.

Fetal abnormalities have been categorized into major and minor malformations and skeletal variants, using the Glossary in Appendix IV as a guide. All fetuses were examined for externally evident abnormalities. Approximately one-half of the fetuses of each litter were further examined for soft tissue abnormalities² and one-half for skeletal abnormalities.³ The number of fetuses and litters examined for external, soft tissue and skeletal abnormalities are presented in Appendix I, Table 6. In addition to the fetuses listed in this table, several pups delivered prematurely and fetuses recovered from a female dying near term were examined. The condition of the pups and fetuses recovered from these females dictated the type of examinations which could be performed, and in some cases only an external examination was possible.

Major and minor malformations which were detected in this study are listed in Appendix I, Table 7. Included in this table are the litter identification number, fetus identification number, litter size, a description of the malformation and an indication as to whether the malformation is classified as major or minor. This table includes only malformations detected in fetuses recovered at a scheduled, near-term hysterotomy, and does not include prematurely delivered pups. Minor malformations have not been tabulated when they are obviously the result of a major malformation in the same fetus, such as split sternbrae as a result of an umbilical hernia. Minor malformations occurring in a fetus with a major malformation have been included in the table when they have no obvious relation to the major malformation. These data are summarized in Table 3.

Table 3

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL
IN THE RABBIT; P-T 1201

	Treatment Group					
	Control	Low Dose	Medium Dose	High Dose	L-Phe	L-Asp
<u>Litters</u>						
Total Affected	5	5	8	6	9	7
Total Examined	35	40	44	9	26	43
<u>Fetuses</u>						
Total Affected	7	6	9	9	14	14
Total Examined	279	339	344	75	186	336
<u>Malformations Detected (individual fetuses)</u>						
Hydrocephalus:	1	-	-	-	-	1
Cleft Palate:	-	-	-	3	1	-
Retinal Folding:	-	-	-	-	1	-
Cyclopia and Microencephaly:	-	-	-	-	-	1
Spina Bifida:	-	1	-	-	-	-
Umbilical Hernia:	-	-	1	-	1	1
Omphalocele:	-	-	-	1	4	1
Diaphragmatic Hernia:	-	-	1	-	-	1
Renal Agenesis:	-	-	-	-	1	-
Arthrogryposis:	-	-	-	-	1	1
Amelia:	-	-	-	-	1	-
Oligodactyly:	-	-	-	-	1	-
Short or Absent Tail:	-	-	-	1	3	-
Supernumerary Nasal Sutures:	-	1	3	-	2	2
Vertebral and Rib Defects:	4	1	1	1	4	2
Sternebral Defects:	2	3	3	3	2	4
Reduced Skull Ossification:	-	-	-	-	-	5
Split Interparietal Bone:	-	-	-	1	-	1

Note: Several fetuses were affected with one or more malformations.

Comprehensive litter examination reports, which contain individual fetal body weight, crown-rump distance and malformation data for all of the fetuses in those litters which contained one or more fetuses with a major or minor malformation, are presented in Appendix III. Certain minor skeletal malformations which are detectable only at detailed skeletal examination would not have been detected in those fetuses subjected to soft-tissue examination. Similarly, certain malformations detectable only by soft tissue examination would not have been detected in those fetuses subjected to skeletal examination.

Commonly occurring anatomical variations detected at skeletal examination are summarized in Appendix I, Table 8. This table includes only those fetuses examined for skeletal malformations and in which skeletal development was not grossly affected as a result of a major malformation. The purpose of this tabulation of ossification data is to assess the degree of skeletal maturation among test groups, and it is appropriate that seriously malformed fetuses be excluded since it is already known that their development has been markedly affected. Statistical analysis of anatomical variant data in only those fetuses not having any major malformations may be of value to indicate the existence of a trend in lower dose groups when a significant incidence of major malformations is found in a higher dose group. Minor malformations have been included in this table only when they represent the primary malformation of an individual fetus, but not when they are secondary to a major malformation.

Statistical analysis of the anatomical variation data derived as a result of fetal skeletal examination is also included in Appendix I, Table 8.

A significantly greater number of high dose fetuses were found to have 13 pairs of ribs, and a trend toward greater numbers of fetuses with 13 pairs of ribs was seen in the L-phenylalanine group. This effect appears to be related to the dose of L-phenylalanine administered to the maternal rabbits, and has also been observed as a result of appropriately timed maternal fasting in the rat.¹² Skull ossification was also significantly reduced in five fetuses of the L-aspartic acid group, which is attributed to random variation. These fetuses represent all of the fetuses examined for skeletal defects from two litters which contained only extremely immature fetuses (see Comprehensive Litter Examination Reports, L-Aspartic Acid females No. 373 and 374, Appendix III). In the high dose and L-phenylalanine groups, the number of metacarpal and tarsal ossification centers was reduced significantly and in the high dose group, the sixth sternebral ossification center was absent and the second sternebral ossification center was small in a significantly large number of fetuses. In the rat these differences are an expression of slowed fetal development.¹² A fewer number of ossification sites is consistent with the smaller mean fetal weight and length measurements of the high dose and L-phenylalanine groups.

Statistical analysis of malformation data.

Malformations were categorized as major or minor using the Glossary of Teratology Terminology in Appendix IV as a guide. Malformation incidences in each of the treatment groups were compared with the malformation incidences in the control group and are presented in Table 4. The malformation incidences in the concurrent control group were also compared with those of a historical control group representing data collected at our laboratory over the past seven years.¹³ Comparisons were made on the basis of the numbers of litters affected and the number of fetuses affected, using the

Table 4

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Fetal and Litter Incidences of Malformations

Malformation	Treatment Group						
	Historical Control	Concurrent Control	Low Dose	Medium Dose	High Dose	L-Phe	L-Asp
			LITTER INCIDENCE				
All Major Malformations	11/233	1/35	1/40	2/44	2/9	6/26*	3/43
Hydrocephalus	1/233	1/35	0/40	0/44	0/9	0/26	1/43
Cleft Palate	2/233	0/35	0/40	0/44	2/9*	1/26	0/43
Ventral Midline Defects	1/233	0/35	0/40	2/44	1/9	5/26*	2/43
All Minor Skeletal Malformations	18/204	4/35	5/40	7/44	4/9*	5/26	7/43
All Major and Minor Malformations	26/233	5/35	5/40	8/44	6/9**	10/26*	9/43
			FETAL INCIDENCE				
All Major Malformations	11/1717	1/279	1/339	2/344	4/75*	7/186**	4/337
Hydrocephalus	1/1717	1/279	0/339	0/344	0/75	0/186	1/337
Cleft Palate	2/1717	0/279	0/339	0/344	3/75**	1/186	0/337
Ventral Midline Defects	1/1717	0/279	0/339	2/344	1/75	5/186**	2/337
All Minor Skeletal Malformations	18/815	6/139	5/169	7/172	5/36	7/87	10/160
All Major and Minor Malformations	29/1717	7/279	6/339	9/344	9/75**	14/186*	14/337

* Differs significantly from the concurrent control group ($p < 0.05$).** Differs significantly from the concurrent control group ($p < 0.01$).

Fisher Exact Test. Comparisons made included incidences of hydrocephalus only, cleft palate only, ventral midline defects only, all major malformations combined, all minor malformations combined, and all major and minor malformations combined. Since the only minor malformations detected in this study were skeletal in nature, the group sizes of fetuses examined for minor malformations consist only of the fetuses processed for skeletal examination. If a fetus contained separate and distinct major and minor malformations, it was counted only once and was placed in the major malformation category. If a litter contained fetuses with both major and minor malformations as primary malformations, then it was counted only once in the category of all major and minor malformations combined, and once each in the categories of all major malformations and all minor malformations.

There were no significant differences in malformation incidence in the low or medium dose SC-18862 or L-aspartic acid groups on either litter or fetal incidence bases when compared with the concurrent control group. Likewise, the litter and fetal incidences of malformations in the concurrent control group did not differ significantly from those of the historical control group.

In the high dose group, the incidence of cleft palate was significantly greater than in the control group when compared on both the incidence per litter or per fetus bases. The incidence of all major malformations in the high dose group on a fetal incidence basis was significantly greater than that of the control group, which was principally due to the cleft palates. The incidence of all major malformations combined for the high dose group was not significantly increased over that of the control group

when compared on a litter incidence basis. The incidence of minor malformations was significantly greater in the high dose group when compared to the control on an incidence per litter basis but not when compared on an incidence per fetus basis. The incidence of all major and minor malformations combined was significantly greater in the high dose group than in the control group when compared on both the incidence per litter and per fetus bases.

In the L-phenylalanine group, the incidence of ventral midline defects was significantly greater than that in the control group when compared on both the incidence per litter and per fetus bases. The incidences of other major malformations or of minor malformations in this group were not significantly increased over those of the control group when compared on either litter or fetal incidence bases. As a result of the ventral midline defects in this group, the incidences of all major malformations combined and all major and minor malformations combined, when compared on both litter and fetal incidence bases were also significantly increased.

Examination of prematurely delivered pups, fetuses recovered from females dying spontaneously, and late resorptions.

Five viable intact pups and one partially cannibalized pup were delivered prematurely to control female No. 125 on gestation day 27. The five intact pups were examined for external and skeletal malformations. No remarkable findings were noted.

Eight viable intact pups were delivered prematurely to control female No. 126 on gestation day 27. These pups were examined for external and skeletal malformations. No remarkable findings were noted.

Five partially resorbed fetuses were delivered to medium dose female No. 335 on gestation day 26. These fetuses were not suitable for examination and were discarded.

Ten nonviable fetuses were recovered at the autopsy of high dose female No. 421, who died on gestation day 28 as a result of purulent bronchopneumonia. External examination of these fetuses was unremarkable. Because of the state of autolysis, the fetuses could only be saved in 95% ethanol for skeletal examination. Skeletal examination of seven of the fetuses was unremarkable. Supernumerary nasal sutures were noted in fetuses 42101M and 42108M and a split second sternebra was noted in fetus 42107F. These findings are classified as minor malformations.

L-phenylalanine group female No. 269 delivered a total of five pups prematurely on gestation days 27 and 28, and had one additional fetus in her uterus at autopsy on gestation day 28. Because of autolysis and cannibalization, only three of these specimens were suitable for external examination, and were found to be unremarkable. These tissues did not stain properly and skeletal examination could not be performed.

L-phenylalanine group female No. 277 delivered five nonviable pups on gestation day 28. Four of these pups were saved for skeletal examination but the fifth was severely autolyzed and was discarded. Supernumerary nasal sutures were noted in pup 22703M. No other remarkable findings were noted.

One late fetal resorption with an umbilical hernia was recovered from L-phenylalanine group female No. 289. This was the only resorption in the litter and there were no other remarkable findings in the seven fetuses of the litter. Because of the advanced state of autolysis, no further examination of this late resorption was attempted.

The above litters have been listed in the Uterine Implantation Data table (Appendix I, Table 5), and those containing fetuses or pups with malformations are presented in the Comprehensive Litter Examination Report (Appendix III). Data derived from these examinations have not been included in calculations of totals or means or in the statistical comparisons, since these litters do not represent normal in utero litters. In some cases it is possible that part of the litter was cannibalized and actual litter size could not be determined, and in other instances the state of autolysis precluded meaningful fetal body weight and crown-rump distance measurements.

SUMMARY AND CONCLUSIONS

This study was designed and conducted to evaluate the embryotoxic and teratogenic potential of SC-18862 (aspartame) in the pregnant rabbit. SC-18862 was suspended in an aqueous solution of Tween-80 and methyl cellulose, and was administered by intragastric intubation in two divided doses daily to artificially inseminated rabbits from post-insemination day 6 through day 18. Dose levels of 0, 0.5, 1.0, and 2.0 g/kg were administered. L-phenylalanine or L-aspartic acid, dietary amino acids which are the principal constituents of SC-18862, were administered in the same manner at dose levels of 0.82 and 1.10 g/kg respectively, levels equivalent to 75% and 134% the amount of these same amino acids theoretically available to the 2 g/kg SC-18862 group. Each treatment group contained fifty inseminated rabbits. On post-insemination day 28 all surviving females were sacrificed and autopsied. Fetuses were removed by hysterotomy and examined, weighed, measured and preserved for either soft tissue or skeletal examination. Appropriate statistical analyses were performed on the data obtained. The fetal malformation data from this concurrent control group were also compared to a historical laboratory control group consisting of 1,717 fetuses from 233 litters.¹³ The incidence of major and minor malformations did not differ significantly between the concurrent and historical control groups.

Significant decreases in food consumption were observed in both the high level (2 g/kg) SC-18862 and L-phenylalanine groups, beginning on the first day of treatment (gestation day 6) and continuing throughout the treatment period (gestation day 18). This decrease in food consumption was followed by body weight loss, first apparent on gestation day 10. These body weight losses were statistically significant in the high level group

beginning on gestation day 13, and were more marked in those females that ultimately aborted, which comprised well over one-half of the pregnant high dose females. Examination of food consumption data demonstrated that food consumption was lower in those high level animals that subsequently aborted than in those that maintained their pregnancies to gestation day 28. It is significant that most abortions occurred during the period from gestation days 18 to 21, which is well after the decrease in food consumption and resulting weight loss were first apparent. It is evident that SC-18862 at a level of 2 g/kg, when administered to the rabbit by intragastric intubation during early-mid pregnancy, significantly reduces food consumption. The degree of reduced food consumption varied between individual animals, and resulted in correspondingly variable individual weight losses. In certain animals this nutritional deprivation was not compatible with continued pregnancy, and abortion occurred about two weeks after the treatment period began. Developmentally, this period coincides with the completion of organogenesis and the onset of a period of rapid fetal growth.^{14,15} It is known that stress of this nature and magnitude, when applied to a pregnant animal, may result in abortion.⁹ The total nutrient intake is no longer adequate to maintain the needs of both the dam and the litter.

L-phenylalanine was administered at a level of 0.82 g/kg, which was equivalent to 75% of the L-phenylalanine received by the high dose SC-18862 group. This dosage regime depressed body weight and food consumption significantly, but to a lesser extent than did 2 g/kg of SC-18862. Abortions and premature deliveries did occur in the L-phenylalanine group, but not in statistically significant numbers. The decrease in body weight and food consumption in the L-phenylalanine and high level SC-18862 groups was

approximately proportional to the amount of L-phenylalanine administered and/or theoretically available, and was thus most marked in the high level SC-18862 group. Likewise, and correspondingly, abortions were more frequent in this latter group. It is apparent that most abortions may be a result of maternal nutritional deprivation, and may not be due to a direct toxic effect of SC-18862 or of L-phenylalanine.

Statistical analysis of the fetal resorption data indicated that those litters with large numbers of resorptions were distributed disproportionately, and occurred significantly more frequently in the L-phenylalanine group than in other groups. As mentioned above, the incidence of abortions was not significantly increased in the L-phenylalanine group, but was increased in the high level SC-18862 group. These data are consistent with the hypothesis that above a certain level, nutritional intake is inversely related to L-phenylalanine intake, and that fetal resorption or abortion are maternal responses reflecting increasingly severe nutritional deprivation. Thus, the number of fetuses resorbed per litter would be expected to increase, and the number of surviving fetuses decrease, as nutritional intake was progressively reduced. Very severe nutritional deprivation would be expected to induce abortion so as to conserve at least the maternal animal.

Mean fetal body weight and length were significantly reduced in the high level SC-18862 and the L-phenylalanine groups. These decreases were approximately proportional to the reduction in food consumption, and were thus more marked in the high level SC-18862 group. Similar effects have been induced in rat progeny by dietary restriction.¹⁵

The number of tarsal and metacarpal ossification centers has been shown to be a useful indicator of normal fetal growth in the rat, and is known to be significantly influenced by the state of maternal nutrition at certain critical periods of gestation.^{12,16} The number of both tarsal and metacarpal ossification centers was significantly reduced in the rabbit fetuses at the high level of SC-18862 and in the L-phenylalanine group in this study. Additionally, a significant increase in the incidence of an additional (13th) pair of ribs and a reduction in sternebral ossification centers was observed in the high level SC-18862 group. In the rat, these changes are known to be caused by appropriately timed maternal fasting and retarded fetal development, respectively.¹² These changes in the development of the rabbit fetus may be therefore attributed to maternal nutrition being compromised during gestation, as a result of the intragastric intubation of L-phenylalanine, either as the pure amino acid or as derived by gastrointestinal hydrolysis of SC-18862.

Comparisons based on either fetal incidence or litter incidence revealed a significantly higher rate of total (major and minor) malformations in both the high level SC-18862 group and the L-phenylalanine group, as compared to the concurrent control group. The increases in major malformations were due primarily to three instances of cleft palate in two litters in the high level SC-18862 group, and five instances of umbilical hernia or omphalocele in five separate litters in the L-phenylalanine group. The increases in minor malformations were due in large part to various vertebral defects and fused or split sternebrae. It is known that similar defects can be induced in fetal mice either by total dietary restriction for as little as 24 hours¹⁷ or by partial dietary restriction over a longer portion of the

gestation period.¹⁸ It is suggestive that dietary restriction resulting from high phenylalanine dosage may be responsible for the fetal malformations in this rabbit study.

Data from the 0.5 and 1.0 g/kg levels of SC-18862 and from the L-aspartic acid only group were compared to the concurrent control group, and no significant differences in the following parameters occurred: maternal survival rates; maternal conception rates; incidences of abortion or of premature delivery; maternal body weights; food consumption; incidences of litters consisting of fetuses only, of both fetuses and resorption sites, or of resorption sites only; mean litter sizes; mean number of resorption sites per litter; mean fetal body weights or crown-rump distances; incidences of major or minor malformations on a per litter or per fetus basis.

In summary, intragastric intubation of 0.5 or 1.0 g/kg of SC-18862 or of 1.1 g/kg of L-aspartic acid in two divided doses daily by the pregnant rabbit exerts no apparent adverse effects. These levels produced no significant changes in any of the parameters measured. Statistically significant effects were produced at the 2 g/kg level; malformations observed may be a result of marked reduction in nutrient intake and resulting body weight loss in the maternal rabbit. Similar effects were produced by the administration of L-phenylalanine. Effects similar to those seen in this rabbit study as a result of severe reduction of nutrient intake because of the intragastric intubation of 2.0 g/kg of SC-18862 have also been observed by others following severe dietary restriction in rodents. Therefore, it appears that SC-18862 may be producing these effects by severely reducing nutrient intake, and not as a direct toxic effect. It is important to recognize that intragastric intubation is necessary to achieve these intake levels of SC-18862.

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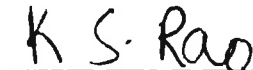
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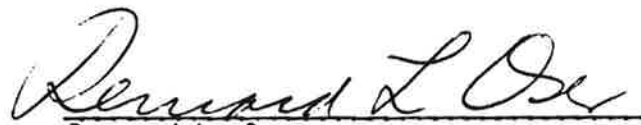
SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT

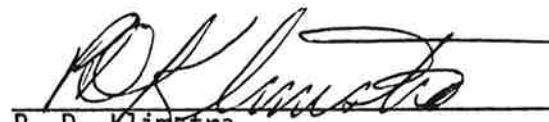
Pathology-Toxicology
Project No. 1201

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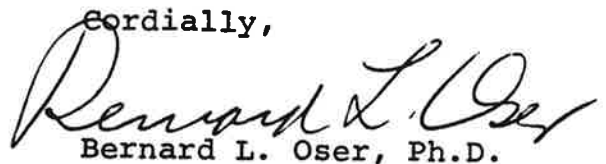
Dr. W. Joseph Potts, Assoc. Director,
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Dear Dr. Potts:

As requested, I have reviewed the protocol and the report of your Path-Tox Project No. 1201S75 entitled "SC-18862: An Evaluation of Embryotoxic and Teratogenic Potential in the Rabbit".

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 at doses up to 1 g/kg was neither teratogenic nor embryotoxic to rabbits under the test conditions employed. The effect at the 2 g/kg Aspartame level was not clear owing to significant reduction in maternal food intake.

Cordially,


Bernard L. Oser, Ph.D.

BLO:b

APPENDIX I

Individual Maternal and Fetal Data

APPENDIX I.

Table 1.

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

MATERNAL BODY WEIGHT DATA (KG)
(ARITHMETIC MEANS WITH STANDARD ERRORS)

TREATMENT GROUP	NO. OF PREGNANT FEMALES	GESTATION DAY									
		0	3	6	10	13	15	18	22	28	
CONTROL	42	3.95 0.063	4.00 0.060	4.00 0.063	3.98 0.062	3.97 0.063	4.04 ^{e,f} 0.066	4.06 ^g 0.071	4.08 0.078	4.13 0.072	
LOW	46	3.95 0.055	3.95 0.058	3.94 0.060	3.94 0.059	3.93 ^{d,c} 0.060	4.00 ^d 0.059	4.01 0.057	4.04 0.059	4.12 ^l 0.054	
MEDIUM	46	3.93 0.055	4.00 0.055	4.04 0.058	3.98 0.052	3.97 0.053	4.04 0.054	4.05 ^h 0.053	4.08 0.050	4.13 0.052	
HIGH	37	3.99 0.062	4.05 0.062	4.05 0.064	3.88 0.060	3.75 [*] 0.062	3.75 [*] 0.062	3.64 [*] 0.068	3.61 ^{m,j} 0.067	3.74 ^{n,l} 0.060	
L-PHE	39	3.96 0.063	4.02 0.063	4.03 0.064	3.96 0.062	3.90 ^{b,c} 0.070	3.93 0.072	3.90 0.076	3.96 ^{j,k} 0.076	4.03 0.072	
L-ASP	44	4.08 0.066	4.14 0.064	4.14 0.066	4.10 0.066	4.09 0.066	4.16 0.066	4.17 0.063	4.20 ^l 0.067	4.27 0.064	

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

^aFemale No. 207 found dead gestation day 11.

^bFemale No. 290 found dead gestation day 12.

^cFemale Nos. 206 and 283 found dead gestation day 13.

^dFemale No. 248 found dead gestation day 13.

^eFemale No. 131 found dead gestation day 14.

^fFemale Nos. 134 and 410 found dead gestation day 15.

^gFemale Nos. 139 and 141 found dead gestation day 17.

^hFemale No. 322 found dead gestation day 17.

ⁱFemale No. 370 found dead gestation day 18.

^jFemale Nos. 424, 438 and 263 found dead gestation day 21.

^kFemale Nos. 280 and 295 found dead gestation day 22.

^lFemale Nos. 214 and 421 found dead gestation day 28.

APPENDIX I

Table 1 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Selected Maternal Body Weight Data (kg)
(Arithmetic Mean \pm S.E.)

Treatment Group	Number of Pregnant Females	Gestation Day									
		0	3	6	10	13	15	18	22	28	
Control	42	3.95 0.06	4.00 0.06	4.00 0.06	3.98 0.06	3.97 0.06	4.04 0.07	4.06 0.07	4.08 0.08	4.13 0.07	
High Dose Non-Aborting	9	4.07 0.16	4.17 0.16	4.17 0.17	4.06 0.15	3.94 0.14	3.95 0.14	3.96 0.13	3.94 0.11	3.97 0.09	
High Dose Aborting	22	3.98 0.07	4.04 0.06	4.04 0.06	3.82 0.06	3.69* 0.07	3.69* 0.06	3.57* Δ 0.06	3.48* Δ 0.07	3.65* Δ 0.07	
L-Phe	39	3.96 0.06	4.02 0.06	4.03 0.06	3.96 0.06	3.90 0.07	3.93 0.07	3.90 0.08	3.96 0.08	4.03 0.07	

*Difference statistically significant from control group ($p < 0.05$).

Δ Difference statistically significant between aborting and non-aborting high dose females ($p < 0.05$).

APPENDIX I
 TABLE 1 (cont.)

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

MATERNAL BODY WEIGHT DATA FOR THE CONTROL GROUP (KG)

ANIMAL NUMBER	GESTATION DAY									
	0	3	6	10	13	15	18	22	28	
101	4.63	4.78	4.56	4.55	4.63	4.59	4.63	4.61	4.71	
102	4.60	4.59	4.64	4.48	4.48	4.49	4.49	4.42	4.39	
104	4.41	4.49	4.57	4.39	4.41	4.41	4.30	N.D.	4.24	
105	4.40	4.42	4.50	4.43	4.38	4.42	4.39	4.44	4.49	
106	3.78	3.81	3.89	3.87	3.86	3.83	3.82	3.90	4.00	
107	4.67	4.31	4.46	4.28	4.03	3.90	3.79	3.50	3.79	
108	3.85	3.89	3.77	3.61	3.52	3.70	3.63	3.69	3.90	
109	3.88	3.95	4.06	3.80	3.71	3.74	3.65	3.64	3.70	
111	3.87	3.83	3.96	3.75	3.83	3.89	3.89	3.97	4.04	
112	4.14	4.15	4.13	4.13	4.15	4.21	4.10	4.06	4.29	
113	4.88	4.88	4.87	4.80	4.83	4.86	4.91	4.89	4.97	
114	4.43	4.51	4.44	4.47	4.48	4.48	4.53	4.55	4.46	
115	4.13	4.09	4.20	4.20	4.20	4.25	4.29	4.34	4.48	
116	4.67	4.63	4.71	4.62	4.75	4.79	4.92	4.87	4.51	
117	4.15	4.08	4.08	3.88	4.00	4.06	4.13	4.18	4.16	
118	4.10	4.19	4.29	4.07	4.15	4.07	4.19	4.19	4.28	
119	3.84	3.85	3.94	3.92	4.00	4.17	4.19	4.22	4.34	
121	4.38	4.63	4.65	4.68	4.70	4.86	4.92	4.96	4.99	
122	3.51	3.62	3.67	3.66	3.62	3.66	3.32	3.14	3.07	
123	4.04	4.22	4.31	4.40	4.34	4.50	4.48	4.72	4.48	
124	3.76	3.85	3.72	3.91	3.94	4.12	4.15	4.33	4.33	
125	3.51	3.48	3.50	3.52	3.37	3.28	3.29	3.19	2.93	
126	4.35	4.29	3.95	4.38	4.38	4.45	4.61	4.63	4.13	
128	3.55	3.43	3.31	3.29	3.46	3.44	3.50	3.68	3.86	
129	3.68	3.76	3.83	3.87	3.87	3.93	3.93	4.04	4.18	

N.D. = No Data.

APPENDIX I
 TABLE 1 (cont.)

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

ANIMAL NUMBER	MATERNAL BODY WEIGHT DATA FOR THE CONTROL GROUP (KG)							
	0	3	6	10	GESTATION DAY			
					13	15	18	22
								28
130	3.31	3.45	3.45	3.48	3.48	3.47	3.43	3.51
131	3.81	3.84	3.87	3.99	3.68	D	--	--
132	3.82	3.84	3.90	3.91	3.93	4.00	4.07	4.09
133	3.60	3.65	3.60	3.59	3.61	3.65	3.66	3.76
134	3.39	3.68	3.69	3.53	3.65	D	--	--
135	3.77	4.07	4.01	3.76	3.85	4.01	4.08	4.28
136	3.78	3.74	3.95	4.00	4.04	4.03	4.10	4.39
138	3.32	3.97	3.48	3.97	3.70	3.57	3.56	3.57
139	3.73	3.70	3.69	3.38	3.30	3.24	D	--
140	3.55	3.52	3.58	3.67	3.52	3.69	3.70	3.94
141	4.30	4.36	4.40	4.47	4.33	4.37	D	--
142	3.94	3.90	3.92	3.98	3.95	4.10	4.12	4.19
143	3.53	3.68	3.68	3.67	3.77	3.83	3.85	4.08
144	3.36	3.38	3.30	3.25	3.28	3.36	3.39	3.44
145	3.73	3.82	3.76	3.81	3.83	3.84	3.91	4.11
146	3.98	4.07	4.12	4.19	4.22	4.16	4.20	4.55
150	3.89	3.67	3.45	3.50	3.51	4.02	4.13	4.21
MEANS	3.95	4.00	4.00	3.98	3.97	4.04	4.06	4.13

D = Dead.

APPENDIX I
 TABLE 1(cont.)

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

MATERNAL BODY WEIGHT DATA FOR THE LOW DOSE GROUP (KG)

ANIMAL NUMBER	GESTATION DAY									
	0	3	6	10	13	15	18	22	28	
201	4.26	4.19	4.24	4.19	4.15	4.15	4.26	4.22	4.18	
202	4.98	5.00	4.94	4.88	4.87	4.94	4.90	4.86	4.93	
203	3.92	3.95	3.87	3.88	3.89	3.99	3.92	3.99	4.13	
204	4.06	4.18	4.16	4.05	4.09	4.20	4.21	4.28	4.27	
205	4.79	4.94	4.91	4.87	4.90	4.97	4.96	4.97	5.00	
206	3.91	4.05	4.09	4.13	D	--	--	--	--	
207	4.33	4.12	4.17	4.04	D	--	--	--	--	
208	3.89	3.85	3.86	3.87	3.79	3.81	3.73	3.90	3.84	
210	4.10	4.20	4.24	4.13	4.11	4.11	4.11	4.08	4.08	
211	3.91	3.86	3.80	3.69	3.73	3.78	3.76	3.82	3.81	
212	4.33	4.36	4.37	4.26	4.27	4.33	4.32	4.35	4.23	
213	4.26	4.17	4.17	4.16	4.12	4.15	4.18	4.22	4.26	
214	4.53	4.44	4.19	4.11	3.84	3.79	3.73	3.30	D	
215	3.82	3.91	3.93	3.86	3.90	3.94	3.91	3.86	3.93	
216	4.37	4.42	4.47	4.41	4.37	4.38	4.40	4.56	4.47	
217	4.15	4.21	4.28	4.24	4.24	4.31	4.30	4.28	4.27	
218	4.34	4.42	4.52	4.54	4.62	4.59	4.63	4.70	4.83	
219	3.69	3.83	3.94	3.87	3.82	3.98	3.95	3.97	4.17	
220	4.35	4.50	4.56	4.54	4.57	4.71	4.71	4.71	4.70	
222	3.64	3.58	3.73	3.78	3.78	3.85	3.85	4.02	3.93	
223	3.48	3.49	3.61	3.64	3.49	3.71	3.73	3.88	3.89	
224	3.57	3.62	3.58	3.62	3.68	3.78	3.78	3.89	4.05	
225	3.91	3.90	3.92	3.97	4.01	4.10	4.16	4.25	4.37	
226	3.90	3.83	3.78	3.87	3.83	3.90	3.98	4.07	4.09	
227	3.66	3.57	3.60	3.74	3.72	3.78	3.75	3.78	3.76	

D = Dead.

APPENDIX I
 TABLE 1 (cont.)

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

MATERNAL BODY WEIGHT DATA FOR THE LOW DOSE GROUP (KG)

ANIMAL NUMBER	GESTATION DAY									
	0	3	6	10	13	15	18	22	28	
228	3.64	3.60	3.61	3.65	3.68	3.65	3.72	3.70	3.87	
229	3.36	3.39	3.33	3.32	3.33	3.41	3.34	3.34	3.41	
230	4.30	4.26	4.26	4.29	4.42	4.43	4.32	4.26	4.27	
231	3.75	3.69	3.73	3.80	3.81	3.86	3.92	3.97	4.05	
232	4.09	3.68	3.60	3.58	3.62	3.70	3.77	3.78	3.94	
233	3.66	4.09	4.16	4.09	4.10	4.21	4.14	4.17	4.30	
234	3.34	3.46	3.46	3.41	3.43	3.47	3.59	3.58	3.75	
236	3.52	3.62	3.70	3.69	3.77	3.86	3.89	3.88	4.16	
238	3.66	3.71	3.63	3.73	3.65	3.66	3.72	3.74	3.78	
239	3.32	3.17	3.13	3.20	3.25	3.24	3.24	3.34	3.39	
240	3.82	3.74	3.73	3.76	3.77	3.79	3.81	3.90	4.03	
241	3.60	3.75	3.76	3.84	3.80	3.83	3.90	3.96	3.97	
242	3.59	3.52	3.55	3.68	3.63	3.78	3.86	3.91	4.01	
243	3.68	3.74	3.61	3.63	3.66	3.76	3.77	3.75	3.91	
244	4.04	4.06	4.02	3.91	3.99	4.07	4.04	4.12	4.25	
245	3.67	3.64	3.60	3.56	3.64	3.84	3.74	3.82	4.00	
246	4.42	4.36	4.35	4.92	4.46	4.63	4.62	4.74	4.65	
247	4.02	4.12	4.11	4.16	4.17	4.26	4.21	4.30	4.25	
248	4.15	4.22	4.15	4.12	4.18	D	--	--	--	
249	4.00	3.63	3.33	3.37	3.36	3.68	4.02	3.97	3.92	
250	3.95	3.53	3.30	3.36	3.31	3.63	3.62	3.71	3.87	
MEANS	3.95	3.95	3.94	3.94	3.93	4.00	4.01	4.04	4.12	

D = Dead.

APPENDIX I
TABLE 1 (cont.)

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

ANIMAL NUMBER	U	MATERNAL BODY WEIGHT DATA FOR THE MEDIUM DOSE GROUP (KG)							
		GESTATION DAY							
		3	6	10	13	15	18	22	28
301	4.64	4.77	4.75	4.63	4.65	4.66	4.62	4.41	4.42
302	3.72	3.79	3.96	3.88	3.97	3.86	3.96	4.00	4.07
303	4.43	4.43	4.55	4.44	4.49	4.55	4.55	4.51	4.34
304	4.40	4.43	4.41	4.30	4.30	4.31	4.24	4.27	4.31
306	4.18	4.31	4.26	4.08	4.10	4.11	4.19	4.17	4.26
307	4.07	4.11	4.09	4.08	4.06	4.12	4.14	4.21	4.29
308	3.99	4.29	4.43	4.32	4.29	4.39	4.38	4.43	4.41
309	4.55	4.64	4.65	4.60	4.59	4.64	4.65	4.61	4.47
310	3.79	3.89	3.97	3.97	4.04	4.14	4.10	4.24	4.33
312	3.80	3.85	3.81	3.74	3.69	3.79	3.85	3.81	3.63
313	4.54	4.63	4.64	4.56	4.63	4.71	4.68	4.41	4.25
314	4.32	4.26	4.20	4.03	3.98	4.05	3.87	4.15	4.13
315	4.53	4.53	4.56	4.40	4.23	4.23	4.20	4.17	4.18
316	4.27	4.33	4.40	4.34	4.39	4.41	4.44	4.28	4.53
317	4.37	4.26	4.33	4.08	3.95	3.87	3.83	3.87	4.13
318	3.95	4.00	3.97	3.82	3.84	3.90	3.89	3.83	3.94
319	4.30	4.54	4.53	4.49	4.52	4.60	4.55	4.57	4.67
320	3.90	3.95	4.05	4.00	4.04	4.10	4.15	3.98	4.07
321	4.07	4.12	4.20	4.21	4.21	4.30	4.27	4.22	4.25
322	3.63	3.64	3.69	3.73	3.70	3.83	D	--	--
323	3.60	3.69	3.65	3.70	3.63	3.74	3.79	3.90	3.99
324	3.85	3.83	3.89	3.87	3.79	3.97	3.94	4.19	4.16
325	3.55	3.52	3.48	3.55	3.49	3.53	3.63	3.66	3.65
326	3.60	3.58	3.56	3.57	3.50	3.54	3.62	3.65	3.67
328	3.80	3.76	3.74	3.78	3.67	3.71	3.78	3.86	3.95

D = Dead.

APPENDIX I
 TABLE 1 (cont.)

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

MATERNAL BODY WEIGHT DATA FOR THE MEDIUM DOSE GROUP (KG)

ANIMAL NUMBER	0	GESTATION DAY					22	28	
		3	6	10	13	15			18
329	4.34	4.39	4.40	4.41	4.21	4.37	4.48	4.59	4.60
330	4.06	4.14	4.07	4.12	4.16	4.26	4.16	4.16	4.21
331	3.83	3.68	4.28	3.67	3.57	3.61	3.74	3.74	3.88
332	3.83	3.94	4.60	4.19	3.74	3.78	3.79	3.86	4.06
333	3.81	3.80	3.92	3.80	3.80	3.87	3.94	3.92	4.09
334	4.19	4.48	4.30	4.32	4.42	4.53	4.47	4.39	4.53
335	3.78	4.08	4.09	3.97	4.07	4.13	4.09	4.09	3.77
336	3.15	3.28	3.25	3.25	3.19	3.24	3.24	3.28	3.39
337	3.54	3.73	3.70	3.57	3.52	3.56	3.60	3.76	3.85
338	3.41	3.57	3.52	3.63	3.63	3.64	3.61	3.43	3.18
339	3.49	3.79	3.84	3.95	3.91	3.98	4.05	4.22	4.30
340	4.16	4.27	4.41	4.39	4.38	4.55	4.62	4.80	4.95
341	3.90	3.88	3.89	3.97	3.81	3.75	3.70	3.97	3.98
342	3.97	3.95	3.97	4.00	3.98	4.06	4.14	4.32	4.27
343	3.28	3.41	3.43	3.40	3.45	3.56	3.55	3.62	3.67
344	3.31	3.32	3.32	3.38	3.41	3.45	3.56	3.60	3.77
345	4.13	4.21	4.23	4.28	4.38	4.56	4.59	4.63	4.76
346	3.44	3.50	3.48	3.52	3.68	3.76	3.71	3.87	3.95
347	3.46	3.75	3.75	3.66	3.80	3.97	3.96	4.21	4.36
348	3.80	3.94	3.87	3.82	3.89	3.99	3.99	4.00	4.12
349	4.00	3.77	3.56	3.69	3.69	3.96	4.15	4.02	4.08
MEANS	3.93	4.00	4.04	3.98	3.97	4.04	4.05	4.08	4.13

APPENDIX I
 TABLE 1 (cont.)

 SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
 TERATOGENIC POTENTIAL IN THE RABBIT
 MATERNAL BODY WEIGHT DATA FOR THE HIGH DOSE GROUP (KG)

ANIMAL NUMBER	GESTATION DAY									
	0	3	6	10	13	15	18	22	28	
402	4.72	4.67	4.74	4.55	4.48	4.36	4.05	3.88	4.00	
404	4.85	5.02	5.04	4.84	4.69	4.64	4.51	4.29	4.14	
405	3.98	3.91	3.87	3.64	3.55	3.55	3.47	3.56	3.66	
406	4.40	4.58	4.60	4.23	4.23	4.08	3.87	3.63	3.35	
407	4.08	4.12	4.14	3.90	3.62	3.50	3.49	3.19	3.15	
408	4.55	4.54	4.56	4.35	4.22	4.23	4.27	4.24	4.17	
409	4.92	4.94	4.90	4.64	4.49	4.50	4.28	4.11	4.35	
410	3.76	3.85	3.85	3.60	3.34	D	--	--	--	
411	4.17	4.20	4.21	3.87	3.74	3.77	3.76	3.36	3.59	
412	4.30	4.41	4.56	4.17	3.92	4.11	4.03	3.89	4.20	
413	3.90	3.87	3.87	3.57	3.39	3.49	3.50	3.41	3.60	
415	3.96	4.18	4.16	3.90	3.80	3.83	3.75	3.61	3.86	
416	3.79	3.99	4.07	3.89	3.84	3.64	3.37	3.19	3.54	
418	3.54	3.59	3.69	3.52	3.38	3.44	3.62	3.51	3.51	
420	3.83	3.93	3.92	3.69	3.45	3.58	3.32	3.10	3.23	
421	3.99	4.21	4.17	4.17	4.07	4.14	4.04	3.92	D	
422	3.73	3.80	3.85	3.61	3.42	3.51	3.39	3.44	3.67	
423	3.77	3.75	3.91	3.51	3.31	3.29	3.15	3.30	3.57	
424	3.84	3.89	3.82	3.67	3.64	3.51	3.01	D	--	
425	3.83	3.89	3.86	3.88	3.72	3.78	3.83	3.79	3.88	
426	4.04	4.14	4.06	4.19	4.11	4.02	4.20	4.25	4.19	
428	3.87	3.88	3.86	3.71	3.62	3.64	3.60	3.52	3.89	
429	3.29	3.32	3.19	3.36	3.21	3.19	2.80	2.92	3.22	
430	3.44	3.43	3.46	3.39	3.32	3.31	3.21	3.38	3.47	
431	3.49	3.60	3.58	3.50	3.44	3.44	3.56	3.62	3.75	

D = Dead.

APPENDIX I
TABLE 1 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBIT

MATERNAL BODY WEIGHT DATA FOR THE HIGH DOSE GROUP (KG)

ANIMAL NUMBER	GESTATION DAY									
	0	3	6	10	13	15	18	22	28	
434	3.55	3.67	3.62	3.38	3.38	3.32	3.16	2.85	3.20	
435	3.63	3.81	3.78	3.45	3.55	3.55	3.62	3.47	3.64	
436	3.89	4.12	4.15	4.05	3.94	3.95	3.91	3.81	3.72	
437	3.79	3.92	3.93	3.84	3.60	3.54	3.39	3.63	3.83	
438	3.70	3.71	3.69	3.51	3.26	3.19	2.97	D	--	
439	3.86	3.98	3.85	3.74	3.60	3.47	3.33	3.10	3.53	
440	4.13	4.06	4.06	3.95	3.93	3.76	3.55	3.73	3.74	
441	4.34	4.24	4.29	4.19	4.11	4.25	4.16	4.08	4.34	
443	4.24	4.38	4.27	4.13	4.07	4.09	4.17	4.22	4.20	
444	4.08	4.07	3.98	3.99	3.76	3.82	3.53	3.47	3.51	
445	4.20	4.33	4.25	4.17	4.00	4.06	3.86	4.01	4.17	
447	4.01	3.99	3.91	3.64	3.49	3.57	3.41	3.28	3.45	
MEANS	3.99	4.05	4.05	3.88	3.75	3.75	3.64	3.61	3.74	

D = Dead.

APPENDIX I
 TABLE 1 (cont.)

 SC-18962: AN EVALUATION OF EMBRYOTOXIC AND
 TERATOGENIC POTENTIAL IN THE RABBIT

MATERNAL BODY WEIGHT DATA FOR THE L-PHE GROUP (KG)

ANIMAL NUMBER	GESTATION DAY									
	0	3	6	10	13	15	18	22	28	
283	3.96	3.96	4.02	4.07	D	--	--	--	--	
284	3.79	3.96	3.92	4.01	4.03	4.21	4.27	4.29	4.46	
296	3.76	4.06	4.09	4.10	4.11	4.20	4.15	4.26	4.49	
297	3.90	3.95	4.04	4.11	4.07	4.10	4.23	4.37	4.47	
288	3.86	3.94	3.91	3.94	3.73	3.80	3.80	3.81	3.86	
289	4.06	4.08	4.09	4.03	3.79	3.81	3.88	3.91	4.12	
290	4.10	4.08	4.16	4.07	D	--	--	--	--	
291	4.03	3.96	3.94	3.94	3.87	4.00	3.98	4.10	4.24	
292	4.06	4.06	4.00	3.81	3.49	3.56	3.53	3.90	3.99	
293	4.14	4.07	3.94	3.78	3.93	3.57	3.36	3.40	3.78	
295	3.92	3.99	4.05	3.91	3.82	3.83	3.63	D	--	
296	3.69	3.87	3.82	3.56	3.56	3.58	3.64	3.76	3.49	
297	3.57	3.70	3.75	3.81	3.75	3.82	3.92	3.90	3.97	
298	3.55	3.68	3.76	3.60	3.53	3.58	3.46	3.46	3.70	
MEANS	3.96	4.02	4.03	3.96	3.90	3.93	3.90	3.96	4.03	

D = Dead.

APPENDIX I
 TABLE 1 (cont.)

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

MATERNAL BODY WEIGHT DATA FOR THE L-ASP GROUP (KG)

ANIMAL NUMBER	GESTATION DAY								
	0	3	6	10	13	15	18	22	28
351	5.65	5.69	5.64	5.56	5.59	5.59	5.44	5.58	5.71
352	4.59	4.59	4.60	4.60	4.71	4.77	4.79	4.56	4.62
353	4.36	4.45	4.51	4.26	4.35	4.52	4.41	4.52	4.72
354	3.95	3.96	3.98	4.00	3.98	4.32	4.01	4.01	4.05
356	3.85	3.89	3.81	3.83	3.88	3.96	3.99	4.05	4.12
358	4.70	4.83	4.56	4.74	4.72	4.77	4.77	4.71	4.32
359	4.28	4.25	4.24	4.12	4.12	4.22	4.11	4.05	4.11
360	4.33	4.52	4.60	4.60	4.62	4.70	4.68	4.69	4.75
361	4.71	4.94	4.94	4.69	4.66	4.69	4.73	4.71	4.83
362	5.06	5.01	5.02	5.03	5.06	5.13	5.14	5.25	5.15
363	4.38	4.42	4.09	4.01	4.05	4.11	4.09	4.13	4.38
364	4.03	4.05	4.38	4.34	4.29	4.30	4.25	4.22	4.27
365	4.39	4.44	4.52	4.48	4.48	4.58	4.53	4.53	4.64
366	3.81	3.98	3.88	3.78	3.75	3.82	3.79	3.69	3.76
367	4.51	4.35	4.29	4.24	4.21	4.22	4.27	4.20	4.18
368	4.09	4.00	4.01	4.00	4.05	4.08	4.03	4.05	4.10
370	4.23	4.37	4.52	4.40	4.35	4.47	4.38	D	--
371	4.14	4.30	4.33	4.25	4.33	4.37	4.45	4.38	4.59
372	4.10	4.11	4.16	4.36	4.35	4.47	4.46	4.57	4.48
373	4.24	4.22	4.36	4.38	4.35	4.41	4.39	4.45	4.35
374	4.12	4.44	4.41	4.07	4.05	4.09	4.23	4.29	4.30
375	3.70	3.75	3.76	3.84	3.73	3.75	3.89	3.91	3.93
376	3.92	3.90	3.89	3.49	3.50	3.56	3.58	3.66	3.71
377	3.79	3.64	3.55	3.51	3.51	3.55	3.52	3.56	3.57
378	3.63	3.74	3.77	3.75	3.77	3.71	3.76	3.70	3.88

D = Dead.

APPENDIX I
 TABLE 1 (cont.)

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

MATERNAL BODY WEIGHT DATA FOR THE L-ASP GROUP (KG)

ANIMAL NUMBER	GESTATION DAY								
	0	3	6	10	13	15	18	22	28
379	4.05	4.16	4.11	4.09	4.07	4.26	4.19	4.21	4.42
380	3.64	3.71	3.71	3.74	3.73	3.81	3.79	3.80	3.91
381	4.08	4.03	4.07	4.06	4.11	4.22	4.23	4.29	4.51
382	3.74	3.83	3.89	3.90	3.91	3.91	4.03	3.99	4.21
383	3.61	3.79	3.86	3.95	3.98	4.00	4.03	4.10	4.23
384	3.67	3.79	3.90	3.73	3.69	3.86	3.81	3.70	3.81
385	3.75	3.92	3.78	3.80	3.81	3.90	3.95	3.93	4.08
386	3.10	3.35	3.19	3.20	3.33	3.41	3.43	3.46	3.63
387	3.99	4.12	4.06	3.82	3.66	3.62	3.64	3.67	3.74
388	3.72	3.97	3.98	4.05	3.95	4.01	3.95	4.10	4.14
389	3.84	3.95	4.07	4.01	4.02	4.01	4.05	4.15	4.14
390	4.25	4.38	4.47	4.56	4.40	4.57	4.67	4.90	4.90
391	3.91	3.87	3.98	4.16	4.15	4.22	4.27	4.29	4.41
392	4.10	4.09	4.17	4.19	4.18	4.33	4.32	4.48	4.63
393	3.74	3.78	3.79	3.74	3.78	3.85	3.83	3.84	3.98
394	4.08	4.08	4.08	4.02	3.82	3.90	3.83	3.97	4.10
395	3.54	3.62	3.67	3.58	3.61	3.76	3.72	3.83	3.98
396	3.75	4.02	3.96	3.95	3.96	4.09	4.17	4.13	4.29
398	4.20	3.82	3.56	3.52	3.52	3.64	4.15	4.37	4.30
MEANS	4.08	4.14	4.14	4.10	4.09	4.16	4.17	4.20	4.27

APPENDIX I
Table 2.

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

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

TREATMENT GROUP	NO. OF PREGNANT FEMALES	0	3	6	7	8	9	10	11	12	13
CONTROL	42	36.0 1.8	38.8 2.0	35.0 2.2	33.9 2.3	34.1 2.6	33.4 2.7	30.7 2.2	34.3 2.2	34.4 2.3	29.9 2.3
LOW	46	34.2 2.0	38.5 1.9	30.8 1.9	30.2 1.8	32.9 1.7	34.4 1.9	31.1 1.8	31.7 ^a 2.0	30.0 1.9	29.0 ^c 2.0
MEDIUM	46	34.8 1.8	41.1 1.7	34.3 1.6	34.5 1.8	33.9 1.9	32.0 2.0	28.6 2.1	30.1 2.0	28.8 2.4	27.6 2.3
HIGH	37	35.9 1.9	39.9 1.4	15.3 [*] 2.1	13.3 [*] 2.1	10.8 [*] 1.6	11.6 [*] 2.0	8.3 [*] 1.7	8.3 [*] 2.0	8.1 [*] 1.7	10.3 [*] 2.1
L-PHE	39	36.0 2.1	39.4 1.9	26.1 [*] 2.0	24.6 [*] 2.2	21.5 [*] 2.2	22.5 [*] 2.5	19.3 [*] 2.7	19.5 [*] 2.7	19.6 ^{ab} 2.7	17.7 ^{ac} 2.4
L-ASP	44	33.5 1.9	37.8 1.8	35.5 1.8	35.2 1.7	33.7 1.7	33.3 2.0	29.0 1.8	30.5 1.8	31.0 1.6	28.6 1.8

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

^aFemale No. 207 found dead gestation day 11.

^bFemale No. 290 found dead gestation day 12.

^cFemale Nos. 206, 248 and 283 found dead gestation day 13.

APPENDIX I
Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

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

TREATMENT GROUP	NO. OF PREGNANT FEMALES	GESTATION DAY						
		14	15	16	17	18	19	20
CONTROL	42	31.0 ^d 2.9	29.3 ^e 2.8	30.4 2.7	31.7 ^f 2.8	34.6 2.6	34.8 2.5	32.3 2.6
								29.6 2.6
LOW	46	31.9 2.4	29.2 2.1	31.5 2.3	32.3 2.0	32.8 2.2	32.8 2.1	30.7 2.0
								29.9 2.0
MEDIUM	46	31.4 2.4	29.9 2.1	30.6 2.0	30.4 2.0	32.09 2.1	36.4 2.7	32.6 2.4
								29.3 2.1
HIGH	37	10.4 [*] 2.2	11.7 ^{*e} 2.6	14.7 [*] 3.0	12.0 [*] 2.3	14.7 [*] 2.8	19.0 [*] 3.1	19.9 [*] 3.4
								29.6 ^h 3.0
L-PHE	39	19.5 [*] 2.5	19.1 [*] 2.7	21.0 [*] 3.0	23.2 [*] 3.2	25.3 [*] 3.3	31.4 3.6	34.8 3.3
								34.2 ^{h,i} 3.2
L-ASP	44	29.7 2.0	29.3 2.0	29.6 2.3	27.9 2.2	32.09 2.3	31.9 2.4	32.9 2.1
								30.6 2.1

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

^dFemale No. 131 found dead gestation day 14.

^eFemale Nos. 134 and 410 found dead gestation day 15.

^fFemale Nos. 139 and 141 found dead gestation day 17.

^gFemale Nos. 322 and 370 found dead gestation day 18.

^hFemale Nos. 424, 438 and 263 found dead gestation day 21.

ⁱFemale Nos. 280 and 295 found dead gestation day 22.

^jFemale Nos. 214 and 421 found dead gestation day 28.

Appendix I

Table 2 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Selected Maternal Food Consumption (g/kg/day)

(Arithmetic Mean \pm S.E.)

Treatment Group	Number of Pregnant Females	Gestation Day										
		0	3	6	7	8	9	10	11	12		
Control	42	36.0 1.8	38.8 2.0	35.0 2.2	33.9 2.3	34.1 2.6	33.4 2.7	30.7 2.2	34.3 2.2	34.3 2.3		
High Dose Non-Aborting	9	44.9* 3.9	48.1 3.2	21.0* 4.4	20.0* 4.6	17.3* 3.2	21.2* 3.9	14.8* 4.6	18.0* 5.0	15.8* 4.0		
High Dose Aborting	22	32.9 Δ 2.1	38.5 Δ 1.5	14.4* 2.8	10.8* 2.5	8.0* Δ 1.9	7.7* Δ 1.9	6.2* 1.9	5.0* Δ 1.9	6.0* Δ 2.1		
L-Phe	39	36.0 2.1	39.4 1.9	26.1* 2.0	24.6* 2.2	21.5* 2.2	22.5* 2.5	19.3* 2.7	19.5* 2.7	19.6* 2.7		

Treatment Group	Number of Pregnant Females	Gestation Day										
		13	14	15	16	17	18	19	20	22	27	
Control	42	29.9 2.3	31.0 2.9	29.3 2.8	30.4 2.7	31.7 2.8	34.6 2.6	34.8 2.5	32.3 2.6	29.6 2.6	23.0 2.3	
High Dose Non-Aborting	9	20.2 3.8	15.6* 4.6	19.4 5.6	22.3 5.2	22.3 5.5	22.7* 5.5	28.9 6.8	30.0 7.6	27.9 5.8	24.6 5.3	
High Dose Aborting	22	7.4* Δ 2.6	9.8* 3.0	9.6* 3.0	12.7* 4.0	9.8* Δ 2.5	13.0* 3.5	14.8* Δ 3.2	16.4* 3.9	31.8 3.9	40.6* Δ 3.5	
L-Phe	39	17.7* 2.4	19.5* 2.5	19.1* 2.7	21.0* 3.0	23.2* 3.2	25.3* 3.3	31.4 3.6	34.8 3.3	34.2 3.2	31.9* 2.8	

* = Difference statistically significant from control group ($p < 0.05$). Δ = Difference statistically significant between aborting and non-aborting high dose females ($p < 0.05$).

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE CONTROL GROUP
(G/KG)

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9
101	16.5	31.4	30.2	25.7	31.8	20.8	6.4	15.9	14.9	20.6
102	30.8	36.5	31.2	33.8	43.3	27.9	17.0	24.4	13.0	13.0
104	37.6	47.5	29.2	28.0	41.8	33.6	27.1	28.7	17.2	15.2
105	38.2	54.9	14.1	31.6	42.7	28.3	27.0	30.1	31.9	30.9
106	33.6	38.6	38.1	29.8	36.0	29.8	24.5	26.9	25.4	34.2
107	2.8	0.6	4.9	22.2	35.5	24.2	36.3	25.7	22.2	1.7
108	19.1	27.9	25.9	25.8	31.3	27.9	28.4	13.5	19.4	12.4
109	33.7	42.2	49.0	46.2	49.0	32.1	7.4	18.0	17.5	15.6
111	31.1	66.5	46.2	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
112	33.3	42.9	28.3	31.7	45.0	29.0	37.0	32.3	37.9	34.0
113	22.7	38.2	36.6	43.0	35.9	36.0	35.9	35.7	31.8	7.9
114	21.2	42.7	42.2	36.6	32.8	36.7	37.0	40.7	32.4	38.1
115	29.8	40.8	60.0	33.5	37.7	36.9	34.4	40.3	34.9	30.3
116	49.6	44.3	45.2	46.9	43.0	47.3	40.9	47.5	49.6	19.6
117	52.6	40.2	49.6	38.3	21.7	43.1	33.5	21.9	18.7	10.1
118	55.1	26.8	49.9	35.3	40.8	36.2	17.8	21.1	13.4	35.4
119	40.9	37.2	29.2	41.1	38.3	38.6	34.1	39.1	32.6	41.3
121	48.8	50.8	45.4	39.5	42.6	40.8	37.8	42.1	42.9	37.4
122	47.6	37.5	40.2	39.6	35.6	48.3	33.7	16.2	56.7	44.4
123	N.D.	N.D.	63.0	50.3	64.4	59.8	50.3	62.4	64.4	58.2
124	48.6	67.7	49.6	53.1	64.4	13.0	19.7	43.5	61.4	72.4
125	28.8	43.8	56.7	54.4	53.2	50.8	45.8	45.0	38.9	41.1
126	35.1	49.4	58.3	43.0	8.0	7.0	44.9	56.0	45.2	N.D.
128	49.3	50.5	19.9	7.4	23.6	21.2	14.7	5.7	21.7	33.1
129	46.5	N.D.	43.7	45.1	52.5	47.7	53.6	39.9	53.4	43.1

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE CONTROL GROUP
(G/KG)

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9
130	48.1	57.5	38.2	45.8	60.4	40.5	60.7	35.3	57.8	N.D.
131	46.1	58.7	55.5	65.0	51.2	61.8	57.7	49.1	N.D.	33.6
132	43.0	47.0	46.3	58.7	47.2	57.6	N.C.	47.0	48.6	54.5
133	31.0	38.1	35.7	41.9	31.4	41.8	27.8	24.6	N.D.	36.0
134	41.0	29.6	54.2	37.4	35.2	47.5	43.9	26.1	31.6	43.8
135	59.5	39.9	61.0	46.0	42.9	49.8	32.8	24.9	10.4	14.5
136	47.9	48.1	15.3	13.7	40.7	58.9	52.4	51.5	44.4	46.0
138	33.6	63.9	43.3	50.6	48.7	51.4	54.7	55.2	26.1	58.9
139	35.9	47.7	32.7	43.7	42.3	41.4	21.8	0.1	2.1	7.4
140	21.0	38.2	38.5	40.5	39.5	30.2	41.3	50.5	41.8	40.6
141	31.0	51.5	53.0	45.0	38.4	36.2	42.1	40.5	44.2	39.8
142	25.8	44.1	52.8	45.1	47.4	40.3	53.4	48.6	48.1	44.8
143	26.2	35.8	41.4	41.1	39.5	34.5	34.8	37.1	43.5	54.3
144	27.2	26.6	26.3	34.7	31.2	30.4	32.7	26.9	33.5	43.7
145	31.4	37.3	43.8	40.4	28.7	24.2	34.1	34.9	50.0	51.7
146	41.2	48.8	43.5	56.9	53.7	59.5	55.8	56.3	47.3	N.D.
150	32.5	10.6	3.9	3.3	N.D.	0.4	9.9	7.3	4.9	10.9
MEANS	36.0	42.0	39.8	38.8	40.7	37.2	35.0	33.9	34.1	33.4

N.D. = No Data.

APPENDIX I
 TABLE 2 (cont.)

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

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

ANIMAL NUMBER	10	11	12	13	14	15	16	17	18	19
130	N.D.	36.6	N.D.	N.D.	64.0	34.6	N.D.	N.D.	N.D.	N.D.
131	0.2	0.2	0.7	N.D.	D	--	--	--	--	--
132	38.5	42.2	56.3	51.1	45.3	N.D.	54.4	N.D.	58.0	58.3
133	26.5	36.1	40.2	39.6	36.5	33.3	26.8	36.2	42.6	39.8
134	46.4	48.8	34.4	27.6	N.D.	D	--	--	--	--
135	41.3	38.4	33.8	37.7	43.7	45.6	51.6	51.0	48.1	40.4
136	44.6	37.2	48.3	31.2	42.2	19.8	34.9	41.2	43.9	36.6
138	41.1	45.3	35.9	39.9	23.6	9.2	8.5	2.7	N.D.	12.8
139	6.3	14.1	10.8	8.1	1.4	N.D.	N.D.	D	--	--
140	33.0	35.7	25.6	39.7	42.8	N.D.	N.D.	N.D.	N.D.	N.D.
141	31.9	28.3	25.1	26.1	N.D.	29.4	N.D.	D	--	--
142	N.D.	40.1	41.4	42.7	45.4	32.9	37.2	46.3	42.4	48.4
143	48.3	41.1	41.7	22.0	34.9	35.8	48.9	28.6	47.3	32.7
144	30.6	35.3	38.6	25.1	N.D.	28.7	32.5	24.2	36.2	27.2
145	N.D.	37.8	N.D.	25.1	29.0	30.0	32.3	30.4	41.5	38.7
146	37.1	51.3	47.8	47.4	7.9	4.2	13.6	49.0	49.0	56.9
150	15.9	N.D.	20.2	N.D.	55.2	N.D.	45.6	47.9	38.2	39.7
MEANS	30.7	34.3	34.3	29.9	31.0	29.3	30.4	31.7	34.6	34.8

N.D. = No Data.

D = Dead.

APPENDIX I
 TABLE 2 (cont.)

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

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

ANIMAL NUMBER	20	21	22	GESTATION DAY				26	27
				23	24	25	26		
101	20.2	13.9	18.6	24.2	23.4	21.9	21.6	14.7	
102	26.6	37.2	N.D.	N.D.	17.2	15.7	21.7	12.6	
104	1.7	8.0	12.3	15.3	13.8	14.4	14.6	23.7	
105	29.7	31.3	33.5	31.5	26.5	32.3	28.2	26.6	
106	30.5	35.6	53.2	36.1	31.7	34.8	29.6	29.3	
107	N.D.	3.1	1.2	N.D.	0.1	N.D.	3.6	1.1	
108	44.9	N.D.	N.D.	43.7	39.3	N.D.	37.4	36.4	
109	17.6	17.8	25.2	28.5	23.2	22.7	17.1	18.8	
111	N.D.	45.7	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	
112	12.0	6.0	15.6	26.7	25.3	16.2	18.7	27.5	
113	N.D.	25.0	31.6	32.0	34.4	28.5	36.9	25.0	
114	30.3	29.9	33.4	36.9	39.6	34.2	31.3	10.9	
115	25.5	35.7	26.4	27.7	45.1	26.2	39.6	22.9	
116	29.7	26.3	9.6	1.0	0.5	4.4	7.2	4.7	
117	31.2	36.4	13.5	34.9	24.7	25.6	25.0	N.D.	
118	30.8	40.7	31.1	43.0	19.5	22.5	32.8	32.0	
119	27.7	30.2	32.0	33.5	16.8	27.2	24.0	18.0	
121	29.2	35.2	18.3	21.8	16.8	19.6	20.2	18.6	
122	N.D.	N.D.	3.3	7.6	12.3	18.5	5.9	0.5	
123	N.D.	47.3	54.0	47.8	48.8	18.9	16.6	11.0	
124	64.3	45.0	36.7	N.D.	35.1	32.9	26.3	N.D.	
125	15.4	10.4	17.8	8.5	12.4	7.1	10.4	18.6	
126	48.6	36.0	34.6	42.9	38.1	34.0	1.8	7.9	
128	N.D.	53.2	49.5	44.8	44.2	45.9	N.D.	N.D.	
129	N.D.	53.0	48.7	46.7	47.9	42.4	41.4	35.0	

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE CONTROL GROUP
(G/KG)

ANIMAL NUMBER	20	21	22	GESTATION DAY			26	27
				23	24	25		
132	N.D.	26.5	19.9	12.0	41.8	N.D.	20.7	N.D.
133	39.3	37.2	31.9	42.7	43.3	30.5	37.5	40.3
135	45.9	48.3	39.3	37.3	43.4	30.9	34.8	36.6
136	52.6	N.D.	48.4	31.2	N.D.	43.3	26.2	24.9
138	N.D.	N.D.	6.4	38.2	N.D.	52.2	39.3	53.7
140	N.D.	N.D.	58.0	N.D.	N.D.	N.D.	N.D.	N.D.
142	20.5	42.9	23.7	40.0	36.6	39.9	34.9	15.3
143	43.3	N.D.	37.7	34.9	42.9	37.8	30.6	35.9
144	33.7	34.2	38.2	36.4	40.1	39.5	25.9	N.D.
145	41.8	44.0	31.8	34.2	35.5	23.5	15.6	35.2
146	47.9	48.8	45.1	37.9	36.2	32.3	32.5	30.7
150	31.2	37.9	25.8	20.8	17.3	37.0	20.1	20.5
MEANS	32.3	33.0	29.6	31.3	29.5	28.5	24.4	23.0

N.D. = No Data.

APPENDIX I
 TABLE 2 (cont.)

 SC-19862: AN EVALUATION OF EMBRYOTOXIC AND
 TERATOGENIC POTENTIAL IN THE RABBIT

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

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9
228	39.7	49.4	36.7	40.0	45.6	31.9	39.4	28.1	27.6	32.4
229	40.4	25.8	28.1	28.2	35.6	31.0	33.4	25.0	37.7	30.7
230	35.2	41.4	39.1	39.1	42.1	38.4	46.3	26.6	43.3	30.8
231	26.3	39.4	36.8	60.0	30.8	N.D.	N.D.	38.2	48.4	45.4
232	18.7	48.6	37.1	61.3	38.2	43.6	2.8	10.5	39.3	44.6
233	50.8	53.5	52.4	49.9	43.1	49.6	33.5	N.D.	44.9	40.0
234	41.9	20.4	45.4	31.1	28.9	42.5	13.5	15.7	13.9	26.6
236	56.0	21.4	55.7	42.2	35.9	51.4	44.9	29.4	39.2	43.6
238	8.3	9.5	9.8	37.4	39.4	36.3	33.6	30.1	25.9	32.2
239	6.6	6.3	3.9	17.4	23.8	18.2	10.5	6.8	8.1	19.9
240	24.8	35.2	42.2	38.4	35.3	33.0	36.6	37.1	37.7	43.1
241	33.5	43.8	44.5	41.4	35.9	35.5	38.8	34.8	40.1	38.0
242	16.6	38.6	45.0	41.1	35.4	40.0	36.5	35.4	41.9	40.8
243	24.8	26.0	35.1	28.5	30.7	30.2	29.9	30.9	36.6	40.0
244	31.3	30.3	41.9	44.6	42.2	34.3	29.6	18.2	35.8	35.2
245	33.9	27.3	37.4	37.1	34.8	31.4	30.3	32.9	23.1	27.8
246	36.7	46.6	44.3	48.7	34.8	43.9	37.3	40.7	37.3	40.7
247	41.3	51.0	51.5	50.7	47.2	62.5	51.4	46.9	49.5	48.0
248	18.8	44.5	43.4	42.5	35.5	38.8	37.7	33.7	32.9	40.3
249	12.8	2.2	1.3	N.D.	1.7	0.3	8.9	3.6	N.D.	11.6
250	18.4	4.1	3.9	1.8	3.4	3.1	N.D.	11.4	16.2	24.3
MEANS	34.2	36.8	34.2	38.5	37.4	35.1	30.8	30.2	32.9	34.4

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE LOW DOSE GROUP
(G/KG)

ANIMAL NUMBER	10	11	12	13	14	15	16	17	18	19
229	26.4	30.4	35.0	19.1	21.8	21.1	22.9	23.0	23.7	20.3
230	32.2	41.1	43.3	24.1	29.7	22.4	8.9	13.0	13.1	12.6
231	64.6	N.D.	N.D.	N.D.	32.6	48.2	44.8	49.6	52.9	N.D.
232	38.1	35.7	26.6	47.9	47.7	39.8	47.3	47.1	50.3	49.7
233	33.6	38.4	34.0	39.6	39.5	33.6	34.0	34.3	34.1	38.5
234	30.6	22.6	25.3	18.3	25.3	15.2	26.8	27.3	38.7	38.2
236	56.7	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	42.4	N.D.
238	32.4	30.1	19.5	14.0	11.0	18.4	29.9	31.6	30.4	38.8
239	17.9	13.2	25.4	27.5	34.5	32.9	28.8	38.0	37.1	35.7
240	34.4	34.4	38.4	34.6	33.0	37.0	53.1	29.9	47.5	36.6
241	32.1	31.0	26.2	31.6	35.5	29.2	35.5	21.2	30.5	34.6
242	45.5	37.1	36.1	46.0	44.3	35.2	39.4	37.5	34.4	44.6
243	51.0	31.5	33.1	33.0	29.5	30.4	34.9	25.4	35.5	25.9
244	39.7	32.1	45.4	29.4	23.7	28.2	N.D.	N.D.	39.2	26.1
245	34.4	37.7	45.3	37.0	31.9	46.5	49.9	N.D.	21.6	23.9
246	27.9	33.4	34.7	36.0	40.0	43.2	38.6	44.7	N.D.	N.D.
247	33.5	31.3	33.7	34.7	30.4	32.2	31.5	32.1	32.6	38.4
248	30.0	28.6	N.D.	D	--	--	--	--	--	--
249	7.6	4.8	3.6	4.1	39.2	52.2	49.2	52.9	55.9	57.0
250	17.9	N.D.	18.8	N.D.	N.D.	51.8	N.D.	50.8	77.9	N.D.
MEANS	31.1	31.7	30.0	29.0	31.9	29.2	31.5	32.3	32.8	32.8

N.D. = No Data.
D = Dead.

APPENDIX I
 TABLE 2 (cont.)

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

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

ANIMAL NUMBER	GESTATION DAY						
	20	21	22	23	24	25	26
201	N.D.	21.8	19.5	16.0	16.5	19.3	23.8
202	0.9	32.6	31.6	33.8	36.6	29.8	35.5
203	31.7	31.6	28.6	38.0	29.0	37.0	34.9
204	33.3	28.8	25.2	26.6	14.9	25.5	22.8
205	16.8	13.9	10.8	11.1	9.0	10.1	10.8
208	29.9	36.5	21.2	22.2	20.9	30.1	20.7
210	N.D.	16.9	13.5	6.1	20.0	8.3	15.1
211	N.D.	21.0	N.D.	16.0	N.D.	N.D.	N.D.
212	27.2	25.9	19.9	17.6	13.1	14.3	9.1
213	25.0	23.3	22.2	16.1	28.3	15.4	29.3
214	0.7	N.D.	3.3	N.D.	1.0	1.2	N.D.
215	7.4	7.8	14.0	8.8	19.8	12.0	16.3
216	32.7	64.8	28.7	24.4	N.D.	18.4	40.0
217	24.4	29.6	22.2	17.1	20.8	16.5	26.1
218	31.8	48.1	33.5	47.4	23.2	23.2	34.0
219	32.2	36.8	37.2	32.4	30.2	36.5	34.5
220	30.6	38.2	36.8	33.2	19.9	27.9	25.5
222	38.9	34.1	27.2	29.4	31.6	22.9	24.5
223	49.4	47.6	44.2	33.5	32.8	26.9	33.4
224	49.0	40.3	41.9	44.3	48.9	40.3	40.4
225	34.1	33.0	26.6	29.3	26.3	16.4	28.0
226	34.4	28.5	18.4	28.3	25.2	24.0	23.4
227	16.7	20.4	18.4	23.1	23.3	19.2	23.0
228	23.3	26.8	34.8	30.4	36.4	28.5	22.8
229	23.7	22.2	22.0	25.4	21.8	19.4	25.2

N.D. = No Data.

APPENDIX I
 TABLE 2 (cont.)

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

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

ANIMAL NUMBER	GESTATION DAY							
	20	21	22	23	24	25	26	27
230	16.5	14.1	13.1	12.2	12.5	12.3	9.6	13.8
231	N.D.	55.6	47.7	N.D.	N.D.	N.D.	N.D.	N.D.
232	39.5	48.1	32.8	32.5	20.8	31.1	41.6	34.1
233	30.9	31.4	30.3	27.8	23.1	1.4	17.0	35.0
234	53.1	48.3	45.0	32.4	47.9	30.3	34.6	38.5
236	N.D.	N.D.	N.D.	N.D.	39.3	20.6	23.6	20.3
238	34.1	31.1	35.8	26.2	19.8	33.7	20.5	30.5
239	22.5	37.1	43.3	33.4	31.2	36.2	N.D.	29.6
240	40.0	32.1	36.3	25.7	32.5	N.D.	39.6	1.9
241	37.6	28.2	32.1	16.4	19.9	16.5	10.1	3.0
242	35.1	30.5	33.9	23.4	24.3	35.9	37.0	32.1
243	28.4	24.0	39.1	30.0	26.4	36.7	27.8	33.0
244	32.3	33.9	29.2	22.8	29.9	N.D.	20.1	N.D.
245	44.7	37.5	N.D.	16.5	32.4	33.2	29.3	N.D.
246	N.D.	N.D.	N.D.	28.7	12.6	13.7	26.6	21.1
247	36.0	35.9	27.4	13.9	9.5	7.5	13.9	9.7
249	47.8	53.5	58.8	51.8	42.2	55.3	12.8	N.D.
250	43.8	63.8	59.6	55.3	50.4	N.D.	41.2	43.7
MEANS	30.7	33.4	29.9	26.5	25.6	23.4	25.8	22.7

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE MEDIUM DOSE GROUP
(G/KG)

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9
329	27.1	41.0	43.4	37.5	35.5	31.7	28.0	24.5	30.8	36.5
330	39.3	45.6	36.1	38.0	45.0	43.4	51.5	35.7	53.8	37.4
331	30.9	37.0	26.8	54.5	27.3	45.6	26.6	6.4	18.3	11.1
332	48.8	62.1	57.6	N.D.	59.0	N.D.	37.8	45.1	55.6	51.0
333	45.0	53.4	38.8	61.5	52.7	N.D.	40.7	26.7	47.1	32.4
334	N.D.	31.2	50.2	44.0	31.6	46.8	46.9	41.3	54.7	52.1
335	59.3	39.8	63.4	N.D.	N.D.	54.5	36.0	43.0	48.3	N.D.
336	44.4	22.7	44.0	33.4	29.8	37.5	37.0	N.D.	27.6	18.9
337	46.0	46.5	42.1	39.1	45.8	44.9	42.6	36.2	35.9	16.6
338	46.3	48.9	37.0	42.1	52.5	40.6	42.3	28.8	30.6	38.1
339	14.1	56.1	54.4	59.9	67.8	61.2	46.3	39.5	46.6	53.7
340	52.1	71.1	72.4	62.0	54.4	54.1	55.3	60.3	51.7	44.7
341	35.2	45.4	39.3	35.2	31.9	30.6	N.D.	54.4	47.6	43.0
342	36.0	47.3	50.6	45.8	39.6	42.5	38.8	42.9	38.9	37.1
343	26.7	23.2	36.5	54.2	47.2	42.5	45.1	44.2	46.6	48.5
344	15.9	31.8	32.4	38.5	36.6	37.2	31.9	33.9	39.8	49.1
345	N.D.	54.9	55.6	59.6	54.8	52.1	50.4	48.2	53.6	49.0
346	35.9	51.9	N.D.	57.0	48.0	56.6	59.4	54.0	51.7	47.4
347	44.4	60.4	47.1	48.0	39.2	50.2	N.D.	49.8	N.D.	N.D.
348	24.6	40.4	44.1	39.8	39.3	40.6	34.5	31.8	23.2	28.8
349	34.5	16.8	7.0	2.1	2.6	2.6	7.0	6.0	N.D.	16.3
MEANS	34.8	41.8	41.5	41.1	41.5	39.2	34.3	34.5	33.9	32.0

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE MEDIUM DOSE GROUP
(G/KG)

ANIMAL NUMBER	20	21	22	GESTATION DAY				26	27
				23	24	25	26		
301	2.7	7.0	N.D.	14.6	9.6	15.6	16.4	10.6	
302	32.3	34.7	27.2	26.3	33.0	30.5	28.0	23.3	
303	17.8	20.5	20.6	17.3	14.1	14.6	13.9	5.8	
304	N.D.	29.4	25.2	28.5	28.5	30.0	30.1	34.0	
306	N.D.	27.6	N.D.	38.1	25.5	18.3	N.D.	42.9	
307	30.4	36.4	38.0	36.6	31.1	38.7	24.8	31.1	
308	N.D.	N.D.	N.D.	N.D.	52.9	15.9	N.D.	9.1	
309	34.2	28.3	27.0	25.1	16.8	15.8	6.1	0.5	
310	35.3	35.8	34.2	28.6	28.3	33.9	28.6	35.6	
312	42.0	22.5	11.7	5.4	0.9	2.3	N.D.	25.2	
313	N.D.	1.0	9.5	4.9	28.4	21.7	1.0	N.D.	
314	31.1	28.4	18.9	16.2	21.9	17.6	30.6	22.8	
315	5.8	15.6	19.5	18.3	15.6	7.9	22.8	N.D.	
316	7.6	14.9	10.1	16.1	19.2	24.4	28.5	19.5	
317	4.6	29.0	13.3	49.3	39.3	25.5	72.2	30.1	
318	23.7	25.0	19.3	43.9	26.4	28.4	27.9	42.3	
319	23.6	24.6	23.9	24.5	17.1	22.6	19.8	19.1	
320	11.6	15.9	17.7	22.4	16.7	23.2	18.9	20.7	
321	19.3	21.0	19.3	17.9	14.5	16.9	17.1	N.D.	
323	39.8	21.5	31.9	38.7	49.3	38.3	32.4	33.9	
324	N.D.	N.D.	43.2	37.9	37.4	32.0	25.2	25.4	
325	29.9	27.0	30.6	53.5	N.D.	18.7	19.6	18.1	
326	36.3	27.5	20.3	28.2	24.0	20.1	25.1	20.9	
328	46.7	N.D.	23.8	N.D.	N.D.	N.D.	26.5	27.2	
329	43.0	35.0	44.6	36.9	35.2	37.9	32.8	26.5	

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)

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

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

ANIMAL NUMBER	20	21	22	23	24	25	26	27
330	23.9	28.1	24.9	22.4	23.1	12.6	15.8	17.2
331	N.D.	N.D.	N.D.	44.1	N.D.	N.D.	N.D.	N.D.
332	31.5	32.0	N.D.	N.D.	N.D.	46.1	N.D.	N.D.
333	42.5	46.8	42.2	42.1	47.7	45.6	N.D.	N.D.
334	21.6	32.9	24.3	27.4	30.8	21.0	22.9	9.8
335	50.9	19.2	17.5	0.3	0.5	2.5	17.3	30.8
336	45.6	45.1	38.2	36.5	N.D.	32.1	38.5	27.7
337	27.1	N.D.	41.3	31.6	N.D.	28.6	21.5	28.2
338	9.8	1.5	1.5	1.7	N.D.	1.4	1.8	4.6
339	52.4	50.0	54.2	51.7	44.5	41.9	31.6	37.5
340	61.6	53.4	62.5	49.7	51.1	50.3	47.3	42.6
341	35.4	37.6	26.2	N.D.	30.9	29.0	34.3	25.7
342	51.2	35.1	37.3	36.4	30.2	N.D.	N.D.	N.D.
343	47.1	46.0	39.2	36.4	42.4	33.5	21.2	25.7
344	41.7	44.8	38.1	37.1	42.5	43.8	34.1	49.3
345	50.5	49.4	49.8	46.7	43.4	36.0	27.6	26.9
346	48.8	56.1	50.6	33.9	32.5	36.7	37.7	33.7
347	47.8	53.3	40.6	27.7	45.2	43.5	45.2	45.0
348	35.4	35.9	27.9	27.4	35.0	33.6	39.3	38.2
349	27.4	32.6	27.2	26.4	24.6	39.6	15.9	20.4
MEANS	32.6	30.7	29.3	29.5	29.2	26.9	26.3	26.0

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE HIGH DOSE GROUP
(G/KG)

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9
402	19.0	37.3	25.9	33.2	42.0	28.7	6.5	5.8	6.1	4.5
404	33.6	46.5	30.5	34.6	44.0	31.5	1.1	5.5	14.8	17.9
405	40.3	14.1	21.2	37.3	29.9	23.8	2.5	1.7	6.1	0.8
406	36.2	N.D.	33.4	34.7	44.7	27.9	2.9	0.8	1.3	N.D.
407	30.8	30.4	30.0	31.7	45.8	30.5	2.8	4.3	2.3	4.7
408	33.2	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	5.4	18.9
409	35.0	44.1	48.1	36.7	45.7	40.6	18.9	24.3	N.D.	4.4
410	41.0	45.6	26.6	36.5	34.0	37.5	9.1	2.8	2.4	1.2
411	28.0	34.2	30.9	34.9	36.6	32.7	6.3	2.3	5.9	5.8
412	54.7	52.2	27.6	51.6	44.7	48.0	16.8	13.3	6.8	3.8
413	21.8	38.5	35.9	42.2	35.8	37.9	17.8	6.4	1.3	1.7
415	24.8	44.9	42.1	47.0	40.3	39.6	36.1	4.7	0.6	N.D.
416	22.7	29.2	38.5	35.3	35.4	40.7	8.4	2.3	0.3	1.7
418	38.1	29.5	33.0	30.7	35.6	48.2	10.2	18.0	14.9	8.7
420	29.6	41.8	45.8	37.3	34.9	39.8	0.4	1.1	1.2	N.D.
421	54.6	46.2	43.6	41.3	38.9	43.3	17.0	39.3	27.0	31.4
422	26.8	43.7	49.5	50.0	N.D.	49.0	16.3	13.8	12.1	2.2
423	46.6	48.9	39.6	44.6	56.0	62.4	14.1	12.5	4.0	1.7
424	33.0	42.7	39.8	34.6	39.9	44.9	3.7	0.7	0.7	1.1
425	46.9	49.4	49.0	48.9	46.9	34.6	26.7	36.1	22.1	26.0
426	53.0	46.7	53.7	50.4	49.7	65.4	38.3	39.0	30.3	43.3
428	41.1	40.0	40.0	36.9	47.2	42.2	28.1	14.0	21.8	6.4
429	23.0	30.4	21.6	22.3	34.5	30.4	16.4	6.3	8.3	0.1
430	35.5	46.9	37.2	38.6	43.1	44.8	21.3	25.4	24.9	9.9
431	34.4	62.0	44.3	64.6	34.7	48.7	20.3	11.6	6.9	15.2

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE HIGH DOSE GROUP
(G/KG)

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9
434	29.7	18.5	44.3	30.0	23.7	38.4	N.D.	N.D.	1.2	1.0
435	44.9	34.1	47.1	31.6	32.3	44.2	4.5	0.1	3.7	2.7
436	65.8	N.D.	N.D.	51.0	48.2	N.D.	34.8	5.4	27.7	30.8
437	43.4	48.7	48.4	45.7	46.0	50.9	33.1	31.1	16.7	16.3
438	31.2	39.6	43.9	36.6	41.9	40.6	12.4	23.8	20.1	20.9
439	36.4	36.4	33.2	36.2	39.3	29.9	2.1	1.6	2.9	3.1
440	10.8	20.1	32.3	35.8	27.5	31.7	20.8	28.6	16.1	21.6
441	37.0	44.8	45.8	41.4	36.9	30.4	32.8	27.0	29.3	30.1
443	46.9	31.2	39.9	44.7	38.8	33.9	8.8	23.6	16.4	25.2
444	24.2	22.1	23.8	32.4	29.1	27.3	2.4	1.2	2.7	6.0
445	50.7	55.4	60.5	58.2	57.4	49.3	40.4	30.3	23.2	22.2
447	24.6	37.1	42.5	35.5	28.3	19.1	0.5	0.9	1.2	4.6
MEANS	35.9	39.2	38.6	39.9	39.7	39.1	15.3	13.3	10.8	11.6

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE HIGH DOSE GROUP
(G/KG)

ANIMAL NUMBER	10	11	12	13	14	15	16	17	18	19
434	N.D.	0.3	N.D.	0.4	0.9	0.3	N.D.	1.5	N.D.	0.7
435	8.3	3.1	4.4	7.2	23.3	29.1	40.5	27.0	39.7	42.6
436	N.D.	45.3	35.8	35.5	N.D.	41.6	40.8	26.8	32.4	25.1
437	12.2	5.2	1.0	0.2	0.1	0.4	N.D.	2.5	0.9	18.3
438	16.8	3.2	3.7	3.7	3.0	N.D.	N.C.	0.2	0.	N.D.
439	N.D.	0.9	0.2	N.D.	N.D.	0.3	N.D.	0.2	N.D.	N.D.
440	24.8	22.4	19.4	N.D.	20.7	5.3	1.8	3.1	6.2	12.1
441	30.2	34.0	36.3	42.6	53.5	31.2	38.3	28.3	33.6	17.9
443	18.1	16.4	22.7	23.7	29.8	29.5	40.0	23.1	38.7	38.0
444	6.8	1.6	4.8	2.7	5.8	2.8	4.9	4.1	9.0	6.7
445	4.8	6.8	13.0	13.6	18.1	40.9	40.9	10.0	19.7	41.6
447	1.5	3.5	1.0	5.2	N.D.	0.9	0.2	1.3	N.D.	2.8
MEANS	8.3	8.3	8.1	10.3	10.4	11.7	14.7	12.0	14.7	19.0

N.D. = No Data.

APPENDIX I
 TABLE 2 (cont.)

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

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

ANIMAL NUMBER	20	21	22	GESTATION DAY			26	27
				23	24	25		
402	0.1	0.8	4.9	9.8	15.5	19.2	23.5	15.5
404	0.9	0.9	1.3	3.4	2.7	7.5	1.6	0.6
405	22.7	30.2	50.4	39.3	32.1	55.9	40.2	44.1
406	N.D.	N.D.	N.D.	1.3	0.3	1.8	N.D.	0.6
407	1.9	3.7	N.D.	3.2	2.4	5.1	11.3	N.D.
408	39.4	43.1	36.9	39.4	33.7	26.7	20.0	19.9
409	N.D.	7.2	8.4	20.9	21.8	N.D.	31.3	38.0
411	0.6	3.4	8.0	15.3	23.8	35.8	28.8	39.1
412	0.4	8.3	23.8	N.D.	24.8	33.2	30.2	28.3
413	11.9	27.2	38.4	40.3	57.5	28.2	49.9	30.0
415	1.8	13.9	30.9	33.7	51.1	32.1	62.2	33.7
416	3.6	1.5	3.3	12.2	4.0	8.4	32.3	23.6
418	37.6	56.5	30.7	53.0	32.2	27.8	34.7	21.4
420	0.4	2.8	3.0	5.7	N.D.	17.4	29.9	42.9
421	14.1	12.8	19.5	10.9	6.0	2.5	0.3	N.D.
422	44.0	33.9	43.3	43.9	43.3	48.7	41.9	47.8
423+	6.6	N.D.	N.D.	52.7	58.8	53.7	52.9	58.2
425	N.D.	N.D.	N.D.	N.D.	N.D.	40.7	N.D.	28.6
426	40.1	34.9	25.9	27.9	17.6	14.5	16.4	15.2
428	N.D.	41.2	50.9	55.1	62.7	49.5	59.7	53.0
429	28.0	54.0	37.8	43.7	47.5	28.7	45.4	30.0
430	35.9	37.6	40.9	33.5	44.8	40.2	46.6	41.0
431	52.8	56.1	46.5	52.7	46.9	37.1	34.4	38.3
434	1.1	1.2	N.D.	5.0	20.4	27.6	54.2	40.5
435	40.8	50.4	45.9	31.9	55.4	36.5	32.7	N.D.

N.D. = No Data.

+ Animal No. 424 died on gestation day 21. Food consumption data for the 24 hour period prior to

APPENDIX I
 TABLE 2 (cont.)

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

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

ANIMAL NUMBER	20	21	22	GESTATION DAY				26	27
				23	24	25	26		
436	16.6	36.0	7.5	3.4	17.1	10.2	15.2	N.D.	N.D.
437 ⁺	31.0	46.3	55.1	61.4	51.7	64.5	45.6	69.4	69.4
439 ⁺	N.D.	1.9	31.3	59.0	34.2	58.5	4.4	65.2	65.2
440	29.5	28.5	36.0	28.8	34.3	30.9	33.7	34.0	34.0
441	21.2	31.2	41.9	26.8	41.5	38.5	56.0	38.9	38.9
443	53.9	47.4	40.0	30.0	37.9	25.1	18.9	N.D.	N.D.
444	2.4	18.1	25.0	26.5	27.3	28.4	21.9	31.6	31.6
445	37.1	59.0	44.9	55.5	28.2	62.4	51.2	53.7	53.7
447	0.2	22.8	25.4	N.D.	N.D.	49.0	53.2	46.0	46.0
MEANS	19.9	26.2	29.6	29.9	31.5	31.7	33.8	35.5	35.5

N.D. = No Data.

⁺ Animal No. 438 died on gestation day 21. Food consumption data for the 24 hour period prior to death was not meaningful and is not included on this table.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE L-PHE GROUP
(G/KG)

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9
251	27.2	32.5	21.7	22.2	17.3	9.4	0.2	1.1	0.2	0.3
252	22.5	13.7	30.9	36.7	33.7	26.2	26.6	25.2	N.D.	16.2
253	17.6	N.D.	36.6	36.5	26.6	30.4	20.8	28.5	27.4	29.4
255	14.9	31.9	N.D.	19.7	23.7	18.2	2.0	6.6	3.9	N.D.
256	43.6	46.1	6.2	N.D.	35.4	N.D.	N.D.	N.D.	N.D.	N.D.
257	20.5	34.6	35.7	41.0	40.8	27.9	21.2	28.5	27.2	28.8
258	32.7	37.2	33.1	46.7	48.6	37.1	39.3	37.4	24.1	27.9
259	31.7	42.8	42.1	40.2	48.4	30.2	32.0	29.9	23.6	32.1
260	39.2	31.0	20.5	35.6	31.0	28.5	4.4	2.9	0.9	0.5
261	55.5	58.6	19.6	53.4	36.0	39.7	15.3	30.3	10.3	8.3
262	N.D.	43.8	28.2	29.4	44.5	30.5	29.7	33.4	25.7	25.7
263	16.7	45.4	40.8	47.6	50.1	37.6	38.8	22.7	8.6	36.0
264	49.0	59.1	46.2	60.0	55.0	57.3	34.7	40.5	24.7	28.0
265	31.0	46.2	35.5	40.6	42.2	44.8	32.2	42.2	31.6	39.9
267	27.1	46.5	55.7	47.9	37.4	44.9	40.9	42.9	27.0	2.4
268	46.2	52.0	46.3	43.4	42.5	40.3	14.5	9.9	8.0	5.5
269	52.0	54.1	43.8	38.6	45.8	36.5	24.0	30.9	32.9	34.2
270	48.4	47.3	41.1	45.7	40.1	41.4	13.9	4.0	6.6	19.0
272	52.1	63.8	58.5	58.5	58.1	61.3	23.0	22.2	28.1	12.1
276	28.6	37.8	36.2	36.6	45.6	31.1	36.7	34.7	28.4	48.0
277	37.0	38.0	N.D.	40.3	51.5	31.2	32.1	36.3	21.5	12.5
278	37.3	46.9	40.2	35.9	46.0	39.1	27.0	14.6	23.8	1.8
279	31.4	52.4	35.8	32.5	45.6	31.6	29.9	30.7	35.4	16.0
280	35.0	43.0	35.0	25.9	44.5	30.6	9.9	5.0	3.9	N.D.
281	37.6	48.4	43.2	N.D.	34.4	40.4	24.5	30.0	15.8	21.3

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE L-PHE GROUP
(G/KG)

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9
283	40.6	40.7	37.2	50.1	35.2	51.9	N.D.	27.6	31.7	51.4
284	61.9	27.5	54.0	30.3	42.2	41.8	42.2	38.8	40.9	44.8
286	65.1	40.4	N.D.	44.9	45.0	51.6	56.0	33.8	42.3	41.3
287	N.D.	31.6	9.9	22.5	51.2	46.7	34.7	41.7	40.1	42.3
288	N.D.	12.2	15.7	11.9	21.5	38.4	30.2	29.2	19.1	24.1
289	23.0	31.8	25.6	21.1	43.7	36.6	25.5	13.2	5.1	11.0
290	27.1	43.9	45.3	39.0	39.3	41.0	36.4	39.1	37.1	31.4
291	20.6	37.3	38.3	38.1	36.4	31.1	29.1	29.6	27.3	29.5
292	28.5	39.7	43.1	41.0	40.3	31.7	18.0	9.7	0.6	2.1
293	31.7	29.0	42.0	45.0	34.5	25.4	11.6	3.1	4.4	5.6
295	48.9	39.4	37.1	57.7	48.0	48.6	26.9	27.1	37.3	27.7
296	43.3	37.9	35.1	38.0	33.1	32.5	21.8	2.6	N.D.	5.0
297	37.5	50.7	N.D.	57.3	50.1	54.6	42.8	42.4	38.5	36.7
298	33.7	47.9	43.5	44.4	40.6	42.2	17.0	7.9	11.0	10.7
MEANS	36.0	41.1	36.0	39.4	40.7	37.4	26.1	24.6	21.5	22.5

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE L-PHE GROUP
(G/KG)

ANIMAL NUMBER	10	11	12	13	14	15	16	17	18	19
251	0.8	7.4	21.3	N.D.	7.6	1.0	1.1	1.5	1.8	N.D.
252	21.2	N.D.	49.6	N.D.	N.D.	37.2	N.D.	25.6	N.D.	N.D.
253	30.6	30.4	N.D.	4.8	16.7	21.6	5.9	1.8	N.D.	N.D.
255	N.D.	7.3	0.4	0.4	1.9	1.8	2.0	0.3	3.0	N.D.
256	N.D.	N.D.	42.8	N.D.	31.6	6.7	16.9	42.5	39.4	N.D.
257	N.D.	29.5	24.5	26.7	18.5	28.2	32.9	23.2	23.9	18.7
258	14.2	N.D.	5.7	3.8	3.0	4.3	10.1	6.6	5.4	12.1
259	25.7	29.8	20.2	31.8	28.6	26.8	24.0	21.4	23.8	18.8
260	1.3	N.D.	2.8	0.8	N.D.	1.1	N.D.	N.D.	N.D.	0.7
261	6.1	1.3	4.3	3.4	18.2	20.6	8.9	30.0	35.3	49.8
262	32.6	29.7	34.8	35.7	34.5	34.4	28.6	38.1	31.5	30.8
263	25.8	25.3	N.D.	0.8	N.D.	0.3	N.D.	1.0	N.D.	N.D.
264	20.2	25.8	23.5	18.6	N.D.	40.3	49.8	53.9	55.9	50.4
265	31.4	32.2	35.5	35.0	33.7	32.2	38.4	36.8	35.7	33.5
267	13.3	27.2	34.8	31.4	28.5	39.6	38.4	20.8	39.4	37.2
268	0.9	N.D.	4.1	2.3	5.2	2.7	3.6	5.7	2.8	3.8
269	29.4	35.9	39.1	26.2	36.4	38.2	33.5	53.8	34.0	53.1
270	11.7	16.0	3.7	3.9	4.9	2.9	3.0	N.D.	11.5	31.6
272	3.8	7.1	9.8	7.1	8.8	3.0	9.3	9.5	12.1	37.6
276	24.8	41.6	30.2	28.1	31.7	37.0	27.3	39.2	41.8	46.3
277	2.6	7.7	0.8	4.0	3.1	2.4	1.8	7.6	5.4	N.D.
278	9.6	7.9	7.2	19.1	11.9	7.3	11.8	4.5	5.1	30.7
279	16.9	31.3	35.2	17.4	36.7	34.0	42.3	36.7	36.1	36.4
280	3.6	0.3	2.2	4.6	1.6	3.2	3.1	1.9	2.3	1.6
281	N.D.	7.0	12.5	28.5	27.5	29.1	34.3	29.8	37.8	43.7

N.D. = No Data.

APPENDIX I
 TABLE 2 (cont.)

 SC-14862: AN EVALUATION OF EMBRYOTOXIC AND
 TERATOGENIC POTENTIAL IN THE RAPBIT

 MATERNAL FOOD CONSUMPTION DATA FOR THE L-PHE GROUP
 (G/KG)

ANIMAL NUMBER	10	11	12	13	14	15	16	17	18	19
283	45.1	N.D.	N.D.	D	--	--	--	--	--	--
284	52.6	45.3	41.0	34.3	36.0	35.2	39.7	32.1	35.6	39.1
286	53.9	40.3	37.1	34.8	27.7	7.8	13.8	21.6	46.2	47.8
287	40.3	41.8	41.4	39.0	39.6	46.8	52.3	50.8	N.D.	N.D.
288	24.2	13.2	12.3	15.5	17.3	23.8	23.6	23.3	N.D.	N.D.
289+	12.1	N.D.	14.9	29.9	5.1	N.D.	48.6	44.0	N.D.	N.D.
291	33.5	28.5	27.0	39.3	41.7	28.6	30.9	24.4	43.0	47.0
292	0.3	0.	1.2	2.5	14.3	3.3	7.1	N.D.	30.0	55.2
293	0.9	0.1	1.0	N.D.	0.3	0.3	N.D.	N.D.	N.D.	0.6
295	20.1	7.3	6.3	1.8	0.6	0.7	2.3	1.0	0.6	1.7
296	N.D.	2.8	1.1	2.2	9.2	2.8	4.2	3.4	N.D.	39.9
297	23.3	28.2	39.9	21.6	37.2	34.2	N.D.	50.9	54.1	48.5
298	3.5	10.9	19.2	28.0	37.4	46.6	N.D.	N.D.	14.1	N.D.
MEANS	19.3	19.5	19.6	17.7	19.5	19.1	21.0	23.2	25.3	31.4

D = Dead.

N.D. = No Data.

+ Animal No. 290 died on gestation day 12. Food consumption data for the 48 hour period prior to death was not meaningful and is not included on this table.

APPENDIX I
TABLE 2 (cont.)SC-19962: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE L-PHE GROUP
(G/KG)

ANIMAL NUMBER	20	21	22	23	24	25	26	27
251	0.5	0.6	2.6	N.D.	N.D.	0.4	1.1	0.1
252	N.D.	27.6	21.4	N.D.	N.D.	N.D.	N.D.	N.D.
253	N.D.	15.3	4.6	N.D.	4.1	14.4	14.6	N.D.
255	N.D.	30.0	41.0	34.8	20.0	30.1	37.2	29.9
256	N.D.	N.D.	16.6	26.5	19.1	24.7	N.D.	1.3
257	N.D.	23.5	25.6	18.6	15.7	17.0	16.3	16.0
258	35.8	32.7	45.9	53.4	50.4	52.1	32.2	36.2
259	28.8	36.5	32.9	N.D.	29.3	19.6	19.1	19.7
260	1.8	0.9	5.9	3.4	3.4	15.2	13.9	18.9
261	51.6	43.2	47.2	36.6	33.6	50.8	32.9	39.4
262+	32.4	5.8	4.1	27.0	34.5	35.9	28.4	35.2
264	30.8	34.3	39.7	30.9	N.D.	N.D.	49.8	26.9
265	31.8	31.4	33.9	31.4	44.2	27.2	32.6	27.5
267	12.6	47.1	28.9	39.2	15.2	7.4	11.5	15.7
268	2.7	2.8	4.7	21.1	35.4	28.7	48.7	53.6
269	40.3	38.3	45.1	46.9	24.2	5.5	0.5	0.4
270	35.0	35.9	42.8	47.5	40.9	40.2	43.0	27.9
272	68.3	54.4	59.4	59.6	63.9	50.8	44.6	41.1
276	42.1	34.5	28.8	36.8	29.0	22.4	23.1	20.8
277	1.2	3.9	N.D.	28.5	41.3	N.D.	N.D.	45.0
278	49.0	55.3	55.8	54.2	58.7	45.2	61.6	43.6
279+	49.7	N.D.	N.D.	33.2	35.9	39.6	35.9	30.1
281	32.4	31.1	24.6	N.D.	N.D.	58.8	N.D.	N.D.
284	43.2	52.7	36.6	22.4	42.7	39.6	35.9	36.3
286	52.9	57.8	48.0	36.5	39.4	39.5	39.4	31.6

N.D. = No Data.

+ Animal No. 263 died on gestation day 21 and animal no. 280 died on gestation day 22. Food consumption data prior to death were not recorded.

APPENDIX I
 TABLE 2(cont.)

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

 MATERNAL FOOD CONSUMPTION DATA FOR THE L-PHE GROUP
 (G/KG)

ANIMAL NUMBER	GESTATION DAY						
	20	21	22	23	24	25	26
287	41.6	43.0	44.1	43.4	35.5	42.8	N.D.
288	33.1	33.2	36.7	41.0	29.4	39.4	29.8
289	41.4	36.1	53.0	42.6	29.8	47.1	21.0
291	41.9	43.2	45.7	27.3	42.5	31.5	N.D.
292	53.0	48.0	63.6	37.5	53.3	51.0	66.0
293 ⁺	N.D.	7.4	40.2	49.8	72.0	71.2	51.2
296	37.9	61.3	62.0	39.5	43.5	N.D.	N.C.
297	51.0	44.2	20.1	N.D.	N.D.	N.D.	N.C.
298	31.9	41.8	N.D.	43.4	40.4	57.6	53.9
MEANS	34.8	32.9	34.2	36.2	35.4	34.7	32.5
							31.9

N.D. = No Data.

+ Animal No. 295 died on gestation day 22. Food consumption data prior to death was not meaningful and is not included on this table.

APPENDIX I
 TABLE 2 (cont.)

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

 MATERNAL FOOD CONSUMPTION DATA FOR THE L-ASP GROUP
 (G/KG)

ANIMAL NUMBER	0	1	2	GESTATION DAY					7	8	9
				3	4	5	6				
379	44.0	45.1	31.2	32.0	38.3	36.8	52.3		27.4	35.8	37.1
380	29.9	N.D.	33.0	N.D.	40.0	33.7	44.4		33.4	44.8	33.1
381	25.5	43.6	35.8	N.D.	31.3	55.4	43.3		36.4	43.5	32.4
382	38.2	49.5	52.6	N.D.	N.D.	69.1	38.9		51.2	49.3	41.7
383	35.4	56.0	52.7	N.D.	N.D.	N.D.	47.1		49.3	47.3	N.D.
384	45.1	33.4	50.7	37.0	25.1	38.2	40.7		24.5	N.D.	27.8
385	46.4	27.3	52.9	24.0	31.3	35.1	46.5		36.7	34.7	36.0
386	49.7	26.3	50.1	31.5	27.8	34.6	39.6		29.2	31.9	35.6
387	5.7	36.5	31.6	29.2	21.7	29.5	1.8		1.0	9.4	15.0
388	9.5	30.3	24.5	43.5	44.7	54.6	45.4		49.1	39.9	31.6
389	N.D.	50.4	46.4	41.1	51.4	53.6	42.5		37.8	37.2	38.8
390	49.1	59.1	57.5	51.2	51.1	47.4	53.2		51.0	51.6	54.6
391	27.2	42.5	41.9	44.3	46.0	45.7	42.6		46.2	N.D.	N.D.
392	35.9	55.0	56.7	N.D.	41.0	33.4	48.9		60.0	44.5	38.9
393	33.6	39.9	40.0	44.9	45.3	38.5	35.6		27.7	36.6	38.0
394	37.5	31.3	47.5	51.2	46.4	42.5	41.5		41.1	34.5	21.2
395	25.5	36.5	47.1	55.7	44.4	44.0	44.7		29.6	49.3	53.6
396	45.1	45.7	53.3	50.2	43.9	38.1	34.4		46.5	33.9	48.4
398	30.1	14.5	6.2	3.5	3.2	3.2	1.7		N.D.	7.6	11.7
MEANS	33.5	42.3	39.8	37.8	38.4	36.2	35.5		35.2	33.7	33.3

N.D. = No Data.

APPENDIX I
 TABLE 2 (cont.)

 SC-19862: AN EVALUATION OF EMBRYOTOXIC AND
 TERATOGENIC POTENTIAL IN THE RABBIT

 MATERNAL FOOD CONSUMPTION DATA FOR THE L-ASP GROUP
 (G/KG)

ANIMAL NUMBER	10	11	12	13	14	15	16	17	18	19
351	24.6	26.8	26.2	N.D.	3.8	3.8	7.1	7.3	2.2	17.3
352	34.5	N.D.	N.D.	N.D.	39.8	N.D.	44.8	21.1	46.6	N.D.
353	20.6	22.3	32.6	N.D.	23.6	42.0	37.9	34.0	38.2	N.D.
354	12.4	33.2	33.6	30.8	34.5	27.0	27.7	33.0	31.2	42.1
356	13.5	38.4	33.3	32.3	35.4	32.7	39.3	36.6	31.0	31.1
358	34.5	45.8	35.7	39.0	36.4	36.2	33.3	N.D.	42.5	27.7
359	30.4	23.4	22.5	19.5	18.4	10.7	13.5	10.7	12.4	5.0
360	36.1	37.0	36.5	32.1	31.5	33.9	24.9	32.4	20.6	22.5
361	5.7	6.2	9.7	9.4	13.4	18.1	11.2	7.7	18.4	N.D.
362	31.2	18.7	30.3	24.1	19.0	17.4	32.8	16.7	42.1	29.0
363	34.6	31.4	26.9	21.6	33.8	N.D.	N.D.	N.D.	N.D.	N.D.
364	31.4	24.2	24.8	24.0	26.3	N.D.	21.2	20.1	24.6	26.9
365	25.9	29.4	24.8	25.4	23.3	23.3	25.8	21.2	20.5	15.8
366	3.9	8.3	11.7	13.3	15.7	5.8	4.2	6.8	7.8	10.6
367	19.9	24.6	13.0	10.4	9.9	7.0	1.4	2.1	20.1	19.4
368	23.1	32.2	28.9	24.6	25.3	17.4	5.9	5.7	10.3	17.6
370	40.7	25.2	29.6	36.8	36.7	42.6	N.D.	N.D.	D	--
371	N.D.	41.7	32.2	21.5	31.5	31.1	25.6	56.3	28.2	53.9
372	23.7	35.7	29.7	24.4	47.0	25.7	38.1	37.4	33.4	34.3
373	29.3	33.0	35.2	24.9	38.9	22.8	34.0	27.5	22.5	22.3
374	23.2	23.1	29.1	27.5	34.0	24.2	35.3	29.0	26.3	31.4
375	29.8	50.8	33.5	29.6	34.0	47.2	N.D.	N.D.	44.7	50.3
376	42.8	57.7	45.7	47.2	43.4	56.0	34.1	42.0	52.4	53.9
377	32.3	47.0	28.9	26.8	32.5	44.9	N.D.	32.1	32.2	40.9
378	29.0	26.3	37.9	21.7	N.D.	33.5	31.6	26.5	26.6	29.9

 N.D. = No Data.
 D = Dead.

APPENDIX I
 TABLE 2.(cont.)

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

 MATERNAL FOOD CONSUMPTION DATA FOR THE L-ASP GROUP
 (G/KG)

ANIMAL NUMBER	10	11	12	13	14	15	16	17	18	19
379	26.0	23.0	40.1	33.1	37.6	35.8	34.6	29.9	36.8	28.3
380	32.1	32.0	37.0	27.0	30.5	34.3	37.6	N.D.	32.6	13.4
381	16.8	24.1	44.1	45.6	44.4	34.1	31.1	34.9	47.7	49.3
382	22.0	31.0	45.2	N.D.	N.D.	8.1	34.0	48.2	42.8	42.8
383	43.9	N.D.	50.5	31.8	N.D.	N.D.	44.0	N.D.	N.D.	N.D.
384	30.2	25.7	19.3	18.4	22.0	21.7	21.1	N.D.	27.6	17.6
385	37.8	31.8	26.1	21.8	37.2	39.7	38.7	31.9	36.6	40.5
386	42.5	39.2	39.2	35.8	45.5	47.2	44.5	37.4	44.9	34.4
387	19.3	25.3	31.4	30.0	28.9	29.4	31.4	28.0	N.D.	N.D.
388	34.0	37.6	31.1	37.7	33.8	25.5	N.D.	26.7	N.D.	N.D.
389	46.0	36.9	35.4	43.5	32.4	52.6	N.D.	45.3	N.D.	N.D.
390	50.2	45.0	22.4	48.9	51.8	33.7	56.4	39.9	54.9	55.8
391	46.0	40.4	45.6	46.5	46.4	40.2	48.6	29.2	49.2	40.7
392	49.5	36.1	50.2	55.5	44.9	38.1	58.3	24.8	49.8	51.5
393	39.9	36.1	36.5	26.0	21.4	25.9	31.0	21.9	40.4	30.5
394	3.2	1.8	7.6	2.8	0.9	15.4	3.8	3.4	3.2	7.6
395	42.3	22.2	41.7	19.7	18.0	26.7	37.8	38.6	49.6	38.5
396	32.6	40.4	29.0	35.9	N.D.	40.9	32.7	38.7	34.1	31.2
398	6.8	9.7	7.8	17.3	6.1	18.7	8.6	48.1	N.D.	53.5
MEANS	29.0	30.5	31.0	28.6	29.7	29.3	29.6	27.9	32.0	31.9

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE L-ASP GROUP
(G/KG)

ANIMAL NUMBER	20	21	22	23	24	25	26	27
351	29.4	23.5	N.D.	18.7	29.3	26.9	30.4	20.3
352	6.5	5.0	N.D.	N.D.	13.2	12.7	13.3	8.4
353	43.4	37.8	N.D.	N.D.	N.D.	32.5	17.3	22.0
354	25.8	28.3	32.5	32.2	20.9	31.5	29.4	22.1
356	N.D.	38.3	36.5	34.0	28.1	25.7	28.8	27.4
358	41.1	36.5	N.D.	N.D.	N.D.	N.D.	26.0	20.2
359	9.2	10.2	10.1	N.D.	18.6	11.9	9.0	10.0
360	28.4	23.8	23.4	22.1	21.6	22.3	19.6	23.2
361	16.7	20.0	24.0	24.3	32.1	N.D.	25.9	39.4
362	29.6	25.0	25.5	11.7	14.8	13.0	10.8	11.2
363	N.D.	N.D.	N.D.	N.D.	N.D.	57.3	N.D.	N.D.
364	15.5	25.9	28.2	30.5	46.8	21.8	28.9	11.2
365	18.8	20.6	20.5	23.4	24.7	19.2	31.3	19.3
366	4.4	5.9	10.8	17.6	16.9	11.6	6.2	12.4
367	17.3	25.8	11.9	37.6	13.5	10.5	17.9	13.7
368	18.5	32.0	16.0	41.3	25.3	17.5	27.6	29.3
371	39.6	32.4	40.4	52.6	35.3	39.6	39.4	29.9
372	45.4	32.6	23.2	17.6	N.D.	12.8	13.2	17.5
373	32.6	18.2	22.2	19.1	23.5	15.4	15.4	11.6
374	30.2	31.6	28.3	30.2	30.8	29.3	22.6	23.6
375	49.3	N.D.	11.4	17.6	19.8	N.D.	37.7	38.3
376	40.7	37.1	26.3	24.6	25.8	N.D.	29.7	27.8
377	33.4	32.0	25.6	31.7	35.1	29.4	30.7	25.6
378	34.6	13.8	23.3	30.6	30.4	30.2	34.9	31.9
379	31.1	40.2	27.9	31.9	40.7	32.1	41.4	33.5

N.D. = No Data.

APPENDIX I
TABLE 2 (cont.)SC-18862: AN EVALUATION OF EMBRYOTOXIC AND
TERATOGENIC POTENTIAL IN THE RABBITMATERNAL FOOD CONSUMPTION DATA FOR THE L-ASP GROUP
(G/KG)

ANIMAL NUMBER	20	21	22	GESTATION DAY			26	27
				23	24	25		
380	N.D.	N.D.	N.D.	N.D.	29.9	23.8	25.1	21.0
381	38.0	42.9	30.3	41.2	N.D.	47.9	N.D.	N.D.
382	44.9	40.3	48.1	N.D.	N.D.	N.D.	N.C.	N.D.
383	N.D.	N.D.	44.6	42.0	N.D.	N.D.	N.D.	N.D.
384	25.4	28.9	27.4	29.4	30.5	25.5	28.7	31.1
385	33.9	38.0	32.1	30.0	47.4	39.2	29.7	35.2
386	41.8	35.9	35.7	36.0	48.8	43.5	39.3	40.1
387	26.9	31.5	38.8	35.3	31.3	36.6	21.3	34.9
388	36.8	31.4	48.0	29.2	32.6	35.8	25.6	30.1
389	34.0	40.1	N.D.	24.8	N.D.	20.9	19.7	18.1
390	53.0	45.9	55.0	39.7	12.9	34.6	19.0	24.1
391	44.0	27.3	28.0	20.0	23.5	28.1	32.1	30.6
392	51.5	37.3	60.8	32.2	41.6	41.2	48.0	42.7
393	36.6	32.0	25.6	28.9	27.4	21.3	16.0	28.0
394	32.7	23.9	29.3	31.1	40.4	N.D.	42.1	41.1
395	42.3	37.0	40.8	38.9	N.D.	N.D.	37.6	49.6
396	35.4	36.4	27.2	21.8	28.1	30.7	35.8	30.4
398	62.9	N.D.	55.9	49.4	48.9	42.6	34.2	22.9
MEANS	32.9	29.7	30.6	29.9	29.1	27.9	26.7	25.9

N.D. = No Data.

APPENDIX I
Table 3

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Abortion and Premature Delivery Data

Treatment Group	Female Number	Evidence of Loss of Litter	Day of Gestation	Day of Death or Sacrifice	Loss Category*	Autopsy Observations
Control	107	One viable pup	28	28	PD	Uterus and ovaries unremarkable; four viable fetuses in the left uterine horn; three viable fetuses in the right uterine horn; delivered one pup, apparently from right horn; fatty liver, trichobezoar in stomach.
	125	One partially cannibalized & five viable pups	27	28	PD	Uterus and ovaries unremarkable; three sites of prior placental attachment in each uterine horn; pyothorax.
	126	Eight viable pups	27	28	PD	Uterus and ovaries unremarkable; five sites of prior placental attachment in the left horn; three sites of prior placental attachment in the right horn.
Low Dose	214	Hemorrhage	16,22,28	28	A	Uterus and ovaries unremarkable; five sites of prior placental attachment in the left uterine horn; three sites of prior placental attachment in the right uterine horn; pulmonary consolidation and pyothorax.
	250	Hemorrhage	15,16	28	A	Uterus and ovaries unremarkable; four sites of prior placental attachment in each uterine horn.
Medium Dose	335	Hemorrhage	25,26	28	PD	Uterus and ovaries unremarkable; four sites of prior placental attachment in the left uterine horn; seven sites of prior placental attachment in the right uterine horn.
		Five nonviable fetuses and seven placental remnants	26			
		Hemorrhage	27,28			

*A = Abortion; PD = Premature Delivery - continued -

APPENDIX I
Table 3 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Abortion and Premature Delivery Data

Treatment Group	Female Number	Evidence of Loss of Litter	Day of Gestation	Day of Death or Sacrifice	Loss Category*	Autopsy Observations
High Dose	405	Hemorrhage	17,18,19	28	A	Uterus and ovaries unremarkable; six sites of prior placental attachment in the left horn; four sites of prior placental attachment in the right horn.
	406	Hemorrhage	21,22,24	28	A	Uterus and ovaries unremarkable; four sites of prior placental attachment in the left horn; six sites of prior placental attachment in right horn; two abscesses approx. 1 inch in diam. in the right side of the pleural cavity; trichobezoar in the stomach.
	407	Hemorrhage	22,23,24	28	A	Uterus and ovaries unremarkable; five sites of prior placental attachment in the left horn; two sites of prior placental attachment in the right horn; trichobezoar in the stomach.
	409	Hemorrhage	19,22,23,24	28	A	Uterus and ovaries unremarkable; five sites of prior placental attachment in the left horn; four sites of prior placental attachment in the right horn.
	411	Hemorrhage	19	28	A	Uterus and ovaries unremarkable; four sites of prior placental attachment in the left uterine horn; five sites of prior placental attachment in the right uterine horn.
		Three placental remnants	20			
		Five placental remnants	21			
	413	Hemorrhage	21	28	A	Uterus and ovaries unremarkable; four sites of prior placental attachment in the left uterine horn; one site of prior placental attachment in the right uterine horn.
		One placental remnant	23			

*A = Abortion

- continued -

APPENDIX I
Table 3 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Abortion and Premature Delivery Data

Treatment Group	Female Number	Evidence of Loss of Litter	Day of Gestation or Sacrifice	Day of Death	Loss Category*	Autopsy Observations
High Dose (cont.)	415	Hemorrhage	17,18,21,23	28	A	Uterus and ovaries unremarkable; eight sites of prior placental attachment in the left uterine horn; two sites of prior placental attachment in the right uterine horn.
	416	Hemorrhage	20,21,22	28	A	Uterus and ovaries unremarkable; six sites of prior placental attachment in the left uterine horn; one site of prior placental attachment in the right uterine horn.
	418	Hemorrhage	21,22,24,28	28	A	Uterus and ovaries unremarkable; three sites of prior placental attachment in the left uterine horn; seven sites of prior placental attachment in the right uterine horn.
	420	Hemorrhage	18,24,25	28	A	Uterus and ovaries unremarkable; three sites of prior placental attachment in each uterine horn; consolidation in the right cardiac lobe of the lung.
	422	Hemorrhage	21,22	28	A	Uterus and ovaries unremarkable; four sites of prior placental attachment in the left uterine horn; one site of prior placental attachment in the right uterine horn.
	423	Hemorrhage	21	28	A	Uterus and ovaries unremarkable; seven sites of prior placental attachment in the left uterine horn; one site of prior placental attachment in the right uterine horn.
	424	Hemorrhage	18,21	21	A	Uterus and ovaries unremarkable; three sites of prior placental attachment in the left uterine horn; six sites of prior placental attachment in the right uterine horn; patchy consolidation throughout the lungs; trichobezoar in stomach.

*A = Abortion

- continued -

APPENDIX I
Table 3 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Abortion and Premature Delivery Data

Treatment Group	Female Number	Evidence of Loss of Litter	Day of Gestation	Day of Death or Sacrifice	Loss Category*	Autopsy Observations
High Dose (cont.)	428	Hemorrhage	20	28	A	Uterus and ovaries unremarkable; four sites of prior placental attachment in each uterine horn.
	434	Hemorrhage	20,21,22	28	A	Uterus and ovaries unremarkable; four sites of prior placental attachment in each uterine horn.
	435	Hemorrhage	20,21	28	A	Uterus and ovaries unremarkable; two sites of prior placental attachment in each uterine horn.
	437	Hemorrhage	19,20,21	28	A	Uterus and ovaries unremarkable; two sites of prior placental attachment in the left uterine horn; one site of prior placental attachment in the right uterine horn.
	438	Hemorrhage	18,19,20	28	A	Uterus and ovaries unremarkable; one site of prior placental attachment in the left uterine horn; eight sites of prior placental attachment in the right uterine horn; all lobes of the lungs and both sides of the thorax filled with purulent material.
	439	Hemorrhage	18,19,20,22	28	A	Uterus and ovaries unremarkable; five sites of prior placental attachment in the left uterine horn; six sites of prior placental attachment in the right uterine horn.
	440	Hemorrhage	19	28	A	Uterus and ovaries unremarkable; three sites of prior placental attachment in the left uterine horn; eight sites of prior placental attachment in the right uterine horn; complete consolidation of left side of lung with multiple abscesses.
		Two placental remnants	20			
		Hemorrhage	24			
	441	Hemorrhage	19	28	A	Uterus and ovaries unremarkable; three sites of prior placental attachment in the left uterine horn; two sites of prior placental attachment in the right uterine horn.

*A = Abortion

- continued -

APPENDIX I
Table 3 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Abortion and Premature Delivery Data

Treatment Group	Female Number	Evidence of Loss of Litter	Day of Gestation or Sacrifice	Day of Death	Loss Category*	Autopsy Observations
High Dose (cont.)	444	Hemorrhage	20	28	A	Uterus and ovaries unremarkable; six sites of prior placental attachment in the left uterine horn; four sites of prior placental attachment in the right uterine horn.
	445	Hemorrhage	20,21	28	A	Uterus and ovaries unremarkable; eight sites of prior placental attachment in the left uterine horn; three sites of prior placental attachment in the right uterine horn.
	447	Four placental remnants	21	28	A	Uterus and ovaries unremarkable; six sites of prior placental attachment in the left uterine horn; six sites of prior placental attachment in the right uterine horn.
L-Phe	268	Hemorrhage	20,21	28	A	Uterus and ovaries unremarkable; two sites of prior placental attachment in the left uterine horn; seven sites of prior placental attachment in the right uterine horn.
	269	One mutilated nonviable pup & one intact nonviable pup	27	28	PD	Uterus and ovaries unremarkable; four sites of prior placental attachment in the right uterine horn; the left uterine horn contained one nonviable fetus and an indeterminate number of sites of prior placental attachment
	277	Two mutilated pups & one intact pup	28			
		Five intact nonviable pups and one nonviable autolyzed pup	28	28	PD	Uterus and ovaries unremarkable; two sites of prior placental attachment in the left uterine horn; four sites of prior placental attachment in the right uterine horn.

- continued -

*A = Abortion; PD = Premature Delivery

APPENDIX I

Table 3 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Abortion and Premature Delivery Data

Treatment Group	Female Number	Evidence of Loss of Litter	Day of Gestation	Day of Death or Sacrifice	Loss Category*	Autopsy Observations
L-Phe (cont.)	280	Hemorrhage	17,20	22	A	Uterus and ovaries unremarkable; five sites of prior placental attachment in each uterine horn; all lobes of lung involved with purulent pneumonia; pyothorax.
	293	Hemorrhage	21	28	A	Uterus and ovaries unremarkable; six sites of prior placental attachment in the left uterine horn; two sites of prior placental attachment in the right uterine horn.
	298	Hemorrhage	18,19,21,24	28	A	Uterus and ovaries unremarkable; ten sites of prior placental attachment in the right uterine horn; none in the left uterine horn.

*A = Abortion; PD = Premature Delivery

APPENDIX I
Table 4

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL
IN THE RABBIT; P-T 1201

Incidence of Spontaneous Disease at Sacrifice
(Number of Females Affected)

Observations	Treatment Group					
	Control	Low Dose	Medium Dose	High Dose	L-Phe	L-Asp
Pulmonary consolidation:	1(114)	-	1(338)	5(403,412, 420,440,442)	1(254)	-
Pleural adhesions:	1(137)	-	-	-	-	-
Pleural abscesses:	-	-	2(332, 338)	3(406, 440,442)	-	-
Pyothorax:	2(122,125)	-	1(327)	-	-	1(369)
Chronic nephritis:	3(129, 143,144)	2(210, 234)	-	-	2(261, 279)	2(356,358)
Fatty liver:	1(107)	-	-	-	-	-
Ketosis:	-	-	-	-	1(260)	-
Peritonitis:	-	-	-	-	1(254)	-
Moderate uterine infection	1(127)	-	-	1(419)	-	-
Pyometra:	-	-	-	-	1(254)	-
Vaginal abscess:	-	-	-	-	1(254)	-
Ovarian cyst:	1(106)	-	1(316)	-	1(267)	1(360)
Uterine cyst:	-	-	-	1(446)	-	-
Segmented uterus:	-	-	-	1(442)	-	-
Gastric trichobezoars:	1(107)	-	1(313)	3(404,406, 407)	1(251)	-
Diarrhea:	-	-	-	-	1(254)	-
TOTAL FEMALES AFFECTED:	10	2	5	10	6	4
TOTAL FEMALES SURVIVING TO SACRIFICE:	46	46	49	46	45	48

Note: Numbers in parentheses identify the affected animals. More than one disease may be diagnosed in an animal.

APPENDIX I
Table 5 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - Control Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
128	4	5	0	0	5	4	29.4	27.4	7.5	7.5	5	4
129	1	2	0	0	2	1	40.6	39.3	7.9	8.0	1	2
130	3	4	0	1	5	2	29.1	27.3	7.1	7.3	4	3
131*												
132	9	1	0	0	5	5	32.4	32.5	7.4	7.4	5	5
133	3	5	0	0	5	3	28.5	25.5	7.6	7.0	4	4
134*												
135	7	5	0	0	3	9	34.7	30.7	8.2	7.4	6	6
136	5	7	1	0	5	7	28.9	29.5	7.3	7.5	6	6
137 (NP)												
138	1	0	0	0	1	0	34.0	-	7.2	-	0	1
139*												
140	4	4	0	0	4	4	40.9	39.2	8.1	7.5	4	4
141*												
142	6	3	0	0	4	5	30.2	27.2	7.5	7.4	4	5
143	5	3	0	0	3	5	34.5	36.4	7.6	7.9	4	4
144	4	2	1	0	3	3	34.6	36.0	7.4	7.8	3	3
145	5	4	0	0	5	4	38.7	36.5	7.7	8.0	5	4
146	4	7	0	0	7	4	33.6	33.1	7.7	7.8	6	5
147 (NP)												
148 (NP)												
149 (NP)												
150	4	6	1	0	5	5	37.7	33.3	7.9	7.6	5	5
TOTAL												
					136	143					140	139
MEAN												
							33.2 ^{††}	32.0 ^{††}	7.9 ^{††}	7.7 ^{††}		

- continued -

APPENDIX I
Table 5

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - Control Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
101	6(1)	4	0	0	4	6	28.8	31.3	7.9	8.1	5	5
102	3	3	1	1	3	3	34.0	29.1	8.4	8.1	3	3
103 (NP)												
104	5	3	1	0	5	3	29.0	31.1	7.9	8.0	4	4
105	2	0	0	0	1	1	42.0	46.1	9.0	8.7	1	1
106+	4	3	0	2	3	4	32.3	35.8	7.8	7.8	4	3
107	4	4	0	0	4	4	41.1	33.2	8.2	8.0	4	4
108	5	4	0	0	7	2	30.8	31.6	7.9	7.5	5	4
109	4	4	1	0	3	5	28.4	27.0	7.8	7.8	4	4
110 (NP)												
111	5	1	1	1	2	4	33.1	29.9	8.2	7.5	3	3
112	6	3	1	4	3	6	23.9	30.7	7.5	8.1	5	4
113	2	2	1	1	3	1	40.3	37.8	8.7	8.2	2	2
114	0	0	3	4	-	-	-	-	-	-	-	-
115	4	4	0	0	3	5	34.6	32.0	7.9	7.9	4	4
116	3	5	0	0	3	5	36.5	33.8	8.1	7.9	4	4
117	3	6	0	0	6	3	33.3	29.4	8.9	8.0	4	5
118	5	4	0	3	4	5	25.0	27.1	7.9	7.5	4	5
119	5	5	0	0	7	3	37.6	32.1	8.4	7.5	5	5
120 (NP)												
121	6	4	1	0	3	7	36.5	32.3	7.8	7.6	5	5
122	5	5	1	1	3	7	14.8	16.8	6.1	6.2	5	5
123	1	3	0	0	2	2	41.2	40.2	8.7	8.7	2	2
124++	4	7	0	0	5	6	30.6	27.8	7.7	7.4	5	6
125+++			3	3								
126			3	5								
127 (NP)			3	8								

- continued -

Footnotes: Summary of Uterine Implantation Data - Control Group

R = right uterine horn.

L = left uterine horn.

(NP) = not pregnant.

CRD = crown rump distance

() = denotes number of fetuses which were nonviable

[] = denotes number of pups observed.

* = female died; see pathology reports in Appendix II.

† = per litter.

†† = per litter which contained fetuses of this sex.

+ = delivered prematurely - one viable pup was observed the morning of gestation day 28. This female was immediately sacrificed and seven viable fetuses recovered in utero. All fetuses and delivered pup were saved for examination. Values for this female are included in calculation of totals and means.

++ = delivered prematurely - five viable intact pups and one partially cannibalized pup were observed on gestation day 27. Values in No. of Resorptions column are indicative of sites of identifiable placental attachment. Data for this female were not included in calculation of totals or means. The five intact pups were saved for skeletal examination.

+++ = delivered prematurely - eight viable intact pups were observed on gestation day 27. Values in No. of Resorptions column are indicative of identifiable sites of placental attachment. Data for this female were not included in calculation of totals or means. The eight pups were saved for skeletal examination.

APPENDIX I
Table 5 (cont..)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - Low Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R L Total		R L Total		Male Female		Male Female		Male Female		Soft Tissue Skeletal	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
201	4	5	9	1	7	2	30.1	27.7	7.8	7.8	4	5
202	0	1	1	0	1	0	46.0	-	8.4	-	0	1
203	3	6	9	1	3	6	29.6	35.5	7.7	7.9	5	4
204	5	2	7	1	2	5	36.6	31.3	8.4	7.9	4	3
205	6	2	8	3	4	4	29.1	27.8	7.5	7.2	4	4
206*												
207*												
208	3	4	7	1	2	5	29.8	29.4	7.4	7.7	4	3
209(NP)												
210	5	6	11	1	5	6	26.0	29.3	7.1	7.6	6	5
211	4	6	10	0	3	7	32.3	28.6	8.2	7.5	5	5
212	0	3	3	0	1	2	33.9	35.1	8.2	8.6	1	2
213 +	4	4	8	1	2	6	32.6	35.1	8.1	8.4	4	4
214*												
215++	6	4	10	0	3	7	25.5	25.7	7.2	7.1	5	5
216												
217	4	5	9	0	4	5	34.5	32.5	7.8	7.5	5	4
218	7	3	10	0	6	4	38.1	38.2	8.4	8.5	5	5
219	5	5	10	0	5	5	30.9	32.9	7.4	7.5	5	5
220	2	4	6	3	3	3	29.8	32.8	7.6	7.7	2	4
221(NP)												
222	4	5	9	0	3	6	28.9	26.6	7.5	7.2	5	4
223	4	4	8	1	4	4	35.4	34.9	8.2	8.0	4	4
224	4	8	12	0	5	7	31.4	27.0	7.7	7.3	6	6
225	4	6	10	1	4	6	28.8	31.6	7.6	7.6	5	5
226	6	3	9	0	7	2	37.1	38.1	8.1	8.3	4	4
227	6	4	10	0	5	5	29.7	26.6	7.7	7.7	5	5
228	6	3	9	0	2	7	34.2	32.5	7.3	7.5	5	4
229	5	5	10	0	6	4	23.8	20.3	6.9	6.5	5	5
230	5	5	10	1	7	3	34.1	30.1	7.6	7.2	5	5

- continued -

APPENDIX I
Table 5 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - Low Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
231	3	5	0	0	5	3	27.8	30.5	7.6	7.6	4	4
232	3	5	0	0	6	2	33.5	35.5	8.2	7.8	4	4
233	4	5	1	0	8	1	33.6	35.2	7.9	8.3	4	5
234	4	3	0	0	5	2	34.3	30.3	7.8	7.6	3	4
235(NP)												
236	3	8	0	0	8	3	32.4	31.6	7.5	7.5	6	5
237(NP)												
238	4	3	0	1	6	1	31.4	31.7	7.5	7.6	3	4
239	3	4	0	0	3	4	32.8	31.9	8.1	7.5	3	4
240	5	3	0	0	2	6	32.0	32.2	7.2	7.4	4	4
241	6	3	0	1	6	3	32.8	30.7	7.6	7.7	5	4
242	3	4	0	0	2	5	42.0	38.3	8.4	7.6	4	3
243	3	5	0	0	5	3	32.8	33.6	7.4	7.5	4	4
244	5	5	0	0	6	4	31.4	33.6	6.8	7.2	5	5
245	8	1	0	0	2	7	37.7	29.5	7.9	7.7	5	4
246	2	7	0	0	7	2	31.4	30.6	7.3	7.6	5	4
247	7	2	0	0	6	3	32.0	28.4	7.4	7.0	5	4
248*												
249+++	4(1)	4(3)	1	1	4	4	28.9	27.2	7.7	7.9	2	6
250			4	4								
TOTAL	339		32		175	164					169	170
MEAN	8.5 [†]		0.8 [†]				32.4 ^{††}	31.3 ^{††}	7.7 ^{††}	7.6 ^{††}		

- continued -

Footnotes - Summary of Uterine Implantation Data - Low Dose Group

R = right uterine horn.

L = left uterine horn.

(NP) = not pregnant.

CRD = crown-rump distance.

() = denotes number of fetuses which were nonviable.

* = female died; see pathology report in Appendix II.

+ = per litter

++ = per litter with fetuses of this sex.

+ = aborted pregnancy - blood in sub-floor cage pan on gestation days 16, 22 and 28. Values in No. of Resorptions column are indicative of identifiable sites of placental attachment. These data are not included in the calculations of totals or means.

++ = all implantation sites were in the process of resorbing. The exact number of implantations could not be determined.

+++ = aborted pregnancy - blood in sub-floor cage pan on gestation days 15 and 16. Values in No. of Resorptions column are indicative of identifiable sites of placental attachment. These data are not included in the calculations of totals or means.

APPENDIX I

Table 5 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - Medium Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
301	3	3	0	3	2	4	29.2	28.5	7.8	7.8	3	3
302	6	2	0	0	5	3	33.7	35.7	7.6	7.8	4	4
303	4	6	0	0	5	5	31.6	31.6	8.0	8.0	5	5
304	0	1	0	0	0	1	-	35.1	-	8.6	0	1
305(NP)												
306	1	2	1	1	1	2	50.8	42.9	9.3	8.4	1	2
307	3	1	0	0	3	1	39.5	43.5	8.5	8.4	2	2
308	7	3	0	1	7	3	32.5	27.8	8.0	7.6	5	5
309	2	2	1	1	1	3	34.9	35.1	8.8	8.3	2	2
310	7	3	1	0	4	6	31.1	30.7	7.7	7.8	5	5
311(NP)												
312	5	1	0	0	4	2	34.7	34.2	8.1	8.4	3	3
313	0	5	1	0	3	2	32.5	32.1	7.8	7.7	2	3
314	5	5	1	0	5	5	26.7	28.0	7.3	7.7	5	5
315	3	6	1	0	3	6	22.8	17.7	6.8	6.0	4	5
316	4	8	0	1	4	8	33.9	26.1	8.3	7.3	6	6
317	2	2	1	2	2	2	23.4	24.3	7.1	7.4	2	2
318	2	6	0	0	5	3	26.4	22.8	7.6	7.4	4	4
319	3	6	1	0	5	4	34.9	35.8	7.5	7.8	4	5
320	6	3	1	0	6	3	34.8	34.9	7.8	8.0	4	5
321	5	7	0	0	5	7	35.5	30.2	7.8	7.4	6	6
322*												
323	5	3	1	0	4	4	32.2	28.6	7.7	7.4	4	4
324	4	3	1	0	4	3	31.9	33.5	7.8	8.3	4	3
325	3	6	0	0	3	6	25.2	25.3	7.1	7.4	5	4
326	5	1	2	0	3	3	27.8	31.2	7.3	7.6	3	3
327(NP)												
328	8	5	0	0	6	7	28.6	24.6	7.2	7.0	7	6
329	5	0	0	6	3	2	32.0	31.9	7.5	7.5	2	3
330	5	5	0	1	7	3	27.1	27.9	7.1	7.4	5	5

- continued -

APPENDIX I

Table 5 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - Medium Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
331	5	3	3	0	4	4	25.5	27.3	7.3	7.5	4	4
332	0	3	5	0	0	3	-	37.3	-	7.9	1	2
333	2	4	1	0	2	4	34.2	35.2	8.4	8.3	3	3
334+	5	6	0	0	4	7	35.1	33.4	7.9	8.0	6	5
335		[5]	7	4								
336	4	5	0	0	5	4	22.2	24.1	6.5	7.2	4	5
337	3	6	0	0	4	5	34.5	30.0	7.6	7.5	4	5
338	4	1	0	0	2	3	18.0	18.1	6.6	6.3	2	3
339	5	0	0	1	3	2	38.4	41.3	8.2	8.8	3	2
340	4	4	1	1	1	7	29.1	36.0	7.3	7.7	4	4
341	7	4	0	0	7	4	31.1	28.9	7.4	7.4	6	5
342	10	3	0	0	7	6	27.3	24.5	7.0	7.0	7	6
343	2	3	0	1	3	2	29.3	34.1	7.5	7.0	3	2
344	3	3	0	0	3	3	32.6	35.0	7.7	8.1	3	3
345	2	7	0	0	4	5	33.3	30.7	7.5	7.7	5	4
346	6	2	0	0	3	5	33.5	32.8	7.7	7.4	4	4
347	7	5	0	0	7	5	35.5	34.5	7.8	7.9	6	6
348	5	6	0	0	3	8	23.3	24.3	6.8	7.1	5	6
349	2	5	0	1	5	2	27.0	30.3	7.1	7.8	4	3
350(NP)												
TOTAL					167	177					171	173
MEAN	7.8 [†]		1.0 [†]				31.0 ^{††}	30.9 ^{††}	7.6 ^{††}	7.7 ^{††}		

- continued -

Footnotes - Summary of Uterine Implantation Data - Medium Dose Group

R = right uterine horn.

L = left uterine horn

(NP) = not pregnant.

CRD = crown-rump distance

* = female died; see pathology report in Appendix II.

[] = denotes number of prematurely delivered pups.

† = per litter.

†† = per litter with fetuses of this sex.

+ = premature delivery, five intact nonviable macerated pups along with seven placental remnants were observed on gestation day 26. Values in the No. of Resorptions column are indicative of identifiable sites of placental attachment. These data are not included in the calculation of totals or means. No pups were saved for examination.

APPENDIX I

Table 5 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - High Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
401(NP)												
402	0	0	8	3								
403(NP)												
404 ^{+a}	7	3	0	0	5	5	18.6	18.0	6.7	6.8	5	5
405 ^{+b}			4	6								
406 ^{+c}			6	4								
407			2	5								
408 ^{+d}	0	3	3	3	1	2	25.6	27.2	7.5	7.7	1	2
409			4	5								
410 ^{+e}												
411 ^{+e}			5	4								
412 ^{+f}	6	4	0	1	4	6	20.8	20.9	7.5	7.3	5	5
413			1	4								
414(NP)												
415 ^{+g}			2	8								
416 ^{+h}			1	6								
417(NP)												
418 ⁺ⁱ			7	3								
419(NP)												
420 ^{+j}			3	3								
421 ^{+Δ}	4	6	0	0	4	6	(ND)	(ND)	(ND)	(ND)	0	10
422 ^{+k}			1	4								
423 ^{+l}			1	7								
424 ^{+m}			6	3								
425	5	6	0	2	4	7	23.7	22.7	7.0	7.0	5	6
426	6	5	0	1	6	5	26.5	23.8	7.4	6.9	6	5
427(NP)												
428 ⁺ⁿ			4	4								
429	0	0	7	0								
430	4	3	1	0	2	5	22.1	19.8	7.3	7.0	3	4

- continued -

APPENDIX I

Table 5 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - High Dose Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
431	3	4	0	0	2	5	28.1	28.3	7.7	7.3	3	4
432(NP)												
433(NP)												
434 th			4	4								
435 ^{to}			2	2								
436 ^{te}			0	0								
437 ^{tp}			1	2								
438 ^{tp}			8	1								
439 ^q			6	5								
440 ^{tr}			8	3								
441 ^{ts}			2	3								
442(NP)												
443 ^{tn}	1	3	2	0	3	1	24.9	27.2	7.2	7.6	2	2
444 ^{to}			4	6								
445 ^{to}			3	8								
446(NP)												
447 ^{tl}			6	6								
448(NP)												
449(NP)												
450(NP)												
TOTAL				75	32	43					36	39
MEAN	8.3 [†]		1.4 [†]				23.5 ^{††}	23.3 ^{††}	7.2 ^{††}	7.2 ^{††}		

- continued -

Footnotes - Summary of Uterine Implantation Data - High Dose Group

- R = right uterine horn.
L = left uterine horn.
(NP) = not pregnant.
(ND) = no data.
CRD = crown-rump distance.
+ = per litter.
++ = per litter with fetuses of this sex.
* = female died; see pathology report in Appendix II.
+ = aborted pregnancy, values in No. of Resorptions column are indicative of identifiable sites of placental attachment. These data are not included in the calculation of totals or means.
a = evidence of abortion observed on gestation days 17, 18 and 19.
b = evidence of abortion observed on gestation days 21, 22 and 24.
c = evidence of abortion observed on gestation days 22, 23 and 24.
d = evidence of abortion observed on gestation days 19, 22, 23 and 24.
e = evidence of abortion observed on gestation days 19, 20 and 21.
f = evidence of abortion observed on gestation days 21 and 23.
g = evidence of abortion observed on gestation days 17, 18 21 and 23.
h = evidence of abortion observed on gestation days 20, 21 and 22.
i = evidence of abortion observed on gestation days 21, 22, 24 and 28.
j = evidence of abortion observed on gestation days 18, 24 and 25.
k = evidence of abortion observed on gestation days 21 and 22.
l = evidence of abortion observed on gestation day 21.
m = evidence of abortion observed on gestation days 18 and 21.
n = evidence of abortion observed on gestation day 20.
o = evidence of abortion observed on gestation days 20 and 21.
p = evidence of abortion observed on gestation days 18, 19 and 20.
q = evidence of abortion observed on gestation days 18, 19, 20 and 22.
r = evidence of abortion observed on gestation days 19, 20 and 24.
s = evidence of abortion observed on gestation day 19.
Δ = Data from this female were not included in calculation of totals or means, though the litter was examined for malformations.

APPENDIX I

Table 5 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - L-Phenylalanine Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	Total	R	L	Total	Male	Female	Male	Female	Soft Tissue	Skeletal
251	0	0	0	1	5	6						
252	6	1	7	0	0	0			8.1	8.4	4	3
253	8	3	11	0	0	0			7.9	7.9	6	5
254(NP)												
255	2	6	8	0	0	0			7.9	7.8	4	4
256	1	2	3	2	2	4			7.3	7.7	1	2
257	3	4	7	0	0	0			7.7	7.9	4	3
258	5	4	9	0	0	0			6.0	6.0	5	4
259	3	5	8	0	1	1			7.7	7.7	4	4
260	0	0	0	3	5	8						
261	2	1	3	4	4	8			6.9	7.4	1	2
262	5	5	10	0	0	0			8.1	8.2	5	5
263*												
264	5	6	11	1	0	1						
265	2	4	6	1	1	2			7.5	7.3	5	6
266(NP)									8.4	7.6	3	3
267	7	6	13	0	0	0			7.8	7.4	6	7
268 ^a				7	2	9						
269 ^b	0	(1)	1[5]	4	0	4			-	7.4	0	3**
270	2	3	5	5	2	7			7.6	7.5	2	3
271(NP)												
272	1	1	2	4	4	8			-	6.1	1	1
273(NP)												
274(NP)												
275(NP)												
276 ^c	5	2	7	2	1	3			7.4	7.6	4	3
277 ^c			[5]	4	2	6			(ND)	(ND)	0	4
278	1	2	3	4	0	4			6.7	6.7	1	2
279 ^d	4	1	5	0	1	1			8.0	7.8	2	3
280*				5	5	10						

- continued -

APPENDIX I
Table 5 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - L-Phenylalanine Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
281	4	1	5	3	3	2	27.2	25.4	7.4	7.0	2	3
282(NP)												
283*												
284	3	8	11	0	6	5	31.7	29.4	7.6	7.1	5	6
285(NP)												
286	4	5	9	0	5	4	32.7	30.9	8.0	7.9	5	4
287	7	2	9	0	3	6	29.7	28.5	7.8	7.4	4	5
288	5	3	8	2	4	4	22.0	28.1	6.7	7.4	4	4
289	4	3	7	1	4	3	30.7	28.7	7.4	7.3	4	3
290*												
291	4	3	7	1	3	4	32.1	34.2	7.1	7.8	4	3
292	1	3	4	4	2	2	23.3	18.1	6.8	6.4	1	3
293e												
294(NP)												
295*												
296	0	0	0	3								
297f	3	5	8	0	3	5	26.2	24.8	7.4	7.0	4	4
298f				10								
299(NP)												
201R(NP)												
TOTAL			186		89	97					91	95
MEAN	7.2 [†]			2.1 [†]			28.2 ^{††}	27.1 ^{††}	7.5 ^{††}	7.4 ^{††}		

- continued -

Footnotes - Summary of Uterine Implantation Data - L-Phenylalanine Group

- R = right uterine horn.
L = left uterine horn.
CRD = crown-rump distance.
(NP) = not pregnant.
(ND) = no data.
() = denotes number of fetuses which were nonviable.
[] = denotes number of prematurely delivered pups.
+ = per litter.
++ = per litter with fetuses of this sex.
* = female died; see pathology report in Appendix II.
** = two pups and one fetus were lost in the skeletal staining procedure.
- a = aborted pregnancy - blood observed in sub-floor cage pan on gestation days 20 and 21 and two placental remnants on gestation day 22. Values in the No. of Resorptions column are indicative of identifiable sites of placental attachment. These data were not included in the calculation of totals or means.
- b = premature delivery - a total of five pups were observed. Two pups (one intact nonviable pup and one partially cannibalized pup) were observed on gestation day 27. One day later, one intact nonviable pup and two nonviable mutilated pups were observed. At sacrifice one nonviable fetus was recovered in utero. Values in the No. of Resorptions column are indicative of identifiable sites of placental attachment and the single fetus. These data were not included in the calculation of totals or means. Data for the single fetus recovered in utero were included in appropriate calculations. In addition, two pups were included in the fetal examinations.
- c = premature delivery - four nonviable pups and one nonviable, severely macerated pup were observed on gestation day 28. Values in No. of Resorptions column are indicative of identifiable sites of placental attachment. These data were not included in calculation of totals or means. Four pups were saved for skeletal examination.
- d = aborted pregnancy - blood observed in sub-floor cage pan on gestation days 17 and 20. Values in No. of Resorptions column are indicative of identifiable sites of placental attachment at necropsy examination. These data are not included in the calculation of totals or means.
- e = aborted pregnancy - blood observed in sub-floor cage pan on gestation day 21. Values in No. of Resorptions column are indicative of identifiable sites of placental attachment. These data are not included in the calculation of totals or means.
- f = aborted pregnancy - blood observed in sub-floor cage pan on gestation days 18, 19, 21 and 24. Values in No. of Resorptions column are indicative of identifiable sites of placental attachment and are not included in calculation of totals or means.

APPENDIX I
Table 5 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - L-Aspartic Acid Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination		
	R	L	R	L	Total	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
351	6	5	0	0	0	4	7	36.6	34.7	8.5	8.3	6	5
352	4	6	0	0	0	6	4	33.4	29.7	8.2	8.1	5	5
353	8	3	1	1	2	3	8	35.2	37.8	8.1	8.7	6	5
354	0	1	0	0	0	0	1	-	76.5	-	11.1	0	1
355(NP)													
356	0	2	0	0	0	1	1	48.7	41.7	9.2	8.8	1	1
357(NP)													
358	3	4	1	0	1	4	3	29.6	28.6	7.6	7.7	4	3
359	7(1)	2	0	0	0	3	6	27.8	28.0	7.6	7.8	4	5
360	4	3	0	3	3	3	4	32.8	26.7	7.8	7.6	4	3
361	4	3	2	1	3	4 ⁺	3	30.8	33.4	7.5	7.6	4	3
362	8	5	0	1	1	8	4	31.9	25.9	7.9	7.1	7	5
363	5	4	0	0	0	3	6	23.6	24.4	6.9	7.0	4	5
364	1	3	0	3	3	2	2	30.6	42.5	7.5	8.1	2	5
365	7	6	0	0	0	6	7	32.0	32.8	8.0	7.9	6	2
366	6	1	0	0	0	4	3	25.5	25.2	6.9	6.8	3	7
367	5	5	0	0	0	5	5	24.3	27.5	7.2	7.3	5	4
368	4	3	0	2	2	3	4	35.6	35.9	8.4	7.6	4	5
369(NP)													
370*													
371	4	1	2	3	5	3	2	43.9	41.3	8.3	7.8	2	3
372	3	4	0	1	1	4	3	30.5	29.8	7.9	7.2	3	4
373	7	1	0	1	1	3	5	10.4	10.0	5.4	5.5	4	4
374	1	1	0	0	0	1	1	9.9	9.2	5.4	5.6	1	1
375	2	5	3	0	3	4	3	35.1	32.4	8.1	7.8	3	4
376	7	3	0	0	0	6	4	30.0	31.3	7.9	8.3	5	5
377	7	1	0	0	0	6	2	28.0	26.3	7.4	7.6	4	4
378	5	2	0	1	1	6	1	29.0	32.3	7.0	6.7	4	3
379	4	4	1	0	1	5	3	35.4	31.8	7.7	7.7	4	4
380	4	5	0	0	0	7	2	25.6	28.1	7.0	7.5	5	4

- continued -

APPENDIX I

Table 5 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Uterine Implantation Data - L-Aspartic Acid Group

Female Number	No. of Fetuses		No. of Resorptions		Sex Distribution		Mean Fetal Body Weight (g)		Mean Fetal CRD (cm)		Fetal Examination	
	R	L	R	L	Male	Female	Male	Female	Male	Female	Soft Tissue	Skeletal
381	3	6	0	0	7	2	34.8	35.1	7.7	7.8	5	4
382	5	3	1	0	5	3	33.5	34.8	8.0	8.0	4	4
383	3	3	0	2	2	4	38.6	33.0	8.4	7.7	3	3
384	2	4	1	1	2	4	32.5	34.8	8.1	7.7	3	3
385	6	3	0	0	7	2	24.8	24.0	7.0	7.0	5	4
386	4	5	0	0	4	5	37.9	32.1	8.1	7.9	5	4
387	1	3	0	0	2	2	31.4	41.8	7.8	8.3	2	2
388	3	3	0	0	1	5	43.7	42.3	8.3	8.2	3	3
389	5	4	0	0	5	4	31.5	28.8	7.9	7.6	5	4
390	6	5	0	0	6	5	38.7	33.6	8.0	7.7	5	6
391	6	5	0	0	8	3	30.5	31.4	7.3	7.4	6	5
392	4(1)	3	1	1	4	3	40.1	35.4	8.0	8.2	4	3
393	6	3	1	0	4	5	30.0	31.2	7.6	7.2	5	4
394	4	4	0	1	6	2	26.2	30.3	6.5	6.9	4	4
395	5	4	0	0	4	5	38.3	33.5	8.2	6.5	5	4
396	6	2	0	0	2	6	35.2	33.7	7.8	7.8	4	4
397*(NP)												
398	4	5	0	0	3	6	27.1	32.0	7.5	7.4	5	4
399(NP)												
301R(NP)												
TOTAL				36	176	160					173	163
MEAN	7.8 ⁺		0.8 ⁺				31.7 ⁺⁺	32.4 ⁺⁺	7.7 ⁺⁺	7.6 ⁺⁺		

- continued -

Footnotes - Summary of Uterine Implantation Data - L - Aspartic Acid Group

R = right uterine horn.

L = left uterine horn.

CRD = crown-rump distance.

(NP) = not pregnant.

() = denotes number of fetuses which were nonviable.

* = female died; see pathology report in Appendix II.

† = per litter.

†† = per litter with fetuses of this sex.

+ = one fetus lost subsequent to external examination.

APPENDIX I
Table 6

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL
IN THE RABBIT; P-T 1201
Fetuses and Litters Examined for Malformations

Treatment Group	Examination Procedure		
	External Fetuses/Litters	Soft tissue Fetuses/Litters	Skeletal Fetuses/Litters
Control	279/35	140/34	139/35
Low Dose	339/40	169/39	170/40
Medium Dose	344/44	171/43	173/44
High Dose	75/9	36/9	39/9
L-Phe	186/26	91/26	95/26
L-Asp	337/43	173/42	163/43

Appendix I, Table 7

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Fetal Malformation Data - Control Group

Number of Litters Examined: 35

Number of Fetuses Examined: 279

Litter Number	Litter Size	Fetus No. and Sex	MALFORMATION	
			Category	Description
124	11	12407F	m	a) Fused ribs (R), 3rd to 4th and 5th to 6th. b) Fused 3rd and 4th thoracic vertebral centra. c) Hypoplastic 5th thoracic vertebral centrum. d) Fused transverse process (R), 3rd to 4th thoracic vertebrae. e) Hypoplastic transverse process (R) of 6th cervical vertebrae and agenesis of transverse process and centrum.
128	9	12809M	M	Hydrocephalus (internal).
132	10	13210M	m	Split 5th sternbra.
143	8	14302F	m	7th cervical ribs (B).
		14304M	m	a) 7th cervical ribs (B). b) Fused ribs (B), 10th, 11th and 12th. c) Fused transverse processes (B) and centra of 10th, 11th and 12th thoracic vertebrae.
150	10	14306F	m	7th cervical ribs (L).
		15002M	m	Split 5th sternbra.

- continued -

M = Major malformation; m = Minor malformation; B = Bilateral; R = Right side; L = Left side.

Appendix I, Table 7 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Fetal Malformation Data - Low Dose Group

Number of Litters Examined: 40
Number of Fetuses Examined: 339

Litter Number	Litter Size	Fetus No. and Sex	MALFORMATION	
			Category	Description
220	6	22001F 22006M	m M	Fused 4th and 5th sternebrae. Spina bifida.
226	9	22603M	m	Split 2nd sternebra.
232	8	23206F	m	Supernumerary nasal sutures.
242	7	24206F	m	Split 5th sternebra.
243	8	24302M	m	Split 2nd and 3rd cervical vertebral centra.

- continued -

M = Major malformation; m = Minor malformation.

Appendix I, Table 7 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Fetal Malformation Data - Medium Dose Group

Number of Litters Examined: 44

Number of Fetuses Examined: 344

Litter Number	Litter Size	Fetus No. and Sex	Category	Description	MALFORMATION
314	10	31409M	M	Diaphragmatic hernia (L).	
315	9	31503F	m	Fused sternbrae, 3rd, 4th and 5th.	
323	8	32302M	m	Agenesis of the transverse process (R) and centrum of the 13th thoracic vertebra.	
331	8	33108M	m	Supernumerary nasal sutures.	
336	9	33609F	m	Split 5th sternbra.	
345	9	34504M	m	Split 5th sternbra.	
347	12	34710M	m	Supernumerary nasal sutures.	
348	11	34806F	m	Supernumerary nasal sutures.	
		34811F	M	Umbilical hernia.	

- continued -

M = Major malformation; m = Minor malformation; B = Bilateral; R = Right side; L = Left side.

Appendix I, Table 7 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Fetal Malformation Data - High Dose Group

Number of Litters Examined: 9

Number of Fetuses Examined: 75

Litter Number	Litter Size	Fetus No. and Sex	Category	Description	MALFORMATION
408	3	40803F	m	a) Hypoplasia of the centrum and agenesis of the transverse process (L) of the 5th cervical vertebra. b) Fusion of the 8th and 9th ribs (L).	
412	10	41202M	M	Cleft palate.	
426	11	42608F	m	Short tail.	
430	7	43001M	M	a) Omphalocele. b) Split interparietal bone.	
		43002M	M	Cleft palate.	
		43006F	M	Cleft palate.	
431	7	43103M	m	Split 2nd sternebra.	
		43105F	m	Fusion of sternebrae, 2nd, 3rd and 4th.	
443	4	44302M	m	Split 3rd sternebra.	

- continued -

M = Major malformation; m = Minor malformation; B = Bilateral; R = Right side; L = Left side.

Appendix I, Table 7 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Fetal Malformation Data - L-Phenylalanine Group

Number of Litters Examined: 26

Number of Fetuses Examined: 186

Litter Number	Litter Size	Fetus No. and Sex	Category	Description	MALFORMATION
256	3	25602F	m	Short kinked tail.	
		25603M	m	Short tail.	
261	3	26103F	m	Additional sternebra.	
264	11	26407F	M	a) Omphalocele.	
			M	b) Arthrogryposis-like defect of hindlimbs (B).	
			M	c) Renal agenesis (L).	
			m	d) No tail.	
			m	e) Fusion of transverse processes of 4th lumbar vertebra.	
			m	f) Scrambled caudal vertebrae.	
270	5	27001F	M	Cleft palate.	
278	3	27803M	m	a) Supernumerary nasal sutures.	
				b) Hypoplasia of the 3rd cervical vertebral centrum.	
279	5	27901M	M	Omphalocele.	
281	5	28105M	M	a) Omphalocele.	
			M	b) Oligodactyly of forelimb (L).	
284	11	28409F	m	c) Hypoplasia of the 3rd cervical vertebral centrum.	
292	4	29201M	M	Umbilical hernia.	
		29202F	m	Retinal folding (L).	
		29203F	M	Fusion of sternebrae, 1st to 5th.	
		29204M	m	a) Omphalocele.	
		29206F	m	b) Amelia, forelimb (R).	
297	8			Supernumerary nasal sutures.	
				Fused ribs (L), 2nd and 3rd.	

- continued -

M = Major malformation; m = Minor malformation; B = Bilateral; R = Right side; L = Left side.

Appendix I, Table 7 (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Fetal Malformation Data - L-Aspartic Acid Group

Number of Litters Examined: 43

Number of Fetuses Examined: 336

Litter Number	Litter Size	Fetus No. and Sex	MALFORMATION	
			Category	Description
352	10	35208F	M	a) Omphalocele. b) Cyclopia. c) Microencephaly. d) Astomia. e) Absence of external nares and philtrum. f) Diaphragmatic hernia. g) Interparietal bone split.
353	11	35304F	m	Fused 4th and 5th sternbrae.
373	8	37302F	m	Skull closure grading 3.
		37304F	m	Skull closure grading 3.
		37306M	m	Skull closure grading 3.
		37308F	m	Skull closure grading 3.
374	2	37401M	m	Skull closure grading 3.
375	7	37502F	M	Hydrocephalus.
		37507F	M	Arthrogryposis-like defect of hindlimb (R).
382	8	38208F	m	Agenesis of the transverse process (R) and centrum of the 1st lumbar vertebra.
387	4	38704M	m	Fused 3rd to 5th sternbrae.
390	11	39004M	M	a) Umbilical hernia. b) Supernumerary nasal sutures. c) Hypoplastic transverse process (R) of 2nd cervical vertebra. d) Fused 4th and 5th sternbrae.
		39008M	m	Split 5th sternbra.
396	8	39604F	m	Supernumerary nasal sutures.

M = Major malformation; m = Minor malformation; B = Bilateral; R = Right side; L = Left side.

APPENDIX I; Table 8

SC-18862: AN EVALUATION OF THE EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Fetal Skeletal Examination Data

	Control Fetuses		Low Dose Fetuses		Medium Dose Fetuses		High Dose Fetuses		L-Phe Fetuses		L-Asp Fetuses	
	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.
No. examined:	139	-	169	-	172	-	37	-	87	-	162	-
(No. litters examined):	(35)		(40)		(44)		(9)		(26)		(43)	
Skull												
Closure grading*	0:	0	0	0	0	0	0	0	0	0	0	0
	1:	0	0	0	0	0	0	0	0	0	0	0
	2:	0	0	0	0	0	0	0	0	0	0	0
	3:	0	0	0	0	0	0	0	0	0	0	0
	4:	139	169	100	172	100	37	100	87	100	157	97
Supernumerary sutures**Δ:	0	0	1	1	3	2	0	0	3	3	1	1
Ribs												
12 pair:	93	67	109	64	128	74	17	46 ⁺	48	55	127	78
13 pair:	46	33	60	36	44	26	20	54 ⁺	39	45	35	22
Rudimentary structuresΔΔ												
unilateral:	4	3	3	2	5	3	1	3	1	1	6	4
bilateral:	0	0	2	1	0	0	0	0	0	0	4	3
Single ribs:	12	9	8	5	15	9	3	8	10	11	10	6
Floating ribs:	6	4	11	7	14	8	2	5	6	7	7	4
Cervical ribs (off 7th cervical vertebra)Δ:	3	2	0	0	0	0	0	0	0	0	0	0
Fused ribsΔ												
2 & 3 (L):	0	0	0	0	0	0	0	0	1	1	0	0
3 & 4 and 5 & 6 (R):	1	1	0	0	0	0	0	0	0	0	0	0
8 & 9 (L):	0	0	0	0	0	0	1	3	0	0	0	0
10, 11 & 12 (Bilat):	1	1	0	0	0	0	0	0	0	0	0	0

* Closure grading

0 = 0% of the skull ossified

1 = 25% of the skull ossified

2 = 50% of the skull ossified

3 = 75% of the skull ossified

4 = 100% of the skull ossified

Δ = Minor malformation.

ΔΔ = Rudimentary structures: ossification centers positioned adjacent to the 13th thoracic or first lumbar vertebrae.

** = Generally in the region of the nasal-frontal junction.

+ = Significantly different from the control group (p < 0.05).

APPENDIX I; Table 3 (cont.)

SC-18862: AN EVALUATION OF THE EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Fetal Skeletal Examination Data

	Control		Low Dose		Medium Dose		High Dose		L-Phe		L-Asp	
	No.	% of Tot.	Fetuses	No.	% of Tot.	Fetuses	No.	% of Tot.	Fetuses	No.	% of Tot.	Fetuses
No. examined:	139	-	169	-	172	-	37	-	87	-	162	-
(No. litters examined):	(35)		(40)		(44)		(9)		(26)		(43)	
Sternebrae												
Centers small												
Center no. 1:	0	0	0	0	0	0	0	0	1	1	0	0
2:	6	4	0	0 ⁺	4	2	9	24 ⁺	3	3	0	0 ⁺
3:	0	0	0	0	0	0	0	0	0	0	0	0
4:	1	1	1	1	0	0	0	0	0	0	0	0
5:	55	40	75	44	64	37	18	49	25	29	62	38
6:	33	24	34	20	31	18	6	16	21	24	26	16
Centers absent												
Center no. 1:	0	0	0	0	0	0	1	3	0	0	1	1
2:	0	0	0	0	0	0	0	0	0	0	0	0
3:	0	0	0	0	0	0	0	0	0	0	0	0
4:	0	0	0	0	0	0	0	0	0	0	0	0
5:	28	20	17	10	22	13	8	22	11	13	32	20
6:	15	11	18	11	30	17	19	51 ⁺	14	16	20	12
Split sternebrae ^Δ												
No. 2:	0	0	1	1	0	0	1	3	0	0	0	0
No. 3:	0	0	0	0	0	0	1	3	0	0	0	0
No. 5:	2	1	1	1	2	1	0	0	0	0	1	1
Fused sternebrae ^Δ												
Nos. 1-5:	0	0	0	0	0	0	0	0	1	1	0	0
Nos. 2-4:	0	0	0	0	0	0	1	3	0	0	0	0
Nos. 3, 4 & 5:	0	0	0	0	1	1	0	0	0	0	1	1
Nos. 4 & 5:	0	0	1	1	0	0	0	0	0	0	1	1
Additional sternebra ^Δ :	0	0	0	0	0	0	0	0	1	1	0	0
Vertebrae												
Centra unossified												
Cervical:	0	0	0	0	0	0	0	0	0	0	0	0
Thoracic:	0	0	0	0	0	0	0	0	0	0	0	0
Lumbar:	0	0	0	0	0	0	0	0	0	0	0	0
Sacral:	0	0	0	0	0	0	0	0	0	0	0	0
Caudal:	0	0	0	0	0	0	0	0	0	0	0	0

Δ = Minor malformation.

+ = Significantly different from the control group ($p < 0.05$).

APPENDIX I; Table 8 (cont.)

SC-18862: AN EVALUATION OF THE EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Fetal Skeletal Examination Data

	Control Fetuses		Low Dose Fetuses		Medium Dose Fetuses		High Dose Fetuses		L-Phe Fetuses		L-Asp Fetuses	
	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.
No. examined:	139		169		172		37		87		162	
(No. litters examined:	(35)		(40)		(44)		(9)		(26)		(43)	
Several caudal vertebrae absent Δ :	0	0	0	0	0	0	1	3	0	0	0	0
Fused caudal vertebrae Δ :	0	0	0	0	0	0	0	0	1	1	0	0
3rd & 4th thoracic vertebral centra & R. transverse processes fused. Hypoplastic 5th thoracic vertebral centrum. Hypo- plastic transverse process (R) of 6th cervical vertebra & agenesis of (R) trans- verse process & centrum Δ :	1	1	0	0	0	0	0	0	0	0	0	0
2nd & 3rd cervical vertebral centra split Δ :	0	0	1	1	0	0	0	0	0	0	0	0
13th thoracic vertebra - unil. (R) agenesis of the transverse process and centrum Δ :	0	0	0	0	1	1	0	0	0	0	0	0
5th cervical vertebra - hypoplastic centrum & unil. (L) agenesis of transverse process Δ :	0	0	0	0	0	0	1	3	0	0	0	0
10th, 11th & 12th thoracic vertebrae - fusion of transverse processes and centra Δ :	1	1	0	0	0	0	0	0	0	0	0	0
3rd cervical vertebra - hypoplastic centra Δ :	0	0	0	0	0	0	0	0	1	1	0	0
1st lumbar vertebra - L. transverse process present, R. transverse process & centrum missing Δ :	0	0	0	0	0	0	0	0	0	0	1	1

Δ = Minor malformation R = Right side. L = Left side.

APPENDIX I; Table 8 (cont.)

SC-18862: AN EVALUATION OF THE EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Summary of Fetal Skeletal Examination Data

	Control		Low Dose		Medium Dose		High Dose		L-Phe		L-Asp	
	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.	No.	% of Tot.
No. examined:	139		169		172		37		87		162	
(No. litters examined:	(35)		(40)		(44)		(9)		(26)		(43)	
Pelvic girdle												
Elements unossified												
R. ischium:	0	0	0	0	0	0	0	0	0	0	0	0
L. ischium:	0	0	0	0	0	0	0	0	0	0	0	0
R. ilium:	0	0	0	0	0	0	0	0	0	0	0	0
L. ilium:	0	0	0	0	0	0	0	0	0	0	0	0
R. pubis:	6	4	0	0+	2	1	4	11	6	7	9	6
L. pubis:	6	4	0	0+	2	1	3	8	6	7	9	6
Axial skeleton												
Forelimb (Bilat.)												
Carpals unossified:	139	100	109	100	172	100	37	100	87	100	162	100
Metacarpals unossified:	0	0	0	0	0	0	0	0	0	0	0	0
1-6 ossifications:	0	0	0	0	0	0	0	0	3	3	5	3
7-8 ossifications:	17	12	24	14	31	18	26	70+	27	31+	30	19
9-10 ossifications:	122	88	145	86	141	82	11	30+	57	66+	127	78
Phalanges unossified:	0	0	0	0	0	0	0	0	0	0	0	0
1-10 ossifications:	0	0	0	0	0	0	0	0	0	0	5	3
11-18 ossifications:	2	1	0	0	3	2	2	5	8	9	2	1
19-28 ossifications:	137	99	169	100	169	98	35	95	79	91	155	96
Hindlimb (Bilat.)												
Tarsals unossified:	0	0	0	0	0	0	0	0	0	0	5	3
1-2 ossifications:	3	2	2	1	10	6	11	30+	12	14+	3	2
3-4 ossifications:	136	98	167	99	162	94	26	70+	75	86+	154	95
Metatarsals unossified:	0	0	0	0	0	0	0	0	0	0	0	0
1-6 ossifications:	0	0	0	0	0	0	0	0	0	0	5	3
7-8 ossifications:	139	100	169	100	172	100	37	100	87	100	154	97
Phalanges unossified:	0	0	0	0	0	0	0	0	0	0	0	0
1-10 ossifications:	0	0	0	0	1	1	0	0	4	5	5	3
11-18 ossifications:	0	0	0	0	1	1	1	3	0	0	2	1
19-24 ossifications:	139	100	169	100	170	98	36	97	83	95	155	96

+ = Significantly different from the control group (p < 0.05).

R = Right side; L = Left side.

APPENDIX II

Individual Maternal Autopsy Reports

Rabbit No. 131

Control Group

P-T 1201

Antemortem

This animal was found dead in the afternoon of gestation day 14. This animal had been dosed for nine days, from gestation days 6 through 14. Labored respirations had been noted for several days prior to death.

Gross Autopsy

The degree of autolysis was negligible.

The carcass contained a normal amount of body fat.

Lung - the entire left lobe was consolidated and patchy consolidation was present in the right lobe.

Uterus - the left uterine horn contained three viable implantations and the right horn contained ten.

All other organs examined were grossly unremarkable.

Probable cause of death: Pneumonia.

Rabbit No. 134

Control Group

P-T 1201

Antemortem

This animal was found dead in the afternoon of gestation day 15. It had been dosed for ten days, from gestation days 6 through 15.

Gross Autopsy

The degree of autolysis was minimal.

The carcass contained a normal amount of body fat. Blood was present around the external nares.

Thorax - contained a large amount of free blood.

Uterus - the left uterine horn contained six viable implantations and the right horn contained one viable implantation near the vagina and one resorption near the oviduct.

All other organs examined were grossly unremarkable.

Probable cause of death: Aspiration pneumonia due to faulty administration of placebo material.

Rabbit No. 139

Control Group

P-T 1201

Antemortem

This animal was found dead in the morning of gestation day 17. It had been dosed for 11 days, from gestation days 6 through 16.

Gross Autopsy

The degree of autolysis was severe.

The carcass contained a normal amount of body fat.

Thorax - both sides of the thorax contained large amounts of purulent material.

Uterus - the left uterine horn contained two viable implantations and none were present in the right horn.

All other organs examined were grossly unremarkable.

Probable cause of death: Purulent pneumonia and pyothorax.

Antemortem

This animal died in the afternoon of gestation day 17. It had been dosed for 12 days, from gestation days 6 through 17. During the morning of the day of death, this animal severed the rubber intragastric tube and swallowed a large portion of it. Removal of the tube with forceps was unsuccessful. Prior to the second daily dose, stomach contents were emanating from the severed portion of the tube and very likely being aspirated, so another attempt was made to remove the tube. During this removal procedure, the animal expired.

Gross Autopsy

The degree of autolysis was mild.

The carcass contained a normal amount of body fat.

Lung - the lungs were moderately edematous.

Trachea - the trachea was hemorrhagic.

Uterus - the left horn contained one viable implantation, and the right horn contained two viable implantations, one resorption site and seven viable implantations.

All other organs examined were grossly unremarkable.

Probable cause of death: Undetermined, but related to the esophageal obstruction by the intragastric tube, and the attempts at removal.

Rabbit No. 206

Low Dose Group

P-T 1201

Antemortem

This animal was found dead in the morning of gestation day 13. It had been dosed seven days, from gestation days 6 through 12.

Gross Autopsy

The degree of autolysis was severe.

The carcass contained a normal amount of body fat.

A healing laceration and hair loss extended from the medial canthus of the left eye to a point on the dorsal midline about 2 cm posterior to the nares.

Lung - the left lobe appeared to be in the stage of gray hepatization leading to consolidation.

Trachea - foamy material was found near the main bronchi and the trachea was mildly hemorrhagic.

Uterus - the left horn contained six viable implantations and the right horn contained three.

All other organs examined were grossly unremarkable.

Probable cause of death: Aspiration pneumonia due to faulty administration of test compound.

Rabbit No. 207

Low Dose Group

P-T 1201

Antemortem

This animal was found dead on gestation day 11. It had been dosed for six days, from gestation days 6 through 11.

Gross Autopsy

The degree of autolysis was severe.

The carcass contained a normal amount of body fat.

Heart - the pericardium was thickened.

Kidney - a slight amount of chronic nephritis was present.

Lung - the lungs contained numerous abscesses, many of which had broken.

Stomach - stomach and intestines were relatively empty.

Thorax - both sides contained purulent material and adhesions.

Uterus - each horn contained three viable implantations.

All other organs examined were grossly unremarkable.

Probable cause of death: Purulent pneumonia and pyothorax.

Rabbit No. 214

Low Dose Group

P-T 1201

Antemortem

This animal was found dead in the morning of post-insemination day 28. It had been dosed for 13 days, from post-insemination days 6 through 18. Blood had been noted in the cage pan on post-insemination days 15, 22, and 28.

Gross Autopsy

The degree of autolysis was severe.

The carcass contained a normal amount of body fat.

Lung - patchy consolidation was evident in left lung.

Thorax - entire right side of thorax was filled with purulent material.

Uterus - five sites of former placental attachment were present in the left uterine horn and three were present in the right horn.

All other organs examined were grossly unremarkable.

Probable cause of death: Purulent pneumonia and pyothorax.

Rabbit No. 248

Low Dose Group

P-T 1201

Antemortem

This animal was found dead in the afternoon of gestation day 13. It had been dosed for eight days, from gestation days 6 through 13.

Gross Autopsy

The degree of autolysis was mild.

The carcass contained a normal amount of body fat.

Lung - a puncture type wound was evident on the posterior surface of the right diaphragmatic lobe of the lung.

Thorax - the right side of the thorax was filled with a bloody fluid.

Uterus - four viable implantations were present in the left uterine horn and five in the right horn.

All other organs examined were grossly unremarkable.

Probable cause of death: Pneumothorax and hemothorax due to faulty administration of test compound.

Rabbit No. 322

Medium Dose Group

P-T 1201

Antemortem

This animal was found dead on gestation day 17. It had been dosed for 12 days, from gestation days 6 through 17.

Gross Autopsy

The degree of autolysis was moderate.

The carcass contained a normal amount of body fat.

A small amount of blood was found around the external nares.

Lung - hemorrhage and consolidation were present in the right diaphragmatic lobe.

Uterus - four viable implantations were present in the left uterine horn and three in the right horn.

All other organs examined were grossly unremarkable.

Probable cause of death: Aspiration pneumonia due to faulty administration of test compound.

Rabbit No. 410

High Dose Group

P-T 1201

Antemortem

This animal was found dead in the morning of gestation day 15. It had been dosed for nine days, from gestation days 6 through 14. Blood was found in the cage pan on gestation days 14 and 15.

Gross Autopsy

The degree of autolysis was severe.

The carcass contained a normal amount of body fat.

Lung - consolidation was present in the dependent portions of the right lung and numerous abscesses were present throughout the lungs.

Stomach - the stomach wall was nearly dissolved due to autolysis. A moderate amount of hair was mixed with the ingesta.

Uterus - four viable implantations were present in the left uterine horn and three in the right horn.

All other organs examined were grossly unremarkable.

Probable cause of death: Purulent bronchopneumonia.

Rabbit No. 421

High Dose Group

P-T 1201

Antemortem

This animal was found dead in the morning of gestation day 28. It had been dosed for 13 days, from gestation days 6 through 18.

Gross Autopsy

The degree of autolysis was minimal.

The carcass contained a normal amount of body fat.

Lung - both lobes were filled with purulent material.

Uterus - the left horn contained six nonviable fetuses and the right horn contained four nonviable fetuses which were saved for examination.

All other organs examined were grossly unremarkable.

Probable cause of death: Purulent bronchopneumonia.

Rabbit No. 424

High Dose Group

P-T 1201

Antemortem

This animal was found dead in the morning of post-insemination day 21. It had been dosed for 13 days, from post-insemination days 6 through 18. Blood was present in the cage pan on post-insemination days 18 and 21.

Gross Autopsy

The degree of autolysis was moderate.

The carcass contained a normal amount of body fat.

Lung - patchy consolidation was present throughout the lungs.

Stomach - no food was present in the stomach but it did contain a trichobezoar. The intestinal tract was essentially empty.

Uterus - the left uterine horn contained three sites of former placental attachment and the right horn contained six sites. Blood was present around the vagina, apparently due to a recent abortion.

All other organs examined were grossly unremarkable.

Probably cause of death: Undetermined.

Rabbit No. 438

High Dose Group

P-T 1201

Antemortem

This animal was found dead in the morning of post-insemination day 21. The animal had been dosed for 13 days, from post-insemination days 6 through 18. Blood had been noted in the cage pan on post-insemination days 18, 19, and 20. At the time of death, the hind quarters were stained with feces.

Gross Autopsy

The degree of autolysis was severe.

The carcass contained only a slight amount of body fat.

Lung - purulent material was present in all lobes of the lung and both sides of the thorax.

Peritoneal cavity - a large amount of purulent material was evident.

Uterus - the left horn contained one site of former placental attachment, and the right horn contained eight sites.

All other organs examined were grossly unremarkable.

Probable cause of death: Purulent pneumonia, pyothorax and peritonitis.

Rabbit No. 263

L-Phenylalanine Group

P-T 1201

Antemortem

This animal was found dead in the morning of gestation day 21. It had been dosed for 13 days, from gestation days 6 through 18.

Gross Autopsy

The degree of autolysis was severe.

The carcass contained a normal amount of body fat.

Lung - all lobes contained numerous abscesses.

Thorax - the right side contained purulent material and adhesions.

Uterus - the left horn contained one fetus near the oviduct and two resorptions near the vagina. The right horn contained two resorptions, one fetus, two resorptions and one fetus, in that order, from the vagina to the oviduct.

All other organs examined were grossly unremarkable.

Probable cause of death: Purulent bronchopneumonia and pyothorax.

Rabbit No. 280

L-Phenylalanine Group

P-T 1201

Antemortem

This animal was found dead in the morning of post-insemination day 22. It had been dosed for 13 days, from post-insemination days 6 through 18. Blood was noted in the cage pan on post-insemination days 19 and 20.

Gross Autopsy

The degree of autolysis was severe.

The carcass contained a normal amount of body fat.

Lung - all lobes were involved with purulent pneumonia and pyothorax, the right side to a greater extent than the left.

Uterus - five sites of former placental attachment were found in each uterine horn.

All other organs examined were grossly unremarkable.

Probable cause of death: Purulent pneumonia and pyothorax.

Rabbit No. 283

L-Phenylalanine Group

P-T 1201

Antemortem

This animal was found dead in the morning of gestation day 13. It had been dosed for seven days, from post-insemination days 6 through 12.

Gross Autopsy

The degree of autolysis was severe.

The carcass contained a normal amount of body fat.

A small amount of blood was present around the external nares.

Trachea - hemorrhage was present.

Uterus - the left uterine horn contained three viable implantations and the right horn contained five.

All other organs examined were grossly unremarkable.

Probable cause of death: Aspiration pneumonia due to faulty administration of test compound.

Rabbit No. 290

L-Phenylalanine Group

P-T 1201

Antemortem

This animal was found dead on gestation day 12. It had been dosed for six days, from gestation days 6 through 11.

Gross Autopsy

The degree of autolysis was moderate.

The carcass contained a normal amount of body fat.

Thorax - a large amount of bloody fluid was found in the thoracic cavity.

Trachea - hemorrhage was present and the trachea contained some foamy fluid.

Uterus - the left horn contained five viable implantations and the right horn contained seven.

All other organs examined were grossly unremarkable.

Probable cause of death: Aspiration pneumonia due to faulty administration of test compound.

Rabbit No. 295

L-Phenylalanine Group

P-T 1201

Antemortem

This animal was found dead in the morning of gestation day 22. It had been dosed for 13 days, from gestation days 6 through 18.

Gross Autopsy

The degree of autolysis was severe.

The carcass contained a normal amount of body fat.

Lung - left lobes were consolidated and contained many abscesses.
Right cardiac lobe was also consolidated.

Uterus - seven viable implantations were present in the left horn
and three in the right horn.

All other organs examined were grossly unremarkable.

Probable cause of death: Purulent pneumonia.

Rabbit No. 370

L-Aspartic Acid Group

P-T 1201

Antemortem

This animal died on gestation day 18. It had been dosed for 12 days, from gestation days 6 through 17. Immediately prior to death, an intragastric tube had been inadvertently placed in the trachea. Before the tube could be removed, the animal severed the tube about 10 cm from the tip. The distal portion remained in the trachea and attempts to remove it were futile.

Gross Autopsy

The degree of autolysis was negligible.

The carcass contained a normal amount of fat.

Trachea - the intragastric tube was found in the trachea between the pharynx and the bifurcation. The tube was nearly the same diameter as the trachea and completely obstructed it.

Uterus - the left horn contained one viable implantation adjacent to the ovary and six resorptions. The right horn contained four resorptions.

All other organs examined were grossly unremarkable.

Probable cause of death: Suffocation due to tracheal obstruction.

Rabbit No. 397

L-Aspartic Acid Group

P-T 1201

Antemortem

This animal was found dead on post-insemination day 16. It had been dosed for 10 days, from post-insemination days 6 through 15.

Gross Autopsy

The degree of autolysis was mild.

The carcass contained a normal amount of body fat.

Lung - all lobes of lung were consolidated and adhesions were present in the right pleural cavity.

Uterus - not gravid but the left ovary contained four corpora lutea and the right ovary contained five.

All other organs examined were grossly unremarkable.

Probable cause of death: Pneumonia.

APPENDIX III

Comprehensive Litter Examination Reports

Key to Footnotes - Appendix III

*Left Uterine Horn - Progression from cephalad to caudad.

**Right Uterine Horn - Progression from caudad to cephalad.

CRD = Crown-Rump Distance

M = Male

F = Female

R = Resorption Site

N.D. = Data not recorded

A single underline (fetal number) indicates a minor malformation
(see glossary in Appendix IV).

A double underline (fetal number) indicates a major malformation
(see glossary in Appendix IV).

Appendix III

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

CONTROL FEMALE NO. 124

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 7 left horn; 4 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Left Horn*							Right Horn**				
12401	12402	12403	12404	12405	12406	12407	12408	12409	12410	12411	
12401	12402	12403	12404	12405	12406	12407	12408	12409	12410	12411	
33.2	25.2	30.0	31.9	30.4	25.4	20.1	28.9	32.7	25.3	36.5	
8.0	7.4	7.3	8.0	7.7	7.1	6.6	7.6	8.1	7.4	8.0	
F	M	F	M	M	F	F	M	F	F	M	
12401	12402	12403	12404	12405	12406	12407	12408	12409	12410	12411	
12401	12402	12403	12404	12405	12406	12407	12408	12409	12410	12411	
	12402		12404		12406		12408		12410		
	12402		12404		12406		12408		12410		

- continued -

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

CONTROL FEMALE NO. 124 (cont.)

UTERINE & LITTER DATA (cont.)

	<u>Left Horn</u>		<u>Right Horn</u>	
Skeletal Exam (Alizarin):	12401	12403	12405	12407
Evisceration unremarkable:	12401	12403	12405	12407
Skeletal examination unremarkable:	12401	12403	12404	12407
Fused ribs (right):				
3rd - 4th				
5th - 6th				
Fused thoracic vertebral centra				
3rd & 4th:				
Hypoplastic 5th thoracic vertebral centrum:				
Fused right transverse processes				
3rd & 4th thoracic vertebrae:				
Hypoplastic right transverse process 6th cervical vertebra and agenesis of the left transverse process and centrum:				

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

CONTROL FEMALE NO. 128

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 5 left horn, 4 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Hydrocephalus (internal):

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Left Horn*					Right Horn**			
12801	12802	12803	12804	12805	12806	12807	12808	12809
12801	12802	12803	12804	12805	12806	12807	12808	12809
32.2	22.3	25.1	31.0	28.2	30.4	31.3	31.2	24.8
7.9	7.1	7.6	7.7	7.4	7.2	7.4	7.6	7.2
M	F	F	F	M	M	F	M	M
12801	12802	12803	12804	12805	12806	12807	12808	12809
12801	12802	12803	12804	12805	12806	12807	12808	12809
12801		12803		12805		12807		12809
18201		12803		12805		12807		
								12809
	12802		12804		12806		12808	
	12802		12804		12806		12808	
	12802		12804		12806		12808	

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

CONTROL FEMALE NO. 132

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 1 left horn, 9 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Split 5th sternebra:

		Right Horn**									
Left Horn*		13202	13203	13204	13205	13206	13207	13208	13209	13210	
13201											
13201											
43.4		38.5	24.5	25.1	31.7	35.2	30.0	30.9	31.9	33.3	
8.5		8.2	6.7	7.1	7.8	8.2	6.7	6.9	6.9	6.6	
F		M	F	M	F	M	M	F	F	M	
13201		13202	13203	13204	13205	13206	13207	13208	13209	13210	
13201		13202	13203	13204	13205	13206	13207	13208	13209	13210	
13201			13203		13205		13207		13209		
13201			13203		13205		13207		13209		
		13202		13204	13206	13206	13207	13208	13209	13210	
		13202		13204	13206	13206	13207	13208	13209	13210	
		13202		13204	13206	13206	13207	13208	13209	13210	
		13202		13204	13206	13206	13207	13208	13209	13210	

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

CONTROL FEMALE NO. 150

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 6 left horn, 5 right horn

Resorptions: None left horn, 1 right horn

Fetal Identification:

Fetal Viability - Viable:

- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Split 5th sternebra:

		Left Horn*			Right Horn**		
15001	15002	15003	15004	15005	15006	R ₁	15007 15008 15009 15010
15001	15002	15003	15004	15005	15006		15007 15008 15009 15010
42.1	38.4	36.0	29.9	26.6	34.7		38.4 34.9 34.3 39.8
7.6	8.0	8.0	7.2	7.0	7.9		8.5 7.6 7.6 8.3
M	M	F	M	F	F	M	F F M
15001	15002	15003	15004	15005	15006		15007 15008 15009 15010
15001	15002	15003	15004	15005	15006		15007 15008 15009 15010
15001		15003		15005			15007 15009
15001		15003		15005			15007 15009
	15002		15004		15006		15008 15010
	15002		15004		15006		15008 15010
			15004		15006		15008 15010

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

Clinical Observations: Unremarkable
Necropsy Findings: Chronic nephritis, moderate
Delivery: By hysterotomy near term

Implantations: 3 left horn, 5 right horn

Fetal Identification:

- Nonviable: None

Fetal CRD (cm):

Fetal External Exam:

Fetal Soft Tissue Exam:

Skeletal Exam (Alizarin):

Skeletal examination unremarkable:

Bilateral:

Fused 10th, 11 & 12th ribs (bilat.):

Fused 10th, 11th & 12th transverse processes (bilat.), and thoracic vertebral centra:

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

LOW DOSE FEMALE NO. 220

Clinical Observations: Unremarkable
Necropsy Findings: Unremarkable
Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 7 left horn, 5 right horn
Resorptions: 3 left horn, 3 right horn

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Spina bifida:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Fused sternebrae, Nos. 4-5:

Left Horn*				Right Horn **							
R ₁	22001	R ₂	22002	R ₃	22003	22004	R ₄	R ₅	22005	22006	R ₆
	22001		22002		22003	22004			22005	22006	
	34.0		37.2		25.3	34.2			27.1	29.9	
	7.9		8.2		7.7	7.4			7.0	N.D.	
	F		F		M	M			F	M	
	22001		22002		22003	22004			22005	22006	
	22001		22002		22003	22004			22005	<u>22006</u>	
			22002			22004					
			22002			22004					
	22001				22003				22005	22006	
	22001				22003				22005	22006	
	22001				22003				22005	22006	

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

LOW DOSE FEMALE NO. 242

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 4 left horn, 3 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Split 5th sternebra:

		Left Horn*		Right Horn**		
24201	24202	24203	24204	24205	24206	24207
24201	24202	24203	24204	24205	24206	24207
42.1	38.5	36.4	38.8	42.3	35.5	41.6
7.2	8.1	7.6	8.0	8.3	7.3	8.4
F	F	F	F	M	F	M
24201	24202	24203	24204	24205	24206	24207
24201	24202	24203	24204	24205	24206	24207
24201		24203		24205		24207
24201		24203		24205		24207
	24202		24204		24206	
	24202		24204		24206	
	24202		24204			

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

LOW DOSE FEMALE NO. 243

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 5 left horn, 3 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

2nd & 3rd cervical vertebral centra split:

		Left Horn*			Right Horn**		
24301	24302	24303	24304	24305	24306	24307	24308
24301	24302	24303	24304	24305	24306	24307	24308
33.9	27.3	34.9	31.0	29.4	34.9	35.8	37.5
8.0	7.1	7.0	7.8	7.0	7.4	7.6	7.6
F	M	M	M	F	M	M	F
24301	24302	24303	24304	24305	24306	24307	24308
24301	24302	24303	24304	24305	24306	24307	24308
24301		24303		24305		24307	
24301		24303		24305		24307	
	24302		24304		24306		24308
	24302		24304		24306		24308
			24304		24306		24308

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

MEDIUM DOSE FEMALE NO. 314

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 5 left horn, 6 right horn

Resorptions: none left horn, 1 right horn

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Diaphragmatic hernia (L. side):

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Left Horn*				Right Horn**			
31401	31402	31403	31404	31405	31406	31407	31408 R ₁ 31410
31401	31402	31403	31404	31405	31406	31407	31408 31409 31410
29.1	28.2	22.6	27.8	30.2	31.0	26.1	25.0 25.6 27.8
7.7	7.6	7.2	7.5	8.1	7.7	6.8	7.2 7.4 7.7
M	F	F	M	F	F	M	M M F
31401	31402	31403	31404	31405	31406	31407	31408 31409 31410
31401	31402	31403	31404	31405	31406	31407	31408 31409 31410
31401		31403		31405		31407	31409
31401	31402	31403		31405		31407	

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

MEDIUM DOSE FEMALE NO. 331

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 3 left horn, 8 right horn

Resorptions: none left horn, 3 right horn

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Supernumerary nasal sutures:

Left Horn*			Right Horn**			
			R ₁	33104	33105	R ₂ 33106 33107 R ₃ 33108
33101	33102	33103				
33101	33102	33103				
28.0	27.2	24.5		24.2	28.0	28.7 25.0 25.7
7.7	7.2	7.8		7.4	7.6	7.0 7.3 7.3
F	M	F		M	F	F M M
33101	33102	33103		33104	33105	33106 33107 33108
33101	33102	33103		33104	33105	33106 33107 33108
33101		33103			33105	33107 33107
33101		33103			33105	33107 33107
	33102			33104		33106 33108
	33102			33104		33106 33108
	33102			33104		33106 33108

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

MEDIUM DOSE FEMALE NO. 336

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 5 left horn, 4 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Split 5th sternebra:

		Left Horn*				Right Horn**			
33601	33602	33603	33604	33605		33606	33607	33608	33609
33601	33602	33603	33604	33605		33606	33607	33608	33609
31.2	26.2	24.2	22.7	13.6		24.0	20.2	22.2	23.3
7.4	7.8	7.1	6.8	5.2		7.1	6.6	6.4	7.0
M	F	F	F	M		M	M	M	F
33601	33602	33603	33604	33605		33606	33607	33608	33609
33601	33602	33603	33604	33605		33606	33607	33608	33609
	33602		33604			33606		33608	
	33602		33604			33606		33608	
33601		33603		33605			33607		33609
33601		33603		33605			33607		33609
33601		33603		33605			33607		33609

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

MEDIUM DOSE FEMALE NO. 348

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 6 left horn, 5 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Umbilical hernia:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Supernumerary nasal sutures:

Left Horn*				Right Horn**						
34801	34802	34803	34804	34805	34806	34807	34808	34809	34810	34811
34801	34802	34803	34804	34805	34806	34807	34808	34809	34810	34811
27.5	28.9	28.9	27.1	18.9	21.3	23.8	17.8	19.2	26.3	20.3
7.5	7.7	7.5	7.2	6.8	6.5	6.3	6.7	6.5	7.4	N.D.
F	F	F	M	M	F	M	F	F	F	F
34801	34802	34803	34804	34805	34806	34807	34808	34809	34810	34811
34801	34802	34803	34804	34805	34806	34807	34808	34809	34810	34811
34801		34803		34805		34807		34809		34811
34801		34803		34805		34807		34809		
	34802		34804		34806		34808		34810	34811
	34802		34804		34806		34808		34810	34811
	34802		34804				34808		34810	34811
					34806					

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

HIGH DOSE FEMALE NO. 421

Clinical Observations: Unremarkable
Necropsy Findings: Purulent pneumonia
Delivery: By hysterotomy following death near term

UTERINE & LITTER DATA

Implantations: 6 left horn, 4 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable: None
- Nonviable:

Fetal Weight (g): N.D.

Fetal CRD (cm): N.D.

Fetal Sex:

Fetal External Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Supernumerary nasal sutures:

Split 2nd sternebra:

		Left Horn*				Right Horn**			
42101	42102	42103	42104	42105	42106	42107	42108	42109	42110
42101	42102	42103	42104	42105	42106	42107	42108	42109	42110
M	F	F	F	M	F	F	M	M	F
42101	42102	42103	42104	42105	42106	42107	42108	42109	42110
42101	42102	42103	42104	42105	42106	42107	42108	42109	42110
42101	42102	42103	42104	42105	42106	42107	42108	42109	42110
42101	42102	42103	42104	42105	42106	42107	42108	42109	42110
	42102	42103	42104	42105	42106			42109	42110
<u>42101</u>							<u>42108</u>		
							<u>42107</u>		

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

HIGH DOSE FEMALE NO. 430

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 3 left horn, 5 right horn

Resorptions: none left horn, 1 right horn

Fetal Identification:

Fetal Viability - Viable:

- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Small omphalocele:

Cleft palate:

Fetal Soft Tissue Exam:

Unremarkable:

Cleft palate:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Interparietal bone split:

Left Horn*		Right Horn**			
43001	43002	43003	43004	43005	43006 43007 R ₁
43001	43002	43003	43004	43005	43006 43007
N.D.	22.1	17.9	16.0	21.4	20.5 23.1
N.D.	7.3	6.8	6.9	7.1	6.8 7.3
M	M	F	F	F	F F
43001	43002	43003	43004	43005	43006 43007
		43003	43004	43005	43007
<u>43001</u>					
	<u>43002</u>				<u>43006</u>
	<u>43002</u>		43004		<u>43006</u>
			43004		
	<u>43002</u>				<u>43006</u>
43001		43003		43005	43007
43001		43003		43005	43007
		43003		43005	43007
<u>43001</u>					

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

HIGH DOSE FEMALE NO. 431

Clinical Observations: Blood in pan gestation day 14

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 4 left horn, 3 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Split 2nd sternbra:

Fused sternbrae, Nos. 2-4:

Left Horn*			Right Horn**			
43101	43102	43103	43104	43105	43106	43107
43101	43102	43103	43104	43105	43106	43107
29.4	28.3	26.8	30.2	23.3	27.5	32.2
8.2	7.2	7.1	8.0	7.2	7.0	7.1
M	F	M	F	F	F	F
43101	43102	43103	43104	43105	43106	43107
43101	43102	43103	43104	43105	43106	43107
	43102		43104		43106	
	43102		43104		43106	
43101		43103		43105		43107
43101		43103		43105		43107
43101		<u>43103</u>				
				<u>43105</u>		

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-PHE FEMALE NO. 264

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 6 left horn, 6 right horn

Resorptions: none left horn, 1 right horn

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Large omphalocele:

Arthrogryposis-like defect
(hindlimbs):

No tail:

Fetal Soft Tissue Exam:

Unremarkable:

		Left Horn*			Right Horn**		
26401	26402	26403	26404	26405	26406	26407	26408 26409 26410 R ₁ 26411
26401	26402	26403	26404	26405	26406	26407	26408 26409 26410 26411
30.3	29.2	30.2	21.7	21.8	26.3	N.D.	21.4 23.3 28.9 23.7
7.5	7.1	7.8	7.4	7.0	8.0	N.D.	7.2 7.2 7.6 7.1
M	M	M	F	M	M	F	F F F F
26401	26402	26403	26404	26405	26406	26407	26408 26409 26410 26411
26401	26402	26403	26404	26405	26406	26407	26408 26409 26410 26411
<u>26407</u>							
<u>26407</u>							
<u>26407</u>							
							26409 26411
							26409 26411

- continued -

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-PHE FEMALE NO. 264 (cont.)

UTERINE & LITTER DATA (cont.)

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Agensis of L. kidney & ureter:

Skeletal examination unremarkable:

Fusion of transverse process of 4th
lumbar vertebra dorsally:

Caudal vertebrae scrambled:

	Left Horn*	Right Horn**
26401	26403	26407 26408 26410
26401	26403	26408 26410
		<u>26407</u>
		<u>26407</u>
		<u>26407</u>

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-PHE FEMALE NO. 270

Clinical Observations: Unremarkable
Necropsy Findings: Unremarkable
Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 5 left horn, 7 right horn
Resorptions: 2 left horn, 5 right horn

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Cleft palate:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Left Horn*				Right Horn**							
27001	27002	R ₁	R ₂	27003	R ₃	R ₄	27004	R ₅	R ₆	R ₇	27005
27001	27002			27003			27004				27005
27.9	26.9			23.1			29.2				25.4
7.4	7.2			7.8			7.8				7.3
F	F			F			M				M
27001	27002			27003			27004				27005
	27002			27003			27004				27005
<u>27001</u>											
	27002						27004				
	27002						27004				
27001				27003							27005
27001				27003							27005
27001				27003							27005

APPENDIX III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-PHE FEMALE NO. 277

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: Prematurely on gestation day 28

UTERINE & LITTER DATA

Implantations: 2 left horn, 4 right horn

Resorptions: 0 left horn, 0 right horn

Fetal Identification:

Fetal Viability - Viable: None

- Nonviable:

Fetal Weight (g):

Fetal CRC (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Supernumerary Nasal Sutures:

Left Horn*		Right Horn**		
PM ₁	PM ₂	PM ₃	PM ₄	PM ₅
PM ₁	PM ₂	PM ₃	PM ₄	PM ₅
15.0	13.0	25.3	18.7	N.D.
-	-	-	-	-
M	F	F	F	-
PM ₁	PM ₂	PM ₃	PM ₄	
PM ₁	PM ₂	PM ₃	PM ₄	
PM ₁	PM ₂	PM ₃	PM ₄	
PM ₁	PM ₂	PM ₃	PM ₄	
PM ₁	PM ₂	PM ₃	PM ₄	
PM ₁	PM ₂	PM ₃	PM ₄	

Note: Since these pups were delivered, numbers were assigned arbitrarily. Pup PM₅ was not in suitable condition for examination.

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-PHE FEMALE NO. 277

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: Delivered prematurely gestation day 28 - 5 pups, 4 intact (nonviable)
and one severely autolyzed.

UTERINE & LITTER DATA

Sites of placental attachment (PA): 2 left horn, 4 right horn

		Left Horn		Right Horn			
		PA ₁	PA ₂	PA ₃	PA ₄	PA ₅	PA ₆
Pup Identification:		27701	27702	27703	27704		
Pup Viability - Viable: None		15.0	13.0	25.3	18.7		
- Nonviable:		N.D.	N.D.	N.D.	N.D.		
Pup Weight (g):							
Pup CRD (cm):							
Pup Sex:		M	F	F	F		
External Exam:		27701	27702	27703	27704		
Unremarkable:		27701	27702	27703	27704		
Skeletal Exam (Alizarin):		27701	27702	27703	27704		
Evisceration unremarkable:		27701	27702	27703	27704		
Skeletal examination unremarkable:		27701	27702		27704		
Supernumerary nasal sutures:				27703			

NOTE: There were more identifiable sites of placental attachment than delivered pups.
The pups were arbitrarily numbered.

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-PHE FEMALE NO. 278

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 2 left horn, 5 right horn

Resorptions: none left horn, 4 right horn

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Supernumerary nasal sutures:

Hypoplastic 3rd cervical vertebral centra:

Left Horn*		Right Horn**			
		R ₁	R ₂	R ₃	R ₄
27801	27802				27803
27801	27802				27803
19.7	19.1				19.7
6.7	6.7				6.7
M	F				M
27801	27802				27803
27801	27802				27803
	27802				
	27802				
27801					27803
27801					27803
27801					<u>27803</u>
					<u>27803</u>

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-PHE FEMALE NO. 279

Clinical Observations: Unremarkable

Necropsy Findings: Chronic nephritis (bilat.), mild

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 2 left horn, 4 right horn

Resorptions: 1 left horn, none right horn

Fetal Identification:

Fetal Viability - Viable:

- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Small omphalocele:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Left Horn*	Right Horn**			
27901 R ₁	27902	27903	27904	27905
27901	27902	27903	27904	27905
N.D.	32.2	28.9	28.9	35.3
N.D.	8.2	6.7	7.4	7.7
M	F	M	F	M
27901	27902	27903	27904	27905
	27902	27903	27904	27905
<u>27901</u>				
	27902		27904	
	27902		27904	
27901		27903		27905
27901		27903		27905
27901		27903		27905

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-PHE FEMALE NO. 281

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 4 left horn, 7 right horn

Resorptions: 3 left horn, 3 right horn

Fetal Identification:

Fetal Viability - Viable: None
- Nonviable:

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Small omphalocle:

Oligodactyly (3 digits present)
L. forelimb

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Hypoplastic 3rd cervical vertebral centrum:

Left Horn*			Right Horn**							
R ₁	R ₂	R ₃	28101	28102	R ₄	R ₅	28103	28104	R ₆	28105
			28101	28102			28103	28104		28105
			25.5	25.5			25.2	28.9		N.D.
			7.1	6.9			7.1	7.7		N.D.
			M	F			F	M		M
			28101	28102			28103	28104		28105
			28101	28102			28103	28104		<u>28105</u>
										<u>28105</u>
				28102				28104		
				28102				28104		
			28101				28103			28105
			28101				28103			28105
			28101				28103			28105

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-PHE FEMALE NO. 284

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 8 left horn, 4 right horn

Resorptions: none left horn, 1 right horn

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Umbilical hernia:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

										Right Horn**	
										Left Horn*	
	28401	28402	28403	28404	28405	28406	28407	28408	28409 R ₁	28410	28411
	28401	28402	28403	28404	28405	28406	28407	28408	28409	28410	28411
	37.0	29.3	27.9	32.0	29.3	30.4	24.3	34.6	24.5	29.5	33.2
	7.6	8.1	7.3	7.2	7.5	7.7	6.6	7.9	N.D.	7.1	7.1
	M	M	M	M	M	F	F	M	F	F	F
	28401	28402	28403	28404	28405	28406	28407	28408	28409	28410	28411
	28401	28402	28403	28404	28405	28406	28407	28408	28409	28410	28411
									28409		
	28401		28403		28405		28407			28410	
	28401		28403		28405		28407			28410	
	28402			28404		28406		28408	28409		28411
	28402			28404		28406		28408	28409		28411
	28402			28404		28406		28408	28409		28411

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-PHE FEMALE NO. 289

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 4 left horn, 4 right horn

Resorptions: 1 left horn, 0 right horn

Fetal Identification:

Fetal Viability - Viable:

- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Umbilical hernia:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Left Horn*		Right Horn**	
28901	28902 R ₁	28904	28905 28906 28907
28901	28902	28904	28905 28906 28907
32.9	27.8	27.7	30.6 29.0 30.6
7.6	7.2	6.9	7.9 7.7 7.2
M	F	F	F M M
28901	28902 R ₁	28904	28905 28906 28907
28901	28902	28904	28905 28906 28907
	R ₁		
28901	R ₁		28905 28907
28901	R ₁		28905 28907
	28902	28904	28906
	28902	28904	28906
	28902	28904	28906

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-PHE FEMALE NO. 297

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 5 left horn, 3 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Fused ribs (unil. L.) nos. 2 & 3:

		Left Horn*			Right Horn**		
29701	29702	29703	29704	29705	29706	29707	29708
29701	29702	29703	29704	29705	29706	29707	29708
24.4	24.1	27.7	25.8	25.0	24.3	26.0	25.0
7.1	6.9	7.4	7.4	7.3	7.0	7.1	6.8
F	F	M	M	M	F	F	F
29701	29702	29703	29704	29705	29706	29707	29708
29701	29702	29703	29704	29705	29706	29707	29708
29701		29703		29705		29707	
29701		29703		29705		29707	
	29702		29704		29706		29708
	29702		29704		29706		29708
	29702		29704				29708

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-ASP FEMALE NO. 352

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 6 left horn, 4 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable: None
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Omphalocele:

Cyclopia:

Microencephaly:

Astomia:

Absence of external nares
and philtrum:

		Left Horn*				Right Horn**			
35201	35202	35203	35204	35205	35206	35207	35208	35209	35210
35201	35202	35203	35204	35205	35206	35207	35208	35209	35210
39.5	28.6	33.0	27.1	27.9	30.8	32.5	N.D.	32.9	37.2
8.3	8.4	8.4	7.7	7.3	7.6	8.6	N.D.	8.0	9.0
M	F	M	M	F	M	F	F	M	M
35201	35202	35203	35204	35205	35206	35207	35208	35209	35210
35201	35202	35203	35204	35205	35206	35207		35209	35210
							35208		
							35208		
							35208		
							35208		
							35208		

- continued -

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-ASP FEMALE NO. 352 (cont.)

UTERINE & LITTER DATA (cont.)

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Diaphragmatic hernia:

Skeletal examination unremarkable:

Interparietal bone split:

Left Horn*		Right Horn**	
35201	35203	35207	35209
35201	35203	35207	35209
35202	35204	35208	35210
35202	35204	35206	35210
35202	35204	<u>35208</u>	
35202	35204	<u>35208</u>	

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-ASP FEMALE NO. 353

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 4 left horn, 9 right horn

Resorptions: 1 left, 1 right horn

Fetal Identification:

Fetal Viability - Viable:

- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Fused sternebrae, nos. 4-5:

Left Horn*				Right Horn**								
R ₁	35301	35302	35303	35304	35305	35306	35307	35308	35309	35310	35311	R ₂
	35301	35302	35303	35304	35305	35306	35307	35308	35309	35310	35311	
	46.9	40.6	38.7	34.5	29.4	30.9	32.6	39.6	34.5	36.6	43.0	
	9.2	9.2	8.5	8.4	7.7	7.9	8.3	8.7	8.8	8.0	9.3	
	F	F	F	F	M	F	F	M	F	M	F	
	35301	35302	35303	35304	35305	35306	35307	35308	35309	35310	35311	
	35301	35302	35303	35304	35305	35306	35307	35308	35309	35310	35311	
	35301		35303		35305		35307		35309		35311	
	35301		35303		35305		35307		35309		35311	
		35302		35304		35306		35308		35310		
		35302		35304		35306		35308		35310		
		35302				35306		35308		35310		
				35304								

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-ASP FEMALE NO. 373

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 2 left horn, 7 right horn

Resorptions: 1 left horn, none right horn

Fetal Identification:

Fetal Viability - Viable:

- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skull closure grading - 3:

	Left Horn*		Right Horn**					
R ₁	37301	37302	37303	37304	37305	37306	37307	37308
	37301	37302	37303	37304	37305	37306	37307	37308
	9.9	8.5	10.4	10.7	10.8	10.5	10.4	10.3
	5.2	5.2	5.5	5.5	5.7	5.4	5.2	5.8
	F	F	M	F	F	M	M	F
	37301	37302	37303	37304	37305	37306	37307	37308
	37301	37302	37303	37304	37305	37306	37307	37308
	37301		37303		37305		37307	
	37301		37303		37305		37307	
	37302			37304		37306		37308
	37302			37304		37306		37308
	37302			37304		37306		37308

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-ASP FEMALE NO. 374

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 1 left horn, 1 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skull closure grading - 3:

<u>Left Horn*</u>	<u>Right Horn**</u>
37401	37402
37401	37402
9.9	9.2
5.4	5.6
M	F
37401	37402
37401	37402
	37402
	37402
37401	
37401	
37401	

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-ASP FEMALE NO. 382

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 3 left horn, 6 right horn

Resorptions: none left horn, 1 right horn

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Vertebral defect - unil. (R) agenesis
of transverse process and centrum of
1st lumbar vertebra:

Left Horn*		Right Horn**				R ₁
38201	38202	38203	38204	38205	38206	38208
38201	38202	38203	38204	38205	38206	38208
35.7	38.2	33.0	32.8	32.6	36.0	33.4
7.9	8.1	8.1	8.0	8.0	7.8	8.0
M	F	M	F	M	M	F
38201	38202	38203	38204	38205	38206	38208
38201	38202	38203	38204	38205	38206	38208
38201		38203		38205		38207
38201		38203		38205		38207
	38202		38204		38206	38208
	38202		38204		38206	38208
	38202		38204		38206	

38208

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-ASP FEMALE NO. 387

Clinical Observations: Unremarkable
Necropsy Findings: Unremarkable
Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 3 left horn, 1 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Fused sternebrae, nos. 3-5:

	Left Horn*		Right Horn**
38701	38702	38703	38704
38701	38702	38703	38704
45.1	44.9	38.4	17.9
8.2	8.9	8.4	6.6
F	M	F	M
38701	38702	38703	38704
38701	38702	38703	38704
38701		38703	
38701		38703	
	38702		38704
	38702		38704
	38702		<u>38704</u>

Appendix III (cont.)

SC-18862: AN EVALUATION OF EMBRYOTOXIC AND TERATOGENIC POTENTIAL IN THE RABBIT; P-T 1201

Comprehensive Litter Examination Report

L-ASP FEMALE NO. 396

Clinical Observations: Unremarkable

Necropsy Findings: Unremarkable

Delivery: By hysterotomy near term

UTERINE & LITTER DATA

Implantations: 2 left horn, 6 right horn

Resorptions: None

Fetal Identification:

Fetal Viability - Viable:
- Nonviable: None

Fetal Weight (g):

Fetal CRD (cm):

Fetal Sex:

Fetal External Exam:

Unremarkable:

Fetal Soft Tissue Exam:

Unremarkable:

Skeletal Exam (Alizarin):

Evisceration unremarkable:

Skeletal examination unremarkable:

Supernumerary nasal sutures:

Left Horn*		Right Horn**					
39601	39602	39603	39604	39605	39606	39607	39608
39601	39602	39603	39604	39605	39606	39607	39608
37.6	38.9	30.0	29.1	33.3	32.9	32.8	38.2
7.9	7.4	7.7	7.3	7.8	7.7	7.7	8.8
M	F	F	F	F	F	M	F
39601	39602	39603	39604	39605	39606	39607	39608
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APPENDIX IV

Glossary of Teratology Terminology

GLOSSARY OF TERATOLOGY TERMINOLOGY NEW ZEALAND WHITE RABBIT

Morphological alterations of varied nature are known to occur in the New Zealand White rabbit. 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 three categories, namely: 1) major malformations; 2) minor malformations; and 3) 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 23,104 New Zealand White rabbits, 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

1) Multiple Defects and General Disorganization

Chondrodystrophy (skeletal structures unrecognizable, eventrated viscera).

Thoracogastroschisis + eventration of viscera + cyclopia + cranioschisis + lumbar and cervical spina bifida + anury + agenesis of right radius and pollex + agenesis of left kidney.

Thoracogastroschisis + eventration of disorganized viscera + acephaly + ectro- and brachydactyly + anury.

Gastroschisis + anal atresia (imperforate anus) + left renal agenesis + distorted right kidney + anury + cebocephaly + dislocated (malrotated) hindlimbs (muscle contracture) + fused ribs + dysmorphic vertebrae.

General lack of ossification + cebocephaly + pulmonary aplasia + cardiac hypertrophy + fusion of pulmonary and systemic arch + dysmorphoses of thoracic vertebrae and ribs.

Malrotation and talipes of all limbs (muscle contracture) + asymmetric lower jaw + wavy ribs + twisted clavicle.

Encephalomeningocoele + agenesis of left pinna + open eye + ocular haemorrhage + harelip + cleft palate + gastroschisis + ectopic kidney + cryptorchia + bipartite and hemicentric vertebrae + branched and missing ribs + short tail.

Encephalomeningocoele + unilateral microphthalmia + ocular opacity + brachygnathia + oligodactyly + gastroschisis + fused pulmonary and systemic arches.

Rabbit; Major Malformations (cont.)

2) Cranial Defects

Acephaly

- a) + forelimb flexure + agenesis of pollex + bifurcated ovary
- b) + multiple skeletal and visceral defects
- c) + thoracoschisis + fused pulmonary and systemic arches
- d) + omphalocele + scoliosis + bilateral flexed forelimbs

Acrania (+ gastroschisis)

Otocephaly

Cyclopia

- a) rhinencephaly
- b) + agnathia
- c) + multiple defects
- d) + encephalomeningocoele + cleft palate

Cebocephaly

- a) enlarged foramen resulting from inadequate ossification of frontals and nasals
- b) short snout + multiple skeletal and visceral defects
- c) short snout + ectopic kidney, hydroureter

Anencephaly (+ iniencephaly, cranioschisis)

- a) alone
- b) + multiple defects

Exencephaly

- a) alone
- b) + cleft palate
- c) + spina bifida
- d) + reduced tail, open eyes
- e) + open eye + hemicentric, ankylosed vertebrae + missing ribs

Hydrocephaly

- a) alone
- b) + cleft palate + diaphragmatic hernia + severe forelimb flexure
- c) + muscle contracture

Rabbit; Major Malformations (cont.)

2) Cranial Defects (cont.)

Encephalomeningocoele

- a) bones absent on one side of head + multiple defects
- b) bones absent on one side of head + cleft palate + cyclopia
- c) enlarged central foramen not identical with reduced skull ossification associated with retarded development

Microphthalmia (unilateral)

- a) alone
- b) + bilateral folding of retina
- c) multiple defects

Open eye

- a) + exencephaly
- b) + exencephaly + hemicentric, ankylosed vertebrae (scoliosis) + missing ribs
- c) + multiple defects
- d) + cleft palate + fused sternum + agenesis of intermediate lung lobe

Cleft palate

- a) alone
- b) + sternal defect
- c) + exencephaly
- d) + exophthalmia
- e) + multiple defects
- f) + cyclopia + encephalomeningocoele
- g) + harelip + misshapen liver
- h) + diaphragmatic hernia + hernia + hydrocephaly + severe forelimb flexure
- i) + open eyes + fused sternum + agenesis of intermediate lung lobe

Harelip

- a) alone
- b) + cleft palate + misshapen liver
- c) + multiple defects

Rabbit; Major Malformations (cont.)

2) Cranial Defects (cont.)

Agnathia

- a) alone
- b) + cyclopia

Brachygnathia

- a) alone
- b) + multiple defects

Pinna agenesis (unilateral)

- a) alone
- b) + multiple defects

Microstomia

- a) alone
- b) + multiple defects

3) Axial Skeleton and Trunk

Unossified atlas vertebra, 1st, 2nd and 6th sternbrae; reduced ossification of skull, remaining sternbrae and phalangeal bones

Craniorachischisis

Spina bifida

- a) lumbosacral
- b) thoracic
- c) + exencephaly
- d) + anury
- e) + multiple defects
- f) + kyphosis + scoliosis + disorganized lumbosacral vertebrae

Meningocele

+ ectrodactyly + fused sternum

Anury

- a) + spina bifida
- b) + multiple defects
- c) + thoracic, lumbar and sacral vertebral defects

Rabbit; Major Malformations (cont.)

3) Axial Skeleton and Trunk (cont.)

Muscle contracture (causing limb malrotation, not to be confused with the minor anomaly of mild forelimb flexure)

- a) alone
- b) + multiple defects
- c) + hydrocephaly + cleft palate + diaphragmatic hernia
- d) + hydrocephaly

Vertebrae and ribs

Hemicentric, bipartite; asymmetrical, ankylosed and missing vertebrae; branched, fused or missing ribs; scoliosis, kyphosis

- a) thoracic alone
- b) thoracic + multiple defects
- c) thoracic + exencephaly
- d) thoracic + anury + agenesis of lumbar, sacral and caudal vertebrae + horseshoe kidney
- e) lumbosacral alone
- f) lumbosacral + multiple defects
- g) lumbosacral + spina bifida

Thoracoschisis (+ ectopic heart)

- a) alone
- b) + amelia + pulmonary hypoplasia
- c) + acephaly + fused pulmonary and systemic arches

Divided sternum

- a) + diaphragmatic hernia
- b) + cleft palate

Fused sternum (all sternebrae)

- a) + unexpanded lungs + gastroschisis
- b) + meningocele + ectrodactyly
- c) + cleft palate + open eye + agenesis of intermediate lung lobe

Subcutaneous oedema (anasarca)

- a) alone
- b) + gastroschisis

Rabbit; Major Malformations (cont.)

3) Axial Skeleton and Trunk (cont.)

Gastroschisis (exomphalos, umbilical hernia)

- a) alone
- b) + acrania
- c) + imperforate anus
- d) + hydronephrosis
- e) + multiple defects
- f) + subcutaneous oedema
- g) + fused sternum, unexpanded lungs

Imperforate anus (anal atresia)

- a) + gastroschisis
- b) + multiple defects
- c) + heart defect

4) Internal Viscera

Situs inversus (lungs)

Ectopic heart

- a) + thoracoschisis
- b) + multiple defects

Fused pulmonary and systemic arches with subsequent coarctation or agenesis of pulmonary artery

- a) alone
- b) + pulmonary hypoplasia
- c) + imperforate anus
- d) + multiple defects
- e) + acephaly + thoracoschisis

Pulmonary hypoplasia (NOT including minor agenesis of intermediate lung lobe)

- a) alone
- b) + fused pulmonary/systemic arches
- c) + thoracoschisis + amelia
- d) + multiple defects
- e) + diaphragmatic hernia

Rabbit; Major Malformations (cont.)

4) Internal Viscera (cont.)

Confluent bladder and rectum

Kidney defects

- a) unilateral agenesis
- b) unilateral agenesis + multiple defects
- c) unilateral agenesis + fused rectum
- d) horseshoe kidney
- e) horseshoe kidney + agenesis of lumbar, sacral and caudal vertebrae
- f) ectopic kidney
- g) ectopic kidney + multiple defects
- h) misshapen + multiple defects
- i) hydronephrosis
- j) hydronephrosis + gastroschisis

Displaced ureter (looped under vena cava)

Diaphragmatic hernia

- a) + divided sternum
- b) + pulmonary hypoplasia
- c) + cleft palate + hydrocēphaly + severe forelimb flexure
- d) + umbilical hernia

• Misshapen liver

+ cleft palate + harelip

Cyst on stomach

Monorchid

- a) male
- b) female

Divided gonad (male)

Interrupted uterus (congenital; found often in nonpregnant adults)

Cryptorchid

- a) alone
- b) + multiple defects

Rabbit; Major Malformations (cont.)

5) Limbs

Agensis of pollex

- a) alone
- b) + multiple defects

Ectro- and brachydactyly

- a) + multiple defects
- b) + meningocoele + fused sternum

Oligodactyly

- + multiple defects

Amelia

- + thoracoschisis + pulmonary hypoplasia

Malrotation of limbs

- a) see muscle contracture
- b) agensis of radius + multiple defects

MINOR MALFORMATIONS

<u>From Gross Autopsy</u>	<u>From Skeletal Staining</u>
Occular opacity (vacuolation of lens fibres)	Sutural bones
Iridial haemorrhage	Reduced skull ossification (closure grading less than 2)
Short tail	Lack of central parietal ossification
Agensis of intermediate lung lobe	Asymmetrical sternebrae
Reduction, bifurcation or agensis of gall bladder	Bipartite or bifurcated sternebrae (including associated effects on the xiphisternum in some cases)
Forelimb flexure	Bifurcated xiphisternum (no associated sternebral effects)
Hindlimb flexure	Fused sternebrae
Misshapen left kidney	Additional sternebrae
Eyelids separated (slight - moderate)	Vertebral and rib anomalies
	All sternebrae unossified
	Shortened ulna and radius

SKELETAL VARIANTS

Observations	Mean (%)	Range (%)
Percentage with 12 ribs	54	25 - 75
a) with all sternebrae ossified	66	46 - 94
b) with reduced or unossified sternebrae	34	6 - 54
Percentage with 13 ribs	46	25 - 75
a) with all sternebrae ossified	80	63 - 100
b) with reduced or unossified sternebrae	20	0 - 38
Percentage with less common variants	7	0 - 20

(Huntingdon Research Centre data; reference cited in the introduction to this Appendix)