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**Report Title: A One-Generation Reproduction and Teratology Study of G0539.02**

**Test Type:** Reproduction Toxicity

**Conducting Laboratory and Location:** P&G, Miami Valley Laboratories, Biological Testing Facility, Cincinnati, OH

**Test Substance(s):** G0539.02 – Octopirox in diet

**Species:** Rat

**# of Animals:** 25 males and 25 females/group

**Test Conditions:** Male and female Charles River CD rats (25 males and 25 females per group) were fed diets containing OP to deliver doses of 0, 50, 100, or 300 mg/kg/day for one generation.

**Results:** OP was extremely toxic to rats at the 300-mg/kg/day-dose level in the diet and was believed to be due to chelation of iron as evidenced by severe anemia. At the 100-mg/kg dose a less severe anemia was produced which was not lethal in adult animals, but decrease survivability of neonates. Although OP was not frankly teratogenic, there were secondary effects on embryos and fetuses as a result of the dam's anemic state. The study was terminated after the F1B generation so no NOEL was established.

**Study #:** B85-0460

**Report Date:** 7/16/87

**Accession #:** 33895

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A One-Generation Reproduction and Teratology Study of G0539.02

BYCR0428

B85-0460

July 16, 1987

## Preface

A two-generation reproduction/teratology study (B85-0319) of G0539.02 was started using doses based upon a two-week pilot study done in adult rats. These doses were 0, 50, 250 and 500 mg/kg/day. However, an error was made during the randomization procedure which resulted in 36 male rats receiving the wrong treatments during the first two days of the study. Although we believed that this would not compromise the study scientifically, it was decided to abort the study and start again, as it was intended as a regulated study.

Moreover, it became quickly apparent that the high dose was very toxic to the young post-weaning animal - more so than was observed in the pilot study. Therefore, it was decided to use lower doses in the restarted study.

The same DRD, protocol (but with different dosing levels), and lots of test substance were used for the restart, but a new study number was assigned.

The data for this short, aborted study are contained in Notebook #YE-885. None of them will be included in this report.

Summary

G0539.02 was dosed to Charles River rats of both sexes continuously in the diet at doses of 0, 50, 100, and 300 mg/kg/day, in a proposed two-generation reproduction/teratology study. The 300 mg/kg dose was highly toxic to both males and females, although the male was more susceptible than the female, killing all males and 13/25 of the females by the 16th week of the study. Only one of the remaining females conceived when mated to untreated stock males. The 100 mg/kg dose was not overtly toxic to adult animals, but was lethal to neonates. These events resulted in the study being aborted after the F<sub>1B</sub> pregnancies of the first generation. Some scattered effects, such as reduced conception rate, and a lower viability index (a measure of neonatal death) which cannot be adequately explained as random events, indicate that a no-adverse-effect-level (NOEL) has not been established.

Clinical chemistries, hematology, and histopathology indicated that the toxicity was caused by severe hypochromic, microcytic anemia due to dietary iron deficiency, and that effects secondary to this parental state are produced in the fetus and neonate. However, G0539.02 is not frankly teratogenic.

## Objective

This study was intended to determine the chronic administration of G0539.02 on reproduction and teratogenicity in two generations of rats. However, because of unexpected toxicity, the study was aborted at the end of the first generation.

The rat is an acceptable model for both reproduction and teratology. The major route of exposure to G0539.02 in the human is topical, but the oral route was chosen in order to maximize systemic exposure and to bypass technical problems accompanying long-term topical exposure in the rat such as unknown oral intakes from grooming.

The study was conducted in the Biological Testing Facility at:

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Study No.: B85-0460  
DRD No.: BYCRO428  
TSIN: G0539.02  
Notebook Nos.: YE-862-I, YE-862-II, YE-1083, YE-1084, VE-6007, and VE-6008  
In-Life Initiation: 10/17/85  
In-Life Completion: 5/1/86  
Study Director: G. A. Nolen

## Methods and Materials

Two containers of G0539.02, weighing 1545 and 1585 g, respectively, were received from the Sponsoring Division on 9/24/85. The samples of test substance were stored at room temperature until used, and the remaining portion was returned to the Divisional Toxicologist.

One hundred and twenty-five Charles River CD weanling (21-23 days old) rats of each sex, littermates identified, were received from Charles River Breeding Laboratories, Portage, MI on 10/17/85. They were inspected for disease conditions, weighed and placed in individual stainless steel cages with raised-wire-floors. They were ear-tagged with metal tags bearing unique numbers and were given access to tap water and Certified Purina Chow pellets on an ad libitum basis. After a 7-day acclimation period, the rats were weighed and randomly distributed into four groups of 25 rats of each sex, but assuring that the littermates were evenly distributed among the groups. The rats were then begun on their respective diets of ground, Certified Purina Chow which contained G0539.02 at concentrations to deliver doses of 0, 50, 100 or 300 mg/kg/day. Neither the feed nor the water was analyzed as there were no known contaminants that might compromise the results of the study.

The animals were weighed and their feed consumption was measured weekly. Separate batches of diet were made for each sex and the concentrations of G0539.02 were changed weekly to allow for growth and changing feed consumption patterns. These concentrations of G0539.02 were calculated on the basis of the most recent body weight and the previous weekly feed consumption.

At the beginning of the study, three 100 g samples of diet were removed from the top, middle, and bottom of each diet preparation and returned to the sponsor for homogeneity testing. One sample of each subsequent diet was also returned to the Sponsor for possible future testing.

The animals were maintained on these regimens throughout the study. The first 13 weeks of the study was a growth phase. At the end of that period the rats were mated on a 1:1 basis.

Because of the high death rate among the males given 300 mg/kg/day G0539.02, the females at this dose were mated with some stock, untreated males. However, the death rate among the females increased and the living ones did not conceive. Therefore, this group was terminated and sacrificed.

Pregnancy was determined by the vaginal smear technique and the finding of sperm in the lavage indicated day 0 of pregnancy. The first pregnancy ( $F_{1A}$ ) was for reproduction and the dams bore their litters naturally. The dams were weighed on days 0 and 20 of gestation, and their feed consumption was measured for this period.

At about day 17, the dams were furnished with a plywood cage liner and shredded paper to make a nest. At birth (postnatal day 1) the number of live and dead pups were counted and both dams and litters of pups were weighed separately. This was repeated on days 8, 15, and 22 (weaning). Feed consumption records were also kept for these periods. Weekly records of body weights and feed consumption also were continued. On postnatal day 4, the litters containing more than 8 pups were randomly reduced to that number to standardize the effects of lactation across the groups. Originally it was intended to select the second generation breeding stock from these litters, but because of excessive mortality in the parents dosed with 300 mg/kg/day and in the pups at 100 mg/kg/day, the study had to be ended with the first generation. Consequently, all of the  $F_{1A}$  pups were discarded at weaning.

After a 10-day rest following the weaning of the first litters, the females were remated and the pregnancies "timed" as described previously. Again, day 0 and 20 body weights and feed consumption were recorded. The dams were sacrificed on day 20 of gestation by excessive ethyl ether, and the ovaries were removed for corpora lutea counts and the uteruses were removed and incised to remove the fetuses and determine the number of resorption sites.

The fetuses were blotted of amniotic fluid, inspected for gross external defects, weighed and their sex determined. One-half of each litter, randomly selected, was eviscerated, cleared in alcoholic KOH and stained with Alizarin Red S for skeletal examinations. The other one-half was fixed in Bouin's for approximately two weeks and then razor-blade sectioned and examined for soft-tissue defects.

All of the rats that were sacrificed were bled from the abdominal aorta and standard hemograms and clinical chemistries were performed (see Appendix 2 for complete details). All of the parent animals, excepting one male and one female

in Group 4, including those that died were necropsied and tissues taken for histopathology (see Appendix 2 for the list of tissues and the preparation methods). At the time of the necropsy, the heart, liver, kidneys, spleen, testes, and ovaries were weighed. The tissues were examined by a Certified Veterinary Pathologist.

The continuous data were analyzed by the Analysis of Variance. Provided the Bartlett's test for homogeneity of variance was not significant, the treated groups were compared to the control group by the least significant difference test. If Bartlett's test was significant, the comparison was made by Wilcoxon's rank sum test. The non-parametric data, such as the number of fetuses with defects, were analyzed by Chi-square methods. All of the data excepting the blood and pathology data, were analyzed using the Argus software package. The blood and pathology data were analyzed by R. D. Bruce using Program #B8944. Because of the deaths and early sacrifice in Group 4, the data for that group were not included in the statistical analyses.

All specimens, raw data, and a copy of this report will reside in the Miami Valley Laboratories' archives.

This study was conducted according to the protocol attached as Appendix 1, and the Standard Operating Procedures of the Test Facility in accordance with Good Laboratory Practices. There were no known deviations that would interfere with the integrity of the study.

#### Results and Discussion

Tables 1 and 2 show the animal numbers and the initial body weights of the animals beginning on study. Within two weeks for the males and about three weeks for the females, toxic symptoms began to show at the 300 mg/kg dose level. These included pale, unformed feces and pale skin and eyes. Later, dermatitis and other symptoms indicative of malnutrition appeared, and all of the symptoms grew more severe with time. The males were more affected than the females.

The animal's feed consumption in Group 4 was affected in the first week of the study and remained significantly lower throughout the study. See Tables 3 and 4 for the data from weeks 1, 5, 9 and 13. Body weight gains in Group 4 were significantly lower than controls beginning during the second week of the study, and the first animals died during the 5th week (one of each sex). By the 9th week six males had died, and by the 13th week one additional female, and 11 more males died.

The feed efficiency (body weight gain/feed eaten X 100) of these animals also was significantly lower than the controls, and the extreme changes in body weight, as well as the inanition, caused the intake of G0539.02 to be somewhat lower (~ 260-290 mg/kg) than the target level of 300 mg/kg.

The groups fed either 50 or 100 mg/kg of G0539.02 were not significantly different from controls in any of these growth characteristics, and there were no deaths. Their intake of G0539.02 was very close to the target levels of 50 and 100 mg/kg.

Since only two of the females fed G0539.02 at the 300 mg/kg dose level had died at the time of the first mating (14th week), attempts were made to mate them with stock males of the same strain which had not received any kind of treatment. These females were transferred to another animal room to prevent any

cross-contamination between the stock males and the animals comprising the main study, although this was unlikely. However, ten females died within the following three weeks, but more importantly only two showed evidence of mating and conceiving by the vaginal smear method. Therefore, the remaining 13 females were sacrificed on February 19, 1986 for blood studies and histopathology. One female was pregnant at sacrifice.

Table 5 shows the results of the  $F_{1A}$  pregnancies. The conception rate was significantly lower in the two treated groups than in the control group, but there were no significant differences in body weight gain or feed eaten during gestation. The actual intakes of G0539.02 during gestation were very close to the target levels, 52 and 101 mg/kg, respectively.

At birth, there were no significant differences in the number of pups born; neither were there significant differences in the number of pups at 4 and 8 days postnatally. However, by day 15 there were fewer pups in the group treated with 100 mg/kg of G0539.02, though not statistically significant, and by weaning (day 22) there were only 3.4 pups per litter remaining compared to 7.3 and 7.5 in the controls and 50 mg/kg group. This led to a highly significant decrease in the lactation index, which is simply the percentage of pups surviving from day 4 to day 22.

Although there were no significant differences in the number of pups alive on day 4, several had died in both treated groups shortly after birth, which resulted in a significantly lower viability index for both of these groups.

During the lactation phase of the  $F_{1A}$  pregnancy, again there were no significant differences in the dam's change in body weight, although there were some differences in the amount of feed eaten. The feed eaten by the dams fed 100 mg/kg of G0539.02 was significantly lower than controls both on a g/day and g/kg/day bases. On a g/kg/day basis, the feed eaten by the 50 mg/kg group was also significantly lower. Because of the tremendous increase in feed consumption during lactation, the dams took in much more than the target levels of G0539.02, 100 and 150 mg/kg, respectively.

The surviving pups in the 100 mg/kg group were significantly smaller than controls at all periods weighed after birth, and at weaning only, the pups in the 50 mg/kg group were also significantly smaller than the control pups.

The results of the  $F_{1B}$  (teratological phase) pregnancies are shown in Table 6. The overall conception rate was lower than normal in all three groups, with the rate in the two treated groups lower than in the controls although the difference was not statistically significant. No significant differences were seen in the weight gains of the dams during gestation, although both treated groups gained less than the controls. The dams fed 50 mg/kg G0539.02 ate significantly less feed on a g/kg/day basis, but this difference was marginal. The intake of G0539.02 was somewhat lower than the target levels during gestation, 45 and 91 mg/kg/day, respectively.

There were no significant differences in any of the reproductive characteristics during this pregnancy. The number of resorptions was slightly higher in the two treated groups, but this was due to a totally resorbed litter in each group, which can happen randomly in the rat, and so these are unlikely to be due to the treatment.

Table 7 shows the results of the fetal examinations. There were no frank structural defects in the soft-tissue, but 73 out of the 101 fetuses examined in the group treated with 100 mg/kg/day of G0539.02 had no blood in the heart and great vessels. This was highly significant. In addition, the variation, hydro-nephrosis was significantly increased in the group treated with 50 mg/kg/day of G0539.02. One fetus in this group also had misshaped cerebral hemispheres, but this could have been a fixation artifact.

There was a high incidence of delayed ossification of sternebrae in all three groups, and it was significantly increased in the two treated groups. However, there were no frank defects.

The pale skin and eyes in the groups of rats fed either 100 or 300 mg/kg/day of G0539.02 suggested anemia. This was confirmed at sacrifice by the blood data shown in Table 8. The rats of both sexes dosed with 100 mg/kg/day of G0539.02 had significantly lower RBC's and values for hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and in the males only, mean corpuscular hemoglobin concentration (MCHC), all indicating a hypochromic, microcytic anemia due to iron deficiency. In addition, the platelet counts were increased in both sexes, while the percentage of reticulocytes were increased in males, and decreased in the female. Additional evidence was also produced in the serum chemistries shown in Table 9, whereas serum iron was significantly depressed in both sexes dosed with 100 mg/kg, and in the females dosed with 50 mg/kg. Iron binding capacity was to be done, but was inadvertently omitted.

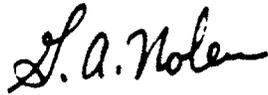
Several of the serum clinical chemistry values were significantly different in the 100 mg/kg group, as well as in the females in the 50 mg/kg group (Table 9). These will not be discussed individually, but are thought to be due to inanition secondary to the anemia (see Appendix 2 for further details and discussion).

Table 10 shows the organ weights and organ/body weight ratios of males and the pregnant females. There were no significant differences in any of the organ weights or ratios in the group treated with 50 mg/kg of G0539.02. However, the livers and spleens of the females dosed with 100 mg/kg/day were significantly lighter than controls, and the hearts of the males were significantly heavier. This resulted in significantly changed organ/body weight ratios. These effects on organs are probably the result of the anemia. Table 11 shows the data for the non-pregnant females from all four groups, but these data were not analyzed statistically because of the different times of sacrifice and the skewness in the number of subjects. However, it is easily seen by inspection, that the livers of the rats treated with 300 mg/kg/day of G0539.02 were extremely small, and their hearts and spleen much enlarged in attempting to cope with the severe anemia.

Microscopically, bone marrow hypercellularity, decreased hemosiderin in the spleen, hypercellular splenic red pulp, and inflammation of the intestinal tract were seen in Groups 3 and 4, with the symptoms being more severe in Group 4. No symptoms were seen in Group 2 rats. These are further signs of anemia (see Appendix 2 for further details).

In conclusion, G0539.02 was extremely toxic to rats at the 300 mg/kg/day dose level in the diet, producing a severe iron deficiency anemia. At the 100 mg/kg dose a less severe anemia was produced which was not lethal in adult animals, but was to young neonates. Although G0539.02 was not frankly teratogenic, there were secondary effects on embryos and fetuses as a result of the dam's anemic

state. Furthermore, although the effects were not pronounced, there were scattered effects at the 50 mg/kg/day dose, such as a lowered conception rate, and viability index, which would preclude a no-adverse-effect-level determination.



G. A. Nolen  
Study Director

GAN1063:cw

Table 1  
The Initial Body Weights of Male Rats in Study No. B85-0460 Administered G0539.02 in the Diet

Group No. G0539.02, mg/kg/day	1		2		3		4	
	0		50		100		300	
	<u>Animal No.</u>	<u>Wt., g</u>						
	2596	105	2597	115	2598	106	2601	112
	2603	110	2602	111	2604	114	2605	114
	2608	96	2602	107	2609	101	2610	103
	2611	105	2613	104	2612	96	2614	106
	2615	91	2617	108	2619	107	2616	102
	2620	112	2618	112	2621	97	2622	104
	2623	99	2632	104	2634	110	2633	106
	2625	101	2636	96	2640	103	2639	102
	2631	111	2638	104	2641	110	2644	113
	2635	109	2648	105	2645	116	2651	110
	2637	98	2650	104	2647	106	2658	116
	2646	109	2652	100	2649	92	2659	102
	2653	106	2657	112	2655	109	2664	113
	2654	111	2662	86	2656	105	2666	98
	2660	112	2674	87	2661	104	2673	106
	2675	100	2676	87	2665	113	2677	83
	2680	91	2678	86	2671	92	2684	92
	2681	88	2685	98	2672	97	2687	96
	2682	89	2689	99	2679	89	2698	89
	2690	108	2695	106	2683	96	2700	88
	2699	95	2696	93	2686	101	2704	97
	2701	100	2703	102	2694	87	2707	99
	2710	103	2706	89	2697	87	2709	93
	2711	84	2708	91	2705	105	2717	83
	2718	87	2714	96	2715	84	2719	88
<b>Means (± SD)</b>	100.8±8.7		100.1±8.9		101.1±9.0		100.6±9.8	

Table 2

The Initial Body Weights of Female Rats in Study No. B85-0460 Administered G0539.02 in the Diet

Group No. G0539.02, mg/kg/day	1		2		3		4	
	0		50		100		300	
	Animal No.	Wt., g						
	2722	101	2724	96	2725	85	2728	96
	2723	93	2730	97	2726	99	2731	81
	2727	94	2732	89	2733	90	2735	89
	2729	95	2734	82	2738	83	2736	86
	2739	81	2737	94	2741	87	2745	90
	2743	88	2740	88	2747	100	2748	98
	2744	87	2742	97	2751	88	2756	86
	2746	94	2750	104	2754	90	2758	88
	2755	92	2752	86	2762	93	2761	98
	2759	90	2753	91	2768	89	2766	103
	2764	106	2765	99	2771	99	2772	90
	2769	95	2767	94	2779	85	2774	91
	2770	85	2773	89	2780	89	2777	100
	2775	87	2778	93	2783	91	2785	92
	2776	86	2782	86	2784	96	2790	103
	2781	95	2788	96	2800	100	2792	98
	2787	90	2789	105	2801	96	2793	99
	2791	103	2794	96	2806	93	2811	101
	2795	100	2802	85	2807	99	2820	82
	2804	98	2810	105	2813	103	2823	92
	2805	96	2812	96	2814	98	2824	90
	2815	97	2821	84	2825	97	2833	85
	2817	86	2822	105	2829	83	2837	97
	2835	84	2826	84	2838	103	2841	87
	2839	97	2842	87	2845	84	2843	90
Means (± SD)	92.8±6.3		93.1±7.1		92.8±6.4		92.5±6.4	

Table 3  
Body Weight Gains, Feed Consumption and Feed Efficiency of Male Rats  
Fed G0539.02 During the 13-Week Premating Period

Group No.	(means±SD)			
	1	2	3	4
G0539.02, mg/kg/day	0	50	100	300
<b>Week 1</b>				
Gain, g	59.0±5.3	60.1±5.0	60.6±5.0	57.3±5.8
Feed, g/day	19.5±1.5	19.7±1.2	19.5±1.2	18.6±1.6* <sup>3</sup>
Feed, g/kg/day	149.8±6.4	151.9±7.2	148.6±6.5	144.3±6.3** <sup>4</sup>
Feed Efficiency, % <sup>1</sup>	43.3±3.0	43.5±3.0	44.4±3.1	43.9±2.3
Intake G0539.02, mg/kg/day	0	53.7±2.6	105.5±4.6	305.8±13.2
<b>Week 5<sup>2</sup></b>				
Gain, g	284.8±21.0	289.9±30.3	277.7±21.2	130.5±35.5**
Feed, g/day	25.6±1.8	25.5±1.9	25.2±1.4	18.9±2.3**
Feed, g/kg/day	102.8±3.4	101.7±4.3	102.2±3.4	104.4±9.7
Feed Efficiency, % <sup>1</sup>	31.9±1.9	32.5±2.0	31.6±1.6	19.5±4.1**
Intake G0539.02, mg/kg/day	0	48.8±2.5	100.0±4.6	266.3±35.7
<b>Week 9<sup>2</sup></b>				
Gain, g	392.3±38.5	391.9±37.7	381.2±29.7	132.6±33.1**
Feed, g/day	26.9±1.7	27.1±2.0	26.9±2.0	18.2±1.7**
Feed, g/kg/day	82.0±2.2	81.8±3.4	82.3±3.5	88.9±7.3**
Feed Efficiency, % <sup>1</sup>	22.9±1.5	22.9±1.4	22.8±1.2	11.5±2.3**
Intake G0539.02 mg/kg/day	0	51.0±5.1	102.7±11.1	271.1±43.3
<b>Week 13<sup>2</sup></b>				
Gain, g	439.0±46.0	447.8±44.5	442.8±48.7	143.0±33.2**
Feed, g/day	27.4±1.5	27.7±1.8	27.3±1.8	17.5±0.7**
Feed, g/kg/day	71.4±2.5	71.4±3.4	71.3±2.8	79.4±7.7**
Feed Efficiency, % <sup>1</sup>	17.8±1.5	17.8±1.2	18.0±1.8	8.9±2.1**
Intake G0539.02, mg/kg/day	0	50.5±6.2	103.5±8.4	288.9±48.1
<b>No. Alive</b>				
Week 1	25	25	25	25
Week 5	25	25	25	24
Week 9	25	25	25	19
Week 13	25	25	25	8

<sup>1</sup>Feed efficiency = body weight gain/feed eaten X 100.

All data are cumulative up to the time indicated.

<sup>3</sup>\* = significantly different from controls; p < .05.

<sup>4</sup>\*\* = significantly different from controls; p < .01.

Table 4  
Body Weight Gains, Feed Consumption and Feed Efficiency of Female Rats  
Fed G0539.02 During the 13-Week Premating Period

Group No.	(means±SD)			
	1	2	3	4
G0539.02, mg/kg/day	0	50	100	300
<b>Week 1</b>				
Gain, g	47.4±4.0	47.4±6.4	45.9±6.6	46.3±6.4
Feed, g/day	17.8±1.0	17.4±1.6	17.4±1.6	16.9±1.3 <sup>3</sup>
Feed, g/kg/day	153.1±7.6	148.6±8.0	150.4±8.6	146.1±8.0 <sup>4</sup>
Feed Efficiency, % <sup>1</sup>	38.3±2.6	38.8±3.5	37.1±3.5	39.0±3.8
Intake G0539.02, mg/kg/day	0	46.5±2.5	93.9±5.5	277.4±15.1
<b>Week 5<sup>2</sup></b>				
Gain, g	146.7±14.3	156.4±24.1	151.±21.5	91.6±24.7**
Feed, g/day	19.4±1.3	19.7±1.8	19.5±2.1	15.6±1.6**
Feed, g/kg/day	109.7±4.0	108.5±4.2	109.1±5.0	103.2±6.3**
Feed Efficiency, % <sup>1</sup>	21.4±1.5	22.6±1.9*	22.0±1.6	16.4±3.0**
Intake G0539.02, mg/kg/day	0	51.7±3.4	105.0±9.8	305.3±42.8
<b>Week 9<sup>2</sup></b>				
Gain, g	190.7±16.2	199.4±27.4	192.7±26.1	151.3±21.8**
Feed, g/day	20.0±1.2	20.3±1.7	20.3±2.3	17.5±1.6**
Feed, g/kg/day	94.4±3.0	93.1±3.3	95.2±5.1	96.7±5.0
Feed Efficiency, % <sup>1</sup>	15.1±0.9	15.5±1.3	15.0±1.2	13.7±1.4**
Intake G0539.02 mg/kg/day	0	50.8±4.0	101.3±22.2	310.3±30.3
<b>Week 13<sup>2</sup></b>				
Gain, g	221.0±20.6	232.8±33.0	227.4±35.4	161.6±31.7**
Feed, g/day	20.4±1.2	20.7±1.7	20.8±2.3	18.1±1.8**
Feed, g/kg/day	85.7±2.8	84.2±3.6	86.4±4.0	89.4±5.5**
Feed Efficiency, % <sup>1</sup>	12.0±0.8	12.3±1.0	12.0±0.9	9.8±1.3**
Intake G0539.02, mg/kg/day	0	51.9±4.5	104.7±5.8	295.5±29.3
<b>No. Alive</b>				
Week 1	25	25	25	25
Week 5	25	25	25	24
Week 9	25	25	25	24
Week 13	25	25	25	23

<sup>1</sup>Feed efficiency = body weight gain/feed eaten X 100.

<sup>2</sup>All data are cumulative up to the time indicated.

<sup>3</sup>\* = significantly different from controls; p < .05.

<sup>4</sup>\*\* = significantly different from controls; p < .01.

Table 5

## The Reproductive and Postnatal Performance During the

F<sub>1A</sub> Pregnancies of Rats Fed G0539.02 (means±SD)<sup>1</sup>

Group No.	1	2	3
G0539.02, mg/kg/day	0	50	100
No. Alive	25	25	25
No. Pregnant (%)	23 (92.0)	14 (56.0)	19 (76.0)
Body Weight, Day 0, g	307±21	315±28	312±36
Body Weight, Day 20, g	425±40	410±54	436±64
Weight Gain, Days 0-20, g	118±34	95±52	124±54
Feed Eaten, Days 0-20, g/day	24.9±2.6	24.6±2.6	25.2±2.6
Feed Eaten, Days 0-20, g/kg/day	67.1±6.1	65.7±6.4	65.8±5.0
Intake G0539.02, Days 0-20, mg/kg/day	0	52.4±6.9	100.8±15.4
No. Litters Born Alive	23	14	18
Mean Pups/Litter	12.8±3.7	13.6±2.7	13.3±3.8
Dam Body Weight, Day 1, g	354±26	355±34	367±42
Dam Body Weight, Day 22, g	340±37	362±35	353±48
Dam Weight Gain, Days 1-22, g	-14±24	8±28	-13±23
Feed Eaten, Days 1-22, g/day	50.0±7.6	45.4±4.9	36.8±8.6* <sup>5</sup>
Feed Eaten, Days 1-22, g/kg/day	145.0±25.1	127.2±15.0*	104.6±24.7** <sup>6</sup>
Intake G0539.02, Days 1-22, mg/kg/day	0	99.9±12.3	149.6±39.2
No. Pups/Litter Alive			
Day 1 <sup>2</sup>	12.4±3.8	13.4±2.7	12.3±3.9
Day 4 <sup>2</sup>	12.3±3.7	12.5±3.1	11.5±3.7
Day 8	7.4±1.2	7.9±0.3	7.4±1.5
Day 15	7.3±1.3	7.6±0.9	6.2±2.5
Day 22	7.3±1.4	7.5±0.9	3.4±3.5**
Viability Index, % <sup>3</sup>	99.0	93.6**	93.2**
Lactation Index, % <sup>4</sup>	96.0	94.6	44.5**
Pup Weights, g			
Day 1	6.1±0.8	6.2±0.6	5.8±0.5
Day 4	8.8±1.3	8.3±1.2	7.4±1.6**
Day 8	16.4±2.9	14.7±2.6	13.1±3.1**
Day 15	33.2±5.2	29.4±3.1*	21.8±6.4**
Day 22	51.9±8.9	47.2±4.7*	33.9±9.5**

<sup>1</sup>Group 4 dosed with 300 mg/kg/day aborted because of deaths and low conception rate.

<sup>2</sup>Litters were standardized to 8 pups per litter where there were more than 8 pups in a litter. Weights shown here are pre-culling.

<sup>3</sup>Viability index = No. alive at 4 days/No. born alive X 100.

<sup>4</sup>Lactation index - No. alive at weaning (day 22)/No. retained at day 4 X 100.

<sup>5</sup>\* = significantly different from controls;  $p \leq .05$ .

<sup>6</sup>\*\* = significantly different from controls;  $p \leq .01$ .

Table 6

The Reproductive and Teratological Performance During the

F<sub>1B</sub> Pregnancies of Rats Fed G0539.02 (means±SD)

Group No.	<u>1</u>	<u>2</u>	<u>3</u>
	<u>0</u>	<u>50</u>	<u>100</u>
G0539.02, mg/kg/day			
No. Alive/Pregnant (%)	25/19 (76.0)	25/17 (68.0)	25/16 (64.0)
Body Weight, Day 0, g	344±24	361±42	367±45
Body Weight, Day 20, g	488±46	502±50	497±67
Weight Gain, Days 0-20, g	145±27	135±29	128±33
Feed Eaten, Days 0-20, g/day	27.9±2.5	27.5±2.0	28.0±2.9
Feed Eaten, Days 0-20, g/kg/day	69.7±2.9	66.4±5.5* <sup>1</sup>	67.6±3.8
Intake G0539.02, Days 0-20, mg/kg/day	0	44.6±3.2	91.4±7.5
No. Corpora Lutea	17.3±3.4	18.0±3.5	18.0±3.2
No. Implants	15.6±3.7	16.3±4.4	15.8±4.3
No. Resorptions	1.6±1.7	2.1±1.5	3.0±4.2
No. Live Fetuses	14.0±4.7	14.2±4.9	12.8±5.5
No. Total Resorptions	0	1	1
Fetal Weights, g			
Male	3.3±0.4	3.4±0.3	3.2±0.2
Female	3.1±0.4	3.2±0.2	3.1±0.5
Total	3.2±0.4	3.3±0.2	3.2±0.4

<sup>1</sup>\* = significantly different from controls; p ≤ .05.

Table 7

The Effects of G0539.02 on the Morphological Development  
of Rat Fetuses (F<sub>1B</sub> Litters)

Group No.	<u>1</u>	<u>2</u>	<u>3</u>
G0539.02, mg/kg/day	<u>0</u>	<u>50</u>	<u>100</u>

Soft-Tissue Examination

No. Fetuses/Litters	136/19	126/16	101/15
No. Fetuses with Defects	0	1	73**
No. Fetuses with:			
No Blood in Heart <sup>1</sup>	0	0	73
Misshaped Cerebral Hemispheres	0	1	0
No. Fetuses with Variations	1	8* <sup>2</sup>	2
No. Fetuses with:			
Hydronephrosis	0	7*	2

Skeletal Examination

No. Fetuses/Litters	130/18	116/16	103/15
No. Fetuses with Defects	0	0	0
No. Fetuses with Variations	95	101** <sup>3</sup>	94**
No. Fetuses with:			
Unossified Sternebrae <sup>4</sup>	94	98*	94**
Rib Variations <sup>5</sup>	3	4	7

<sup>1</sup>Not a true morphological defect in the usual sense.

<sup>2</sup>\* = significantly different from controls;  $p \leq .05$  by Fishers Exact Test.

<sup>3</sup>\*\* = significantly different from controls;  $p \leq .01$  by Fishers Exact Test.

<sup>4</sup>Includes all sternebrae, but primarily consisted of unossified 5 and 6 sternebrae.

<sup>5</sup>Includes supernumerary and wavy ribs.

Table 8

The Effects of G0539.02 Administered in the Diet on the  
Hematology of Male and Pregnant Female Rats (means±SE)

Group No. <sup>1</sup> G0539.02, mg/kg/day	1		2		3	
	0		50		100	
	Male	Female	Male	Female	Male	Female
RBC (millions)	8.92±0.09	6.01±0.12	9.05±0.12	6.05±0.15	7.76±0.35 <sup>2</sup>	6.90±0.20 <sup>3</sup>
HGB (g/dl)	15.8±0.2	11.6±0.2	15.8±0.2	11.6±0.3	9.4±0.6 <sup>3</sup>	9.5±0.5 <sup>3</sup>
Hematocrit (%)	46.1±0.4	35.7±0.6	45.9±0.6	34.8±0.8	25.0±1.9 <sup>3</sup>	28.7±1.4 <sup>3</sup>
MCV (FL)	51.8±0.7	59.3±0.6	50.8±0.7	57.6±0.7	31.4±1.5 <sup>3</sup>	41.4±1.4 <sup>3</sup>
MCH (PG)	17.8±0.2	19.3±0.2	17.4±0.2	19.2±0.2	12.0±0.5 <sup>3</sup>	13.8±0.5 <sup>3</sup>
MCHC (%)	34.4±0.4	32.7±0.3	34.7±0.5	33.2±0.5	38.6±0.7 <sup>3</sup>	33.2±0.3
WBC (thousands)	8.97±0.5	6.55±0.3	8.63±0.4	6.63±0.4	8.58±0.9	6.34±0.4
Platelet (thousands)	1003±24	986±28	1028±31	927±38	2124±249 <sup>3</sup>	1073±46
reticulocyte (%)	2.3±0.1	3.1±0.1	2.4±0.2	2.3±0.1	6.4±0.7 <sup>3</sup>	1.7±0.1 <sup>3</sup>

<sup>1</sup>Only one male and 13 females were sacrificed in Group 4; their data not shown.

<sup>2</sup>Significantly different from control;  $p \leq .05$ .

<sup>3</sup>Significantly different from control;  $p \leq .001$ .

Table 9

The Clinical Serum Chemistries of Male and Pregnant Female Rats  
Administered G0539.02 in the Diet (means±SE)

Group No. <sup>1</sup> G0539.02, mg/kg/day	1		2		3	
	0		50		100	
	Male	Female	Male	Female	Male	Female
Glucose (mg/dl)	232.2±11.8	107.8±6.0	221.7±15.4	107.6±3.9	236.1±16.3	118.2±9.8
BUN (mg/dl)	14.6±0.6	17.2±0.8	15.4±0.5	14.7±0.9* <sup>2</sup>	15.1±0.5	15.9±0.7
Creatinine (mg/dl)	0.7±0.01	0.6±0.02	0.7±0.01	0.6±0.01	0.7±0.01	0.6±0.02
Total Protein (g/dl)	6.6±0.1	6.0±0.1	6.7±0.1	5.8±0.1	6.2±0.1*** <sup>3</sup>	6.0±0.2
Albumin (g/dl)	4.1±0.04	3.9±0.08	4.2±0.05	3.9±0.09	4.1±0.03	4.0±0.1
Globulin (g/dl)	2.50±0.05	2.03±0.06	2.49±0.05	1.95±0.05	2.13±0.05***	2.04±0.09
A/G Ratio	1.68±0.04	1.95±0.04	1.69±0.04	1.99±0.04	1.94±0.05***	1.97±0.07
Alkaline Phosphatase (IU/l)	117.1±10.6	93.3±9.3	104.9±9.7	69.2±5.7*	107.7±7.5	86.7±10.2
Aspartate Amino Transferase (IU/l)	155.3±42.9	162.9±15.9	162.6±22.3	147.9±17.4	141.0±11.9	135.7±10.5
Alanine Amino Transferase (IU/l)	93.0±35.8	61.5±6.2	67.1±9.9	45.2±3.1*	53.0±7.3	41.1±3.1** <sup>4</sup>
Cholesterol (mg/dl)	93.7±5.1	95.2±3.3	86.5±5.2	89.4±4.4	61.9±2.6***	73.8±3.6***
Triglycerides (mg/dl)	89.0±11.2	518±48	98.8±11.5	571±71	60.1±5.3	325±45**
Total Bilirubin (mg/dl)	0.25±0.02	0.13±0.02	0.23±0.02	0.11±0.01	0.23±0.02	0.11±0.02
Sodium (meq/l)	146±0.3	141±0.5	145±0.3	142±0.6	145±0.3	141±0.5
Potassium (meq/l)	6.88±0.3	6.43±0.2	7.32±0.3	5.27±0.2***	6.76±0.3	5.62±0.3*
Calcium (mg/dl)	11.08±0.14	9.99±0.27	11.03±0.18	9.65±0.20	10.86±0.17	10.06±0.18
Phosphorus (mg/dl)	6.47±0.18	4.55±0.29	6.70±0.23	3.49±0.26*	7.17±0.25*	4.51±0.28
Iron (mg/dl)	166.6±9.6	120.5±17.2	164.8±10.8	68.2±17.5**	61.8±9.8***	37.7±27.3***
Vitamin B <sub>12</sub> (pg/ml)	84±43	673±79	913±90	521±79	855±59	527±31
Folic Acid (ng/ml)	79.4±4.7	66.3±8.7	81.2±4.2	55.3±9.4	89.4±4.9	48.0±5.0

<sup>1</sup>Only one male and 13 females were sacrificed in Group 4; their data not shown.

<sup>2</sup>\* = significantly different from control;  $p \leq .05$ .

<sup>3</sup>\*\*\* = significantly different from control;  $p \leq .001$ .

<sup>4</sup>\*\* = significantly different from controls;  $p \leq .01$ .

Table 10

The Organ Weights and Organ/Body Weight Ratios of Male and Pregnant  
Female Rats Administered G0539.02 in the Diet (means±SE)

Group No. <sup>1</sup> G0539.02, mg/kg/day	1		2		3	
	0		50		100	
	Male	Female	Male	Female	Male	Female
Final Body Weight, g (N)	609±11 (25)	481±11 (19)	615±15 (25)	493±12 (17)	592±11 (25)	482±18 (16)
Liver Weight, g	19.3±0.7	19.3±0.6	20.5±0.7	18.0±0.5	18.2±0.7	16.5±0.7** <sup>1</sup>
Kidney Weight, g	3.84±0.07	2.40±0.06	3.91±0.08	2.38±0.06	3.77±0.07	2.42±0.08
Spleen Weight, g	0.92±0.03	0.78±0.05	0.84±0.03	0.79±0.05	1.08±0.15	0.65±0.03* <sup>2</sup>
Heart Weight, g	1.53±0.03	1.17±0.03	1.63±0.06	1.18±0.05	1.67±0.05* <sup>2</sup>	1.23±0.06
Testes Weight, g	3.64±0.11	—	3.40±0.18	—	3.78±0.08	—
Ovaries Weight, g	—	0.162±0.012	—	0.154±0.010	—	0.161±0.011
Liver/Body Weight Ratio, %	3.17±0.09	4.01±0.07	3.35±0.11	3.67±0.07*** <sup>3</sup>	3.06±0.09	3.41±0.06*** <sup>3</sup>
Kidney/Body Weight Ratio, %	0.63±0.01	0.50±0.02	0.64±0.02	0.48±0.01	0.64±0.01	0.51±0.01
Spleen/Body Weight Ratio, %	0.151±0.004	0.162±0.009	0.138±0.004* <sup>1</sup>	0.161±0.009	0.185±0.025	0.134±0.004*** <sup>3</sup>
Heart/Body Weight Ratio, %	0.252±0.006	0.245±0.005	0.267±0.010	0.240±0.010	0.284±0.009* <sup>2</sup>	0.258±0.014* <sup>2</sup>
Testes/Body Weight Ratio, %	0.600±0.019	—	0.563±0.033	—	0.642±0.014	—
Ovaries/Body Weight Ratio, %	—	0.033±0.002	—	0.031±0.002	—	0.034±0.002

<sup>1</sup>\* = significantly different from control; p < .01.

<sup>2</sup>\*\* = significantly different from control; p < .05.

<sup>3</sup>\*\*\* = significantly different from controls; p < .001.

Table 11

The Organ Weights and Organ/Body Weight Ratios of Non-Pregnant  
Female Rats Administered G0539.02 in the Diet (means $\pm$ SE)

Group	<u>1</u>	<u>2</u>	<u>3</u>	<u>4<sup>1</sup></u>
G0539.02, mg/kg/day	<u>0</u>	<u>50</u>	<u>100</u>	<u>300</u>
Final Body Weight, g (N)	374 $\pm$ 11 (6)	399 $\pm$ 19 (8)	371 $\pm$ 22 (8)	230 $\pm$ 10 (12)
Liver Weight, g	12.9 $\pm$ 0.4	12.9 $\pm$ 0.5	12.2 $\pm$ 1.0	6.9 $\pm$ 0.3
Kidney Weight, g	2.20 $\pm$ 0.14	2.28 $\pm$ 0.12	2.37 $\pm$ 0.12	2.40 $\pm$ 0.07
Spleen Weight, g	0.57 $\pm$ 0.05	0.52 $\pm$ 0.04	0.53 $\pm$ 0.05	1.02 $\pm$ 0.18
Heart Weight, g	1.16 $\pm$ 0.05	1.17 $\pm$ 0.03	1.18 $\pm$ 0.09	2.25 $\pm$ 0.08
Ovaries Weight, g	0.104 $\pm$ 0.01	0.119 $\pm$ 0.01	0.089 $\pm$ 0.01	0.067 $\pm$ 0.01
Liver/Body Weight Ratio, %	3.47 $\pm$ 0.09	3.25 $\pm$ 0.12	3.27 $\pm$ 0.10	3.03 $\pm$ 0.10
Kidney/Body Weight Ratio, %	0.59 $\pm$ 0.03	0.57 $\pm$ 0.02	0.64 $\pm$ 0.02	1.06 $\pm$ 0.04
Spleen/Body Weight Ratio, %	0.151 $\pm$ 0.012	0.130 $\pm$ 0.010	0.143 $\pm$ 0.011	0.443 $\pm$ 0.080
Heart/Body Weight Ratio, %	0.310 $\pm$ 0.012	0.297 $\pm$ 0.012	0.320 $\pm$ 0.018	0.996 $\pm$ 0.043
Ovaries/Body Weight Ratio, %	0.028 $\pm$ 0.003	0.030 $\pm$ 0.002	0.024 $\pm$ 0.002	0.031 $\pm$ 0.005

<sup>1</sup>These animals were sacrificed earlier than the other three groups.

Appendix 1 - Protocol

I N T E R D E P A R T M E N T A L   C O R R E S P O N D E N C E

FROM: Operations Section

DATE: September 9, 1985

TO: G. A. Nolen

R/L:

SUBJECT: STUDY PLACEMENT AUTHORIZATION

This is to authorize you to carry out the following study according to the attached protocol.

Notice: This study is expected to be submitted to the following regulatory agency: FDA, EEC Agencies & Member Countries. The stipulations of the protocol are to be implemented in complete conformance with Good Laboratory Practices Regulations (21 CFR, Part 58) for nonclinical laboratory studies.

Test: Two-Generation Reproduction and Teratology  
Protocol No.: Special Protocol Dated 8/8/85  
Test Substance No.: G0539.02  
Physical Form: Powder  
Doc. Req. No: BYCR 0428

Matters involving the scientific aspects of the work can be handled directly with the Divisional Toxicologist. All unused samples are to be returned to the Divisional Toxicologist at the following address:

J. E. Weaver  
SWTC HB-2D37  
8-55-2430

Complete both copies of the attached protocol by adding your study number and proposed start and completion dates. The Study Director should define the start and completion dates on the protocol and sign and date both copies. Retain one and return one copy to the BTP's Quality Assurance Unit.



H. A. Derner  
Human & Environmental Safety Division

Attachments

cc: Quality Assurance Unit  
J. E. Weaver

SUBJECT

NONCLINICAL STUDY - REGULATORY  
STATUS

ATTENTION

Notifications pertaining to:

IND #  
TSIN

BYCRO428

GU539.02

1. Studies requested on the above document:

- are expected to be submitted to the following regulatory agencies a  
a GLP regulated study: FDA, EEC Agencies & Member Countries

- are expected to be submitted to the following regulatory agencies  
but is not a GLP regulated study: \_\_\_\_\_

Metabolism,  Pharmacological Screen,  Other: \_\_\_\_\_

- are not expected to be submitted to a regulatory agency. (Boxes  
#3 and #4 below need not be checked).

2.  - The test substance has been characterized and results are shown  
on the test substance characterization report which accompanies  
the IND.

3.  - The method of synthesis fabrication or derivation of the test  
related substances has been documented. (Required for regulated  
studies).

4.  - Stability testing has been done or will be done on the test  
substance. (Required for regulated studies).

Sponsor's Divisional Toxicologist: James E. Weaver

Date: 8/8/85

By: WELQAUZ



**TEST SUBSTANCE CHARACTERIZATION REPORT  
(TSCR)**

For Tox Office  
Use Only:  
DRD 8BYR0428  
TSIN 86053302

**Characterization, Microbial and Properties Information:**

	<u>Date Submitted</u>	<u>Submitter Code (if exists) or Lab Notebook #</u>	<u>Component or Property</u>	<u>(✓)</u>	<u>Measured Value</u>	<u>Limits</u>	<u>Testing Lab or Data Source</u>
1	7/29/85	JDM-121	NCT	✓	Pass	Must Pass	Microbial
2	7/10/85	85149005	Assay		99.5	98-102	1B21
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							

**12. Approvals:**

The test substance as made and characterized is a representative example of the intended formulation. Making records for plant-made product should be obtained and evaluated by Products Research.

a. Process Development: Jon (Signature) JOW MELANON (Name) 8/6/85 (Date)

b. Products Research: [Signature] (Signature) J.S. DOLANSON (Name) 8/6/85 (Date)

       finished product samples will be retained by Quality Assurance.  
# samples

c. GMP-Quality Assur.: \_\_\_\_\_ (Signature) \_\_\_\_\_ (Name) \_\_\_\_\_ (Date)

13. The characterization tests requested are appropriate and the test substance is acceptable for:  acute animal test;  subchronic animal test;  chronic animal test;  human safety test;  in vitro test;  environmental safety test.

James E. Weaver (Toxicologist's Signature) \_\_\_\_\_ (Name) 8-6-85 (Date)

TSCR Distribution: Original - Tox Office; Copies - Toxicologist, GMP/QA, Products REsearch and Process Dev.

Protocol

Two-Generation Reproduction and Teratology

Issue Date 10/11/85

Divisional Request Document (DRD) Number BYCRO428

Test Substance Identification Number (TSIN) G0539.02

Study Number B85 0460

Sponsor:

The Procter & Gamble Company  
Cincinnati, Ohio

Testing Facility:

The Procter & Gamble Company  
Miami Valley Laboratories  
Biological Test Facilities  
P.O. Box 39175  
Cincinnati, OH 45247

Study Director:

G. A. Nolen

Divisional Toxicologist:

J. E. Weaver

Purpose:

To assess the reproductive and developmental toxicity of a substance administered continuously in the diet to two generations of rats.

Justification for Selection of Test System:

The rat has been used historically for such studies because of the short generation time and large litter sizes.

Route of Administration of Test Substance and Reason for Choice:

The test substance will be administered in the diet for practical purposes, and to maximize the systemic exposure.

Diet and/or Water Analysis required:

No diet or water analysis for contaminants will be required. Diet analysis for the test substance will be described later.

Records to be Maintained:

All records that would be required to reconstruct the study and to demonstrate adherence to the protocol.

**Test Substance:**

<u>TSIN:</u>	<u>Description</u>		<u>Expiration Date</u>
	<u>Color</u>	<u>Physical Form</u>	
G0539.02	White	Powder	7/29/85

**Storage Conditions: (Check One)**

Room temperature     Refrigerator     Freezer     Other

**Hazards: Check One)**

None known. Take ordinary precautions in handling.

As Follows: May be eye and skin irritant. For eye contact, flush promptly and thoroughly with water. For skin contact, flush with water.

**Special Instructions: (Check One)**

None

As Follows: See diet preparation

**Animals:** Charles River, Sprague-Dawley CD. Weanling (21-23 days of age), litter-mates identified. Each group will consist of 25 females and 25 males. These animals will be designated F<sub>0</sub> (First Parental Generation). Order 20% more animals than needed. Follow SOP G3 for receipt of animals.

**Acclimation/Quarantine:** Animals will be placed in an animal room housing only this study and they will be acclimated for a minimum of 7 days before the start of the study.

**Animal Care:** Follow the approved standard operating procedures of the test facility. Special instructions for reproducing animals will be given in later sections.

**Environmental Conditions:** Follow standard operating procedures of the test facility, with special attention to the lighting cycle.

**Animal Identification:** All animals will be ear-tagged with Monel tags bearing unique numbers. Color-coded cage cards identifying the study animal, and TSIN numbers and the concentration of the test substance in the diet will be used.

**Caging:**

During the growth phases of the study, and between matings, all animals will be housed in individual stainless steel cages with raised wire floors. During the mating, gestation, and lactation phases, the animals will be transferred to larger breeding cages of the same type. See the section on lactation for special instructions for nesting.

**Group Assignment:**

After the acclimation period, the rats will be weighed and distributed into four (4) groups according to SOP G4 or a computerized equivalent, each containing 25 females and 25 males. The excess animals will then be discarded.

**Diet Preparation:**

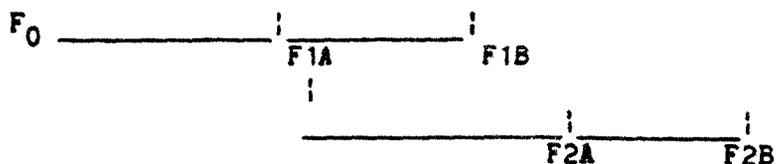
The basal diet will be ground certified Purina Laboratory Chow 5002, and will be obtained at about two-month intervals. The test diets will be prepared on an as-needed basis, ranging from semi-weekly to biweekly as the study progresses in each generation. The test substance will be mixed into the basal diet at levels to deliver doses of 0, 50, 100, or 300 mg/kg/day and separate diets will be made for each sex. The concentration of the test substance in the diet will be determined by the average feed consumption during the preceding week and the last weekly body weight. Prior to mixing the test substance in the basal diet, it will be sifted through -20 mesh screen. All diet preparation data will be recorded including the lot numbers of the Chow on form NF-300. All diets will be stored in air-tight plastic containers and be kept in a refrigerator until fed. Each diet container will be identified with a label containing study no., group no., diet no., date made and study director's name, etc. and a tape of the appropriate color. The animal feed jars will be filled weekly and at any other times, as needed, to insure ad libitum consumption. The feed jars will be cleaned weekly, discarding any diet remaining at the end of each week.

**Diet Analysis:**

Prior to the beginning of the study, a batch of each diet will be made with the appropriate levels of test substance to deliver the targeted dosages in young rats. Three (3), 100 g samples will be taken from the top, middle, and bottom of the mixing pot for homogeneity and stability tests by the sponsor (operating division). At each subsequent mixing, a single 100 g sample will be taken at random from each diet to be analyzed for test substance to determine that the doses are within  $\pm 10\%$  of the targeted levels.

General Design:

The design of the study is a two-generation reproduction and teratogenic study. Weanling rats ( $F_0$ ) will be obtained and started on the study at about 28-30 days of age. After a 91-day growth-to-sexual maturity period, the animals will be mated on a one-to-one basis. This mating will produce the  $F_{1A}$  animals during the reproduction phase. Some of these animals will be retained as the second generation parent animals. The  $F_0$  animals will be mated again, and will be sacrificed on day 20 of gestation for the teratological evaluation of the fetuses ( $F_{1b}$ ). Twenty-five animals of each sex per group will be selected to continue the study three days after being weaned. These rats will be treated during the growth, reproduction, and teratology periods as described for the first generation, except that the  $F_{2A}$  rats will be sacrificed at weaning, unless the results dictate otherwise. The following chart illustrates the above.



Animal Growth:

The rats will be weighed weekly throughout the study, as well as at other times specified later. The feed consumption records will also be calculated on a weekly basis, and from these data a feed efficiency (weight gain  $\div$  feed eaten  $\times 100$ ) calculated. Both weekly and cumulative records will be maintained for these three parameters. A viability check of all animals will be performed daily, noting any pathological conditions (SOP, G5). This will be documented in the notebook.

**Reproduction:**

After the completion of each growth phase, the rats will be transferred into mating cages, and vaginal smearing will commence with the pregnancies being determined as outlined in SOP RT-4. A vaginal smear showing sperm will indicate day 0 of pregnancy. During mating, the feed consumed by the mating pair will be measured, and the average of the two will be recorded as that pair's individual feed consumption. Additional weighings of the feed cups will be done on days 0 and 20 of pregnancy, so that the consumption during gestation can be calculated. The dam will be weighed on days 0 and 20 of gestation also. These and the subsequent reproduction-lactation data will be recorded on form RTF-100. About day 16 or 17 of gestation, the dam will be furnished a cage liner and shredded paper to make a nest. From this time until the birth of the litters, the dams should be inspected at least two times per day for births, abortions, or pathology. The date of birth, and the numbers born, including dead or abnormal pups, will be recorded, as well as the weight of the live litters and the dam. The day of birth will be postnatal day 1. On day 4, the pups will be weighed individually, their sex will be determined, and any litter containing more than eight (8) pups will be reduced to that number with an equal sex distribution. At that time they will be assigned eartag numbers, with a number which begins with the letter A. These tags will be affixed later. The pups will be temporarily identified by tail tattoo during the lactation period. The pups will be weighed again on days 8, 15, and 22 (weaning). The dam will also be weighed on day 22. The feed cups will be weighed on days 1 and 22 in addition to the other weighings to calculate a feed consumption during lactation. Viability (% of animals born alive surviving to day 4) and lactation (% alive on day 4 surviving to weaning) indices will be calculated for each dam, as well as gestation length, and weight changes during gestation and lactation.

After the F1A pups are weaned, they will be ear-tagged with the appropriate number set aside for them at birth, and transferred to a cage as a litter, and remain there until day 29. Then they will be weighed, and 25 rats of each sex will be randomly selected from each group to continue the study into the second generation. See SOP, RT-3. The remaining pups will be discarded. The foregoing procedures will be repeated in the second generation, except that the F2A pups will be sacrificed at weaning, unless circumstances dictate other actions, or a continuation of the study.

During the gestation and lactation periods the cages and racks will not be cleaned biweekly, as stated in the facility SOP's, to minimize the disturbance to the animals.

**Teratology:**

The dams will be rested for 10 days following the weaning of their first-born litters, and then will be remated, with the pregnancies, determined as outlined before, to produce the F1B litters, in the first generation and the F2B litters in the second generation. Again, the dams will be weighed and additional weighings of feed cups will be done on days 0 and 20 of gestation.

The dams should be inspected twice daily for abortions or other problems, but no nesting materials will be furnished. On day 20 of gestation, the dams will be sacrificed by excessive ethyl ether, and the teratological parameters will be assessed as outlined in SOP, RT-6, recording the data on form RTF-200. One-half of each litter, randomly selected, will be cleared and stained with alizarin Red S for skeletal examinations (SOP, RT-7), and the other half will be fixed in Bouins' solution and examined for soft-tissue defects after razor-blade sectioning (SOP, RT-8).

**Necropsy:**

As the dams are sacrificed during the teratology phases, they will be grossly examined for internal pathology under the supervision of the pathologist or his designate. The males will be sacrificed at a comparable time and necropsied, as described for the females. All necropsies will follow the SOP's of the Pathobiology unit except that in the pregnant females, the uteri and ovaries will be removed at the beginning and subjected to the teratological examinations prior to fixation according to Teratology SOP's. All animals will be weighed just prior to sacrifice, and blood will be obtained from the posterior vena cava immediately after the animal is opened, for a standard hemogram (CBC), including white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (mcv), mean corpuscular hemoglobin (mch), mean corpuscular hemoglobin concentration (mchc) and WBC differential. Serum chemistries will be done according to the clinical chemistry SOP's and will include glucose, BUN, creatinine, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, albumin, total protein, CA, P, K, Na and Fe.

The tissues or organs listed in Appendix A will be removed, fixed in 10% neutral, buffered formalin, sectioned, stained with haematoxylin-eosin and examined by a Certified Veterinary Pathologist for histopathology. The heart, liver, spleen, kidneys, testes, and ovaries will be trimmed of fat and connective tissue, and weighed prior to fixation.

**Dead/Moribund Animals:**

Animals found dead or moribund will be necropsied. Unless putrescent (as determined by the prosector or pathologist) the tissues listed in Appendix A will be taken and processed for histopathology. If a necropsy cannot be performed within 60 minutes after being found, the animal will be opened head to anus and placed in 10% neutral buffered formalin and necropsied within 72 hours. No blood or organ weights will be taken.

**Statistical Analyses:**

The continuous data will be analyzed by the Analysis of Variance. Provided the Bartlett's test for homogeneity of variance is not significant, treated groups will be compared to the control group by the least significant difference test. If Bartlett's test is significant, the comparison will be made by Wilcoxon's rank sum test. The non-parametric data, i.e., number of dams pregnant, number of pups deformed, will be analyzed by Chi-square techniques. See Snedecor and Cochran, Statistical Methods, 6th Edition, Iowa University Press, 1967.

**Protocol Changes:**

If it becomes necessary to change the approved protocol, verbal agreement should be made between the Study Director and the Divisional Toxicologist (Sponsor). As soon as practical, the change should be written, signed by the two parties, and added to the protocol as an amendment.

**Report:**

The report will include the dates of the initiation and completion of the study, and

1. Growth, feed consumption and feed efficiencies for the first 91 days, and for the total elapsed time in each generation.
2. Body weight changes, feed intake, and test substance intake during gestation and lactation in each generation.
3. Reproductive characteristics of number pregnant, gestation length, numbers born, number and indices of pups surviving to days 4 and 22, and weights of pups at the different intervals.

4. Teratological characteristics of number pregnant, the number of corpora lutea, implants, resorptions, and fetuses; the fetal weights and the number and descriptions of the abnormalities.
5. Results of necropsies, hemograms, clinical chemistries, histopathological examinations, and organ weights and organ/body weight ratios.
6. All elements required by GLP's.

Retention of Specimens: All wet tissues, blocks, slides, fetal skeletons, and fetal slices will be placed in the Test Facility Archives and be retained according to the Standard Operating Procedures of the Test Facility.

Proposed Starting Date: Oct. 24, 1985

Defined as Randomization of animals and beginning exposure to test substance

Proposed Completion Date: Nov. 1, 1986

Defined as Completion of second generation fetal examinations

Study Director: S. A. Nolan  
Date: 10/11/85

Divisional Toxicologist: James E. Weaver James E. Weaver  
Date: 10-22-85  
Cost: \$194,912.00

APPENDIX A  
STANDARD COMPLETE TISSUE COLLECTION LIST (RATS)

STUDY #: \_\_\_\_\_

1  
\_\_\_\_\_

HEART  
AORTA, thoracic

TONGUE  
TRACHEA, ESOPHAGUS, THYROID (parathyroid  
if included in plane of section)  
SUBMANDIBULAR LYMPH NODE

ILEOCECAL LYMPH NODE  
STOMACH (forestomach, fundic, pyloric region)  
SUBMANDIBULAR SALIVARY GLAND

R  
DUODENUM  
JEJUNUM  
ILEUM  
CECUM  
COLON  
RECTUM

URINARY BLADDER  
KIDNEY (longitudinal section of left, cross  
section of right; similar sections for  
save)

MALE

TESTICLE with EPIDIDYMIS  
PROSTATE  
SEMINAL VESICLE

FEMALE

OVARY  
UTERUS (horns)  
VAGINA

ADRENAL  
THYMUS  
PSOAS MUSCLE  
SPLEEN  
PANCREAS

BONE/MARROW (femur)  
SKIN (inguinal mammary gland region including  
mammary tissue if visible)

BRAIN  
THORACOLUMBAR SPINAL CORD  
SCIATIC NERVE  
PITUITARY

EYES

12

SAVE JAR Paired organs (save right &  
process left except kidney)

Unpaired organs (duplicate save  
and process samples, with  
exception of pituitary)

LESIONS NOT INCLUDED IN STANDARD SAMPLES  
CONSIDERED BY THE ATTENDING PATHOLOGIST  
TO POTENTIALLY REPRESENT TEST SUBSTANCE EFFECT:

1983

INTERDEPARTMENTAL CORRESPONDENCE

FROM: G. A. Nolen

DATE: February 13, 1986

TO: Study File

R/L: Non-discretionary

SUBJECT: PROTOCOL AMENDMENT TO  
STUDY B85-0460

ATTENTION:

The females fed 300 mg/kg/day of G0539.02 are not exhibiting a normal estrous cycle after 18 days of vaginal smearing. Only two of the 21 remaining females have been sperm positive, and presumably pregnant. Therefore, it is deemed advisable to sacrifice these females and the two remaining living males for clinical chemistry and histopathology.

The details of the sacrifices, necropsies, hematology, clinical chemistry, and histopathology will be as listed in the protocol. The animals will be sacrificed on February 19, 1986.

  
J. E. Weaver  
Divisional Toxicologist

  
G. A. Nolen  
Study Director

GANIC2:cw



# INTERDEPARTMENTAL CORRESPONDENCE

FROM G. A. Nolen  
TO The Record  
SUBJECT PROTOCOL AMENDMENT TO STUDY B85-0460

DATE 1/22/86  
RETENTION LIMIT Until Superseded  
ATTENTION

The males fed 300 mg/kg/day of G0539.02 have exhibited a greater response than indicated in the range-finding study, with 15/25 of them dying during 12 weeks of the 13-week growth period (2/25 of the females died during the same period). Moreover, the males grew only about half as much as the controls, while the females grew at about 80% of controls.

Since the primary questions of this study are the effects of G0539.02 on female reproduction and teratogenicity, these females will be mated with a group of untreated stock males for the F<sub>1A</sub> and F<sub>1B</sub> pregnancies. To do this, they will be moved into a separate room (L-42), so that the other animals in the study will not be exposed to the separate batch of stock males. These females will remain in the separate room until sacrificed, at the same time as the other F<sub>0</sub> rats. Any of the males receiving the high dose will remain in the room originally assigned, and unless their condition warrants early sacrifice, will continue on treatment, and be sacrificed along with the other F<sub>0</sub> rats. Where possible, they will be subjected to the same necropsy and pathological procedures as the other rats.

The stock males will be utilized only for breeding purposes. Their ear tag numbers and body weights will be recorded at the time of each mating. After the matings are accomplished they will be returned to the stock pool. However, the same males will be used for both the F<sub>1A</sub> and F<sub>1B</sub> matings.

After the F<sub>1A</sub> pups are weaned, at the time of the selection of the pups for the second generation breeders, an extra group of 25 males and 25 females will be randomly selected from the control pups. This extra group will be placed on a diet containing 200 mg/kg/day of G0539.02 as the new high dose during the second generation. Otherwise, these animals will be handled in the same manner as the other groups, as specified in the protocol.

  
G. A. Nolen  
Study Director

  
J. E. Weaver  
Divisional Toxicologist

GANREC/sw

cc: H. A. Derner  
QAU  
R. A. Jamieson



INTERDEPARTMENTAL CORRESPONDENCE

FROM: G. A. Nolen

DATE: March 25, 1986

TO: Study File

R/L: Non-discretionary

SUBJECT: ABORTION OF B85-0460

ATTENTION:

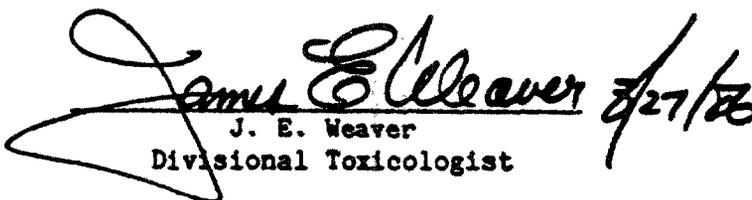
This study will be ended with the completion of the teratological phase (F<sub>1B</sub>) of the first generation, because of the low number of survivors in the 100 mg/kg/day group at weaning.

All of the F<sub>1A</sub> offspring, except the controls, will be sacrificed on March 25, 1986. The control pups will be transferred to another study.

Additional tests to be added at the necropsy of the first generation parent animals are:

1. Examine all bone marrow sections for stainable iron.
2. Determine iron binding capacity and/or transferrin levels in serum.
3. Total and direct bilirubin in the serum.
4. Measurement of the serum vitamin B<sub>12</sub> and folic acid levels in 5 rats of each sex from each group, randomly selected at necropsy.

  
G. A. Nolen  
Study Director

  
J. E. Weaver  
Divisional Toxicologist

GANIC6:cw

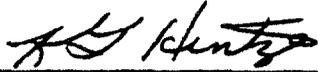
cc: J. F. Powers  
C. L. Slough

Two Generation Reproduction and Teratology

Protocol Addendum For BYCR0428

Study No.: B85-0460  
TSIN: G0539.02

Effective April 15, 1987, Dr. Kenneth L. Hintze replaced Dr. James E. Weaver as the sponsor's division toxicologist. This reflects a change in personnel job responsibilities and does not effect the integrity of the study.

  
K. L. Hintze, Ph.D., D.A.B.T.

5/20/87  
Date

  
Study Director 5/22/87

Appendix 2 - Clinical and Anatomical Pathology

INTERDEPARTMENTAL CORRESPONDENCE

From: K. A. Stitzel, C. L. Hudson, Date: May 20, 1987  
D. L. Rothacker

To: G. A. Nolen R/L: Non-Discretionary

Subject: Pathology Report for Study B85-0460,  
DRD BYCR-0428, TSIN G0539.02

CONCLUSIONS

ORGAN AND BODY WEIGHT ANALYSIS

Statistical analysis of whole body, heart, liver, spleen, kidney, testis, and ovary weights recorded at necropsy showed significantly increased absolute and relative heart weights for Group 3 males as compared to controls. Linear regression suggested this increase to be a dose related trend. A similar increase in relative heart weights for Group 3 females was noted. The absolute and relative spleen and liver weights for Group 3 females were decreased compared to controls. Group 2 male relative spleen weights were statistically significantly decreased. The increased heart weight may be secondary to anemia.

Group 4 organ and body weights were not statistically analyzed due to the high mortality rate and rescheduled early terminal sacrifice. However, the average body weight of Group 4 was less than could be expected for rats of this age and this decrease ultimately affected the absolute and relative organ weights for the group.

Biologically significant changes in the other organs were not noted.

CLINICAL PATHOLOGY

In Groups 3 and 4, anemia, compatible with iron deficiency, was indicated by depressed red cell parameters, hypochromic and microcytic red cells noted microscopically, and depressed serum iron values. The anemia was severe and life threatening in the surviving Group 4 animals, and in some Group 3 males. These effects appeared to be related to test substance administration.

Decreases in serum iron were seen in all pregnant females, including Group 2, but not in the Group 2 males or Group 2 and 3 non-pregnant females. This effect appeared to be test substance related. Other changes in clinical chemistry values were secondary to the anemia seen in the test groups.

ANATOMIC PATHOLOGY

Macroscopically, treatment related observations were noted in Group 3 and 4 males and females. Alterations noted were heart enlargement, splenic enlargement, tan feces, and pale tissues in Group 4 indicative of anemia. Twenty-three males and twelve females died on study in Group 4.

Microscopically, bone marrow hypercellularity, decreased hemosiderin in the spleen, hypercellular splenic red pulp, and inflammation of the stomach and intestinal tract were treatment related alterations in Groups 3 and 4. Changes in Group 4 were histopathologically more severe than in Group 3.

## INTRODUCTION

One hundred male and one hundred female rats were divided into four groups to assess the reproductive and developmental toxicity of the test substance (G0539.02, octopirox) administered continuously in the diet.

## MATERIALS AND METHODS

### EXPERIMENTAL MODEL

Refer to the report submitted by Experimental Pathology Laboratories, Inc. (Anatomic Pathology Appendix I) for a description of experimental design and animal group assignment.

### ORGAN AND BODY WEIGHT ANALYSIS

Refer to the report submitted by Experimental Pathology Laboratories, Inc. (Anatomic Pathology Appendix I).

### CLINICAL PATHOLOGY

Blood for hematology and chemistry determinations was collected at necropsy from the posterior vena cava into tubes containing an appropriate amount of EDTA anticoagulant for hematology determinations and serum separator tubes for chemistry determinations. Hematology and chemistry determinations were performed at the Clinical Pathology Laboratory (MVL). Serum iron, folic acid and Vitamin B12 analyses were performed on selected animals at Vet-Path Labs, Kensington, MD.

### Parameters

#### Hematology

White blood cell count (WBC)  
Red blood cell count (RBC)  
Hemoglobin (HGB)  
Hematocrit (HCT)  
Mean corpuscular volume (MCV)  
Mean corpuscular hemoglobin (MCH)  
Mean corpuscular hemoglobin concentration (MCHC)  
Platelet count  
Differential leukocyte count  
Reticulocyte count (RETIC)

#### Chemistry

Albumin (ALB)  
Alkaline Phosphatase (ALK)  
Blood Urea Nitrogen (BUN)  
Albumin/Globulin Ratio (A/G)  
Calcium (CA)

Cholesterol (CHOL)  
Creatinine (CREAT)  
Globulin (GLOB)  
Glucose (GLUC)  
Phosphorus (PHOS)  
Potassium (K)  
Aspartate Amino Transferase (AST/SGOT)  
Alanine Amino Transferase (ALT/SGPT)  
Sodium (NA)  
Total Bilirubin (TBILI)  
Direct Bilirubin (DBILI)  
Total Protein (TP)  
Triglycerides (TG)  
Iron (Fe)  
Vitamin B12  
Folic Acid

Hematology and chemistry results were statistically analyzed by R. D. Bruce and P. J. Sprong using Procter and Gamble Computer Program #B8944. All test groups were compared to the Vehicle Control Group 1. In addition, linear regression was applied to groups 1, 2, and 3.

All statistical tests were conducted at a 5%, two-sided risk level. Data from the Clinical Pathology testing and statistical analyses were further evaluated by K. A. Stitzel, D.V.M., and C. L. Hudson.

#### ANATOMIC PATHOLOGY

Refer to the report submitted by Experimental Pathology Laboratories, Inc. (Anatomic Pathology Appendix I).

#### RESULTS

##### ORGAN AND BODY WEIGHT ANALYSIS

Refer to the report submitted by Experimental Pathology Laboratories, Inc. (Anatomic Pathology Appendix I).

##### CLINICAL PATHOLOGY

Summaries of the hematology and chemistry statistical analyses are given in Clinical Pathology Tables 1 and 2 respectively. Tables of the hematology and chemistry data are given in Clinical Pathology Appendices I, II, and III, respectively. Data from the study are located in notebooks YE-857 and 961 in the Clinical Pathology Laboratory.

Several linear regression values have a "?" next to the value; this indicates a lack of fit. Although statistically significant, the results do not fit a dose response and are not considered in the following discussion.

The study had three test groups: Group 2 was the low dose 50 mg/kg; Group 3 was the mid dose 100 mg/kg; Group 4 was the high dose 300 mg/kg. Group 4 animals began dying during the study and the remaining male and thirteen females in Group 4 were necropsied early. For this reason the data from Group 4 was not included in the statistical analyses. Pregnant and non-pregnant females were analyzed separately.

Several results are marked missing (-M-) on the individual data forms even though results were generated. These include: Group 2 male #2650 iron = 231 mcg/dl, Group 1 male #2620 globulin = 2.6 gm/dl and A/G ratio = 1.57 and Group 2 female #2752 total bilirubin = 0.1. These results were not included in the statistical analysis because they were not entered into the computer inadvertently. This does not compromise statistical results. Values were manually entered on individual result data forms beside the -M- notation. Other missing (-M-) results include: Group 3 male # 2649 AST and ALT -- results were not acceptable; Group 1 male #2608, Group 2 male #2606 and Group 2 female #2778 have no hematology results due to clotted samples.

Direct bilirubin was discontinued after results were found to be almost entirely negative numbers. Negative results occur because of the slight instrument variation around zero but are not accepted by the computer. Thus, samples were all negative for direct bilirubin. The lack of this data does not effect the interpretation of the study.

Iron binding capacity or transferrin requested in the Study Director's memo dated 3/25/86 inadvertently was not performed on these specimens. These results would have helped confirm the iron deficiency but the reduced MCV, hemoglobin, and serum iron values are very good evidence that iron deficiency was the cause of the anemia.

#### Hematology

The effect of test substance administration was the development of a microcytic anemia. We have subsequently shown that the ELT-8/ds does not accurately enumerate red blood cells and platelets when the red cell volume drops much below 50 fl. For this reason the RBC, HCT, MCH, MCHC and platelet values for the severely anemic animals are somewhat incorrect. Because of the severity of the anemia, this inaccuracy does not interfere with the interpretation of the study results.

For the pregnant females, changes from the control Group 1 were moderate for Group 3. None of the Group 4 pregnant females survived to sacrifice, so no data on these animals was available. In the females statistically significant differences were as follows:

1. Hemoglobin and hematocrit were depressed for mid dose Group 3. Group 3 RBC was slightly but statistically elevated. The elevated value appears to be in attempted response to the anemia. The red blood cells in Group 3 were hypochromic and microcytic, therefore even with slightly increased numbers of cells, the hematocrit and hemoglobin levels were still depressed. The average control value for RBC's was  $6.008 \times 10^6/\text{ul}$  compared to 6.900 for Group 3. The average control HGB was 11.59 gm/dl compared to 9.52 for Group 3. The average control HCT was 35.68% compared to 28.69% for Group 3.

2. MCV and MCH were depressed for Group 3. The average MCV was 59.3 fl for the controls and 41.4 for Group 3. The average MCH was 19.32 pg for the controls and 13.75 for Group 3.
3. Reticulocytes were depressed in Groups 2 and 3 and the linear regression was statistically significant. The differences were very small and the individual values were similar to the controls. Thus, these results were considered fortuitous.

For the males, statistically significant changes from control Group 1 occurred only in the mid dose Group 3. The one surviving male in Group 4 was also anemic. Alterations were similar to those for Group 3 females but of greater intensity. Statistical significance was noted for the following:

1. RBC, HGB and HCT were all depressed in Group 3. The average RBC value for the controls was  $8.916 \times 10^6/\text{ul}$  compared to 7.764 for Group 3. The average HGB for the controls was 15.81 gm/dl compared to 9.37 for Group 3. The average HCT for the controls was 46.13% compared to 25.00% for Group 3.
2. MCV and MCH were depressed and MCHC was elevated for Group 3. The average MCV for controls was 51.8 fl compared to 31.4 for Group 3. The average MCH for the controls was 17.75 pg compared to 11.96 for Group 3. The average MCHC for the controls was 34.42% compared to 38.56% for Group 3. The accuracy of the MCH and MCHC must be questioned because the electronic cell counter had problems differentiating microcytic red cells from platelets.
3. Platelets and reticulocytes were elevated for Group 3. The average platelet value for the controls was  $1003.0 \times 10^3/\text{ul}$  compared to 2124.1 for Group 3. Platelet values may be elevated in iron deficiency anemia. In addition, the hematology instrument counted the very microcytic red cells as platelets, artificially elevating the platelet number. The average reticulocyte count for the controls was 2.32 % compared to 6.38 for Group 3.

Because of these small group sizes the statistical tests on the non-pregnant female data were not as sensitive. Group 4 results were not included in the statistical evaluation because they were sacrificed early. In Group 4 the surviving non-pregnant females were extremely anemic, and anemia was probably the cause of death in the animals which died during the study. The anemia was microcytic and hypochromic.

Platelet counts were elevated for Group 4, but this finding was not confirmed by examination of the blood smears. The spurious increase may have been caused by the hematology instrument counting very microcytic red cells as platelets, artificially elevating the platelet number.

In the non-pregnant females statistical significance was noted for the following:

1. HGB, and HCT were decreased in Group 3 when compared to Group 1, HGB 14.45 gm/dl for Group 1 and 13.02 for Group 3, HCT 44.50% for Group 1 and 39.00% for Group 3. The RBC was slightly but statistically elevated when Group 3 was compared to Group 1 and the linear regression was significant, RBC 7.488 for Group 1 and 8.005 for Group 3.

2. MCV and MCH were both depressed in Group 3 compared to Group 1, MCV 59.7 fl for Group 1 and 49.1 for Group 3, MCH 19.33 pg for Group 1 and 16.38 for Group 3.

#### CHEMISTRY

Except for iron parameters, changes that occurred in chemistry values were secondary to the anemia. Since these changes are secondary, the values are not included in this narrative, all the values are listed in Table 2.

Direct bilirubin results generated were zero or negative numbers. Since these numbers are meaningless for statistical purposes and clinically unimportant, the analyses were discontinued. Serum iron, folic acid and Vitamin B12 were performed on selected specimens only.

Statistically significant alterations of clinical chemistry values for the pregnant females were as follows:

1. Serum iron values were statistically decreased in Groups 2 and 3, and the linear regression was significant. The group averages were 120.5 mg/dl for Group 1, 68.2 for Group 2, and 37.7 for Group 3.
2. Potassium values were decreased for Groups 2 and 3 compared to Group 1. All values for both groups were within the range of the control group. It is not clear if the slight decrease in the means was secondary to test substance administration or the result of biological variation.
3. ALT was decreased in Group 2 and 3 and the linear regression was significant.
4. Triglyceride and cholesterol values were decreased for Group 3 females. For cholesterol the linear regression was also significant.
5. BUN and alkaline phosphatase were decreased for Group 2 females. Small decreases in these values, as seen here, are not considered toxicologically significant. These results are most likely due to biological variation.

The following statistically significant differences were reported for the males:

1. Serum iron values were statistically decreased for Group 3. Average group serum iron values were 166.6 mcg/dl for Group 1, 164.8 for Group 2, and 61.8 for Group 3.
2. Total protein, globulin, and cholesterol were decreased in Group 3 and the linear regression was significant for cholesterol.
3. A/G ratio and phosphorus were elevated for Group 3 males and the linear regression was significant for phosphorus.
4. One control animal, #2699, had elevated AST and ALT values.

For non-pregnant females no statistically significant differences were reported.

### ANATOMIC PATHOLOGY

Refer to the report submitted by Experimental Pathology Laboratories, Inc. (Anatomic Pathology Appendix I).

### DISCUSSION

#### ORGAN AND BODY WEIGHT ANALYSIS

Refer to the report submitted by Experimental Pathology Laboratories, Inc. (Anatomic Pathology Appendix I).

#### CLINICAL PATHOLOGY

The 50 mg/kg dose Group 2 had no statistically significant changes in the hemogram. However the serum iron values for this group were low when compared with the controls. The test substance appeared to have an effect on serum iron levels, thus Group 2 cannot be considered a no-effect level for the pregnant females.

The primary effect of test substance administration seemed to be the development of anemia. The number of red cells and the hemoglobin levels both decreased moderately in Group 3 and severely in Group 4. At the time of sacrifice most of the animals in Group 4 had died, thus only the more resistant survivors remained. The anemia present in the survivors was life threatening and anemia must be considered strongly as the cause of death in the other Group 4 animals even though hematology examination was not performed.

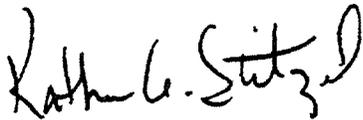
The anemia was microcytic and hypochromic, classic evidence for an iron deficiency anemia. This diagnosis is supported by the very low serum iron values. The serum iron values are somewhat higher in the Group 4 animals, however these animals were sacrificed early and may not have had time to become as iron depleted as the Group 3 animals. Also only the few surviving Group 4 animals were available for evaluation, this may have resulted in selection of the most resistant subpopulation. Vitamin B12 and folic acid levels were measured in a select group of rats, no differences between the groups were seen.

Besides the decrease in serum iron, the changes in serum chemistry parameters were the result of metabolic alterations occurring secondarily to anemia and resultant tissue anoxia.

Final mention should be made of the non-pregnant females. Although there were fewer animals in these groups, it appears they were not affected by test substance administration to the same extent as either the pregnant females or the males.

ANATOMIC PATHOLOGY

Refer to the report submitted by Experimental Pathology Laboratories, Inc. (Anatomic Pathology Appendix I).



CLINICAL PATHOLOGIST



REVIEWING ANATOMIC PATHOLOGIST

BB50460 - FEMALES  
SUMMARY OF STATISTICAL ANALYSES

4/13/87

		GROUP 1		GROUP 2		GROUP 3		OTHER TESTS	PROB
		N	F	F	F	F	F		
RBC MILLION	AVG		6.008	6.049	6.800+++	LINEAR REGRESSION	0.000***?		
	SE		0.116	0.145	0.195				
	PROB			1.000	0.000				
HGB (GM/DL)	AVG		11.59	11.58	9.52+++	LINEAR REGRESSION	0.000***?		
	SE		0.22	0.27	0.49				
	PROB			0.731	0.000				
HCT (%)	AVG		35.68	34.76	28.69+++	LINEAR REGRESSION	0.000***?		
	SE		0.62	0.81	1.38				
	PROB			0.208	0.000				
MCV (FL.)	AVG		59.3	57.6	41.4+++	LINEAR REGRESSION	0.0	***?	
	SE		0.6	0.7	1.4				
	PROB			0.156	0.000				
MCH (PG.)	AVG		19.32	19.24	13.75+++	LINEAR REGRESSION	0.0	***?	
	SE		0.15	0.18	0.50				
	PROB			0.778	0.000				
MCHC (%)	AVG		32.68	33.24	33.19	LINEAR REGRESSION	0.350		
	SE		0.32	0.50	0.34				
	PROB			0.531	0.567				
WBC THOUSAND	AVG		6.55	6.63	6.34	LINEAR REGRESSION	0.708		
	SE		0.32	0.38	0.40				
	PROB			0.876	0.909				
PLATELET THOUSAND	AVG		986.1	927.3	1072.9	LINEAR REGRESSION	0.124		
	SE		27.5	37.8	45.5				
	PROB			0.219	0.182				
RETIC (%)	AVG		3.09	2.30+++	1.71+++	LINEAR REGRESSION	0.0	***	
	SE		0.12	0.14	0.11				
	PROB			0.000	0.000				

SYMBOLS APPEARING BY GROUP AVERAGES/MEDIANS INDICATE DIFFERENCES FROM GROUP 1 F  
 \*, \*\*, \*\*\* DENOTE SIGNIFICANCE BY NORMAL DISTN. METHODS WITH P<.05, .01, .001 RESPECTIVELY  
 +, ++, +++ DENOTE SIGNIFICANCE BY DISTN.-FREE METHODS WITH P<.05, .01, .001 RESPECTIVELY  
 ? DENOTES SIGNIFICANT LACK-OF-FIT TEST AT P<.05

CLINICAL PATHOLOGY TABLE 1a

B850480 - MALES  
SUMMARY OF STATISTICAL ANALYSES

4/13/87

	N	GROUP 1	GROUP 2	GROUP 3	OTHER TESTS	PROB
		M 24	M 24	M 25		
RBC MILLION	AVG	8.916	9.050	7.764+	LINEAR REGRESSION	0.000***?
	SE	0.090	0.118	0.349		
	PROB		0.533	0.019		
HGB (GM/DL)	AVG	15.81	15.81	9.37+++	LINEAR REGRESSION	0.0 ***?
	SE	0.18	0.22	0.63		
	PROB		0.678	0.0		
HCT (%)	AVG	46.13	45.88	25.00+++	LINEAR REGRESSION	0.0 ***?
	SE	0.44	0.60	1.92		
	PROB		0.783	0.0		
MCV (FL.)	AVG	51.8	50.8	31.4+++	LINEAR REGRESSION	0.0 ***?
	SE	0.7	0.7	1.5		
	PROB		0.410	0.0		
MCH (PG.)	AVG	17.75	17.42	11.98+++	LINEAR REGRESSION	0.0 ***?
	SE	0.15	0.16	0.45		
	PROB		0.109	0.0		
MCHC (%)	AVG	34.42	34.67	38.56+++	LINEAR REGRESSION	0.000***?
	SE	0.39	0.45	0.70		
	PROB		0.588	0.000		
WBC THOUSAND	AVG	8.97	8.63	8.58	LINEAR REGRESSION	0.665
	SE	0.52	0.37	0.91		
	PROB		0.785	0.220		
PLATELET THOUSAND	AVG	1003.0	1028.1	2124.1+++	LINEAR REGRESSION	0.000***?
	SE	24.2	31.3	249.2		
	PROB		0.707	0.000		
RETIC (%)	AVG	2.32	2.39	6.38+++	LINEAR REGRESSION	0.000***?
	SE	0.13	0.16	0.69		
	PROB		0.996	0.000		

SYMBOLS APPEARING BY GROUP AVERAGES/MEDIANS INDICATE DIFFERENCES FROM GROUP 1 M  
 \*, \*\*, \*\*\* DENOTE SIGNIFICANCE BY NORMAL DISTN. METHODS WITH P<.05, .01, .001 RESPECTIVELY  
 +, ++, +++ DENOTE SIGNIFICANCE BY DISTN.-FREE METHODS WITH P<.05, .01, .001 RESPECTIVELY  
 ? DENOTES SIGNIFICANT LACK-OF-FIT TEST AT P<.05

CLINICAL PATHOLOGY TABLE 1 A

STATISTICAL ANALYSIS SUMMARY

B850460 - NONPREGNANT FEMALES

PERIOD 1 VALUES

RESPONSE:		RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL.)	MCH (PG.)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)
GROUP 1	AVG.	7.488	14.45	44.50	59.7	19.33	32.50	6.37	862.7	2.37
F	S.E.	0.080	0.20	0.62	0.8	0.21	0.34	1.16	41.0	0.37
GROUP 2	AVG.	7.448	14.58	45.00	60.4	19.71	32.43	5.27	800.7	2.39
F	S.E.	0.117	0.24	0.58	0.8	0.29	0.37	0.74	54.5	0.20
	P(C)	0.834	0.836	0.731	0.534	0.445	0.836	0.445	0.366	0.534
GROUP 3	AVG.	8.005	13.02	39.00	48.1	16.38	33.13	4.72	913.4	2.35
F	S.E.	0.182	0.37	1.31	2.7	0.86	0.48	0.53	53.3	0.38
	P(C)	0.043+	0.020+	0.003++	0.001++	0.020+	0.491	0.181	0.862	1.000
LIN. REGR	P(O)	0.016*	0.0027	0.0017	0.0017	0.0027	0.281	0.169	0.431	0.967

P(C) DENOTES P-VALUE FOR COMPARISON OF OTHER GROUPS WITH CONTROL, GROUP 1 F  
P(O) DENOTES P-VALUE FOR LINEAR REGRESSION OR FOR A CONTRAST.  
\*, \*\*, \*\*\* DENOTE SIGNIFICANCE BY NORMAL DISTRIBUTION METHODS WITH P<.05, .01 OR .001 RESPECTIVELY.  
+, ++, +++ DENOTE SIGNIFICANCE BY DISTRIBUTION-FREE METHODS WITH P<.05, .01 OR .001 RESPECTIVELY.  
? INDICATES A "LACK OF FIT" IN LINEAR REGRESSION OR IN A CONTRAST.

STUDY B850460 - FEMALES  
SUMMARY OF STATISTICAL ANALYSES

4/13/87

		GROUP 1	GROUP 2	GROUP 3	OTHER TESTS	PROB
	F	F	F	F		
GLUC (MG/DL)	AVG	107.8	107.8	118.2	LINEAR REGRESSION	0.295
	SE	6.0	3.9	9.8		
	N	19	17	16		
	PROB		0.950	0.935		
BUN (MG/DL)	AVG	17.22	14.72+	15.91	LINEAR REGRESSION	0.214
	SE	0.78	0.88	0.69		
	N	19	17	16		
	PROB		0.035	0.172		
CREAT. (MG/DL)	AVG	0.63	0.62	0.63	LINEAR REGRESSION	0.861
	SE	0.02	0.01	0.02		
	N	19	17	16		
	PROB		0.638	0.935		
TP (GM/DL)	AVG	5.86	5.83	5.89	LINEAR REGRESSION	0.917
	SE	0.13	0.14	0.18		
	N	19	17	16		
	PROB		0.285	1.000		
ALB (GM/DL)	AVG	3.93	3.88	3.95	LINEAR REGRESSION	0.875
	SE	0.08	0.09	0.11		
	N	19	17	16		
	PROB		0.433	0.987		
GLOB (GM/DL)	AVG	2.03	1.95	2.04	LINEAR REGRESSION	0.989
	SE	0.06	0.05	0.08		
	N	19	17	16		
	PROB		0.471	0.935		
A/G	AVG	1.949	1.994	1.971	LINEAR REGRESSION	0.724
	SE	0.040	0.038	0.065		
	N	19	17	16		
	PROB		0.531	1.000		
ALK (IU/L)	AVG	93.3	89.2+	88.7	LINEAR REGRESSION	0.528
	SE	9.3	9.7	10.2		
	N	19	17	16		
	PROB		0.042	0.683		
AST (IU/L)	AVG	162.9	147.9	135.7	LINEAR REGRESSION	0.208
	SE	15.9	17.4	10.5		
	N	19	17	16		
	PROB		0.318	0.385		
ALT (IU/L)	AVG	61.5	45.2+	41.1++	LINEAR REGRESSION	0.003**
	SE	6.2	3.1	3.1		
	N	19	17	16		
	PROB		0.025	0.008		

SYMBOLS APPEARING BY GROUP AVERAGES/MEDIANS INDICATE DIFFERENCES FROM GROUP 1 F  
 \*, \*\*, \*\*\* DENOTE SIGNIFICANCE BY NORMAL DISTN. METHODS WITH P<.05, .01, .001 RESPECTIVELY  
 +, ++, +++ DENOTE SIGNIFICANCE BY DISTN.-FREE METHODS WITH P<.05, .01, .001 RESPECTIVELY

CLINICAL PATHOLOGY TABLE 2

STUDY B050460 - FEMALES  
SUMMARY OF STATISTICAL ANALYSES

4/13/87

		GROUP 1	GROUP 2	GROUP 3	OTHER TESTS	PROB
		F	F	F		
TBILI (MG/DL)	AVG	0.13	0.11	0.11	LINEAR REGRESSION	0.346
	SE	0.02	0.01	0.02		
	N	19	16	16		
	PROB		0.659	0.707		
NA (MEQ/L)	AVG	141.1	141.6	141.2	LINEAR REGRESSION	0.818
	SE	0.5	0.6	0.5		
	N	19	17	16		
	PROB		0.910	0.756		
K (MEQ/L)	AVG	6.43	5.27+++	5.62+	LINEAR REGRESSION	0.008** ?
	SE	0.22	0.19	0.28		
	N	19	17	16		
	PROB		0.000	0.029		
CA (MG/DL)	AVG	9.89	9.65	10.06	LINEAR REGRESSION	0.867
	SE	0.27	0.20	0.18		
	N	19	17	16		
	PROB		0.285	0.857		
PHOS (MG/DL)	AVG	4.55	3.49+	4.51	LINEAR REGRESSION	0.811
	SE	0.29	0.26	0.28		
	N	19	17	16		
	PROB		0.011	0.835		
FE (MG/DL)	AVG	120.5	68.2++	37.7+++	LINEAR REGRESSION	0.006**
	SE	17.2	17.8	27.3		
	N	19	17	16		
	PROB		0.008	0.000		
CHOL (MG/DL)	AVG	95.2	89.4	73.8+++	LINEAR REGRESSION	0.000***
	SE	3.3	4.4	3.6		
	N	19	17	16		
	PROB		0.582	0.000		
TG (MG/DL)	AVG	516.2	571.1	324.5++	LINEAR REGRESSION	0.023* ?
	SE	48.3	71.1	45.2		
	N	19	17	16		
	PROB		0.573	0.006		
VIT. B12 (PG/ML)	AVG	673.0	521.0	527.3	LINEAR REGRESSION	0.167
	SE	78.7	79.4	30.9		
	N	4	3	3		
	PROB		0.400	0.114		

SYMBOLS APPEARING BY GROUP AVERAGES/MEDIANS INDICATE DIFFERENCES FROM GROUP 1 F  
 \*, \*\*, \*\*\* DENOTE SIGNIFICANCE BY NORMAL DISTN. METHODS WITH P<.05, .01, .001 RESPECTIVELY  
 +, ++, +++ DENOTE SIGNIFICANCE BY DISTN.-FREE METHODS WITH P<.05, .01, .001 RESPECTIVELY  
 ? DENOTES SIGNIFICANT LACK-OF-FIT TEST AT P<.05

CLINICAL PATHOLOGY TABLE 2 A

STUDY 8850460 - FEMALES  
SUMMARY OF STATISTICAL ANALYSES

4/13/87

		GROUP 1	GROUP 2	GROUP 3		
		F	F	F	OTHER TESTS	PROB
FOLIC A.	AVG	66.3	55.3	48.0	LINEAR REGRESSION	0.152
(NG/ML)	SE	8.7	9.4	5.0		
	N	4	3	3		
	PROB		0.629	0.400		

NO SIGNIFICANT DIFFERENCES AT THE 5% LEVEL

STUDY 8850480 - MALES  
SUMMARY OF STATISTICAL ANALYSES

4/13/87

		GROUP 1	GROUP 2	GROUP 3	OTHER TESTS	PROB
	M	M	M			
GLUC (MG/DL)	AVG	232.2	221.7	236.1	LINEAR REGRESSION	0.853
	SE	11.8	15.4	16.3		
	N	25	25	25		
	PROB		0.369	0.718		
BUN (MG/DL)	AVG	14.58	15.42	15.06	LINEAR REGRESSION	0.548
	SE	0.63	0.53	0.50		
	N	25	25	25		
	PROB		0.418	0.604		
CREAT. (MG/DL)	AVG	0.70	0.68	0.70	LINEAR REGRESSION	1.000
	SE	0.01	0.01	0.01		
	N	25	25	25		
	PROB		0.389	0.896		
TP (GM/DL)	AVG	6.64	6.68	6.20 <sup>+++</sup>	LINEAR REGRESSION	0.000 <sup>***?</sup>
	SE	0.05	0.07	0.05		
	N	25	25	25		
	PROB		0.663	0.000		
ALB (GM/DL)	AVG	4.14	4.18	4.07	LINEAR REGRESSION	0.217
	SE	0.04	0.05	0.03		
	N	25	25	25		
	PROB		0.545	0.127		
GLOB (GM/DL)	AVG	2.50	2.48	2.13 <sup>+++</sup>	LINEAR REGRESSION	0.0 <sup>***?</sup>
	SE	0.05	0.05	0.05		
	N	24	25	25		
	PROB		0.658	0.000		
A/G	AVG	1.677	1.691	1.942 <sup>+++</sup>	LINEAR REGRESSION	0.000 <sup>***?</sup>
	SE	0.041	0.040	0.050		
	N	24	25	25		
	PROB		0.663	0.000		
ALK (IU/L)	AVG	117.1	104.9	107.7	LINEAR REGRESSION	0.479
	SE	10.6	9.7	7.8		
	N	25	25	25		
	PROB		0.288	0.617		
AST (IU/L)	AVG	155.3	162.6	141.0	LINEAR REGRESSION	0.734
	SE	42.9	22.3	11.9		
	N	25	25	24		
	PROB		0.087	0.202		
ALT (IU/L)	AVG	93.0	67.1	53.0	LINEAR REGRESSION	0.206
	SE	35.8	9.9	7.3		
	N	25	25	24		
	PROB		0.525	0.578		

SYMBOLS APPEARING BY GROUP AVERAGES/MEDIANS INDICATE DIFFERENCES FROM GROUP 1 M  
<sup>\*</sup>,<sup>\*\*</sup>,<sup>\*\*\*</sup> DENOTE SIGNIFICANCE BY NORMAL DISTN. METHODS WITH P<.05, .01, .001 RESPECTIVELY  
<sup>+</sup>,<sup>++</sup>,<sup>+++</sup> DENOTE SIGNIFICANCE BY DISTN.-FREE METHODS WITH P<.05, .01, .001 RESPECTIVELY  
<sup>?</sup> DENOTES SIGNIFICANT LACK-OF-FIT TEST AT P<.05

CLINICAL PATHOLOGY TABLE 2 *2*

STUDY B850460 - MALES  
SUMMARY OF STATISTICAL ANALYSES

4/13/87

		GROUP 1	GROUP 2	GROUP 3	OTHER TESTS	PROB
		M	M	M		
TBILI (MG/DL)	AVG	0.25	0.23	0.23	LINEAR REGRESSION	0.546
	SE	0.02	0.02	0.02		
	N	25	25	25		
	PROB		0.575	0.594		
NA (MEQ/L)	AVG	145.9	145.2	145.0	LINEAR REGRESSION	0.067
	SE	0.3	0.3	0.3		
	N	25	25	25		
	PROB		0.127	0.090		
K (MEQ/L)	AVG	6.88	7.32	6.76	LINEAR REGRESSION	0.768
	SE	0.28	0.28	0.24		
	N	25	25	25		
	PROB		0.349	0.406		
CA (MG/DL)	AVG	11.08	11.03	10.86	LINEAR REGRESSION	0.341
	SE	0.14	0.18	0.17		
	N	25	25	25		
	PROB		0.850	0.238		
PHOS (MG/DL)	AVG	6.47	6.70	7.17+	LINEAR REGRESSION	0.028*
	SE	0.18	0.23	0.25		
	N	25	25	25		
	PROB		0.258	0.026		
FE (MG/DL)	AVG	166.6	164.8	61.8+++	LINEAR REGRESSION	0.0 ***?
	SE	9.6	10.8	9.8		
	N	25	24	25		
	PROB		0.845	0.000		
CHOL (MG/DL)	AVG	93.7	86.8	61.9+++	LINEAR REGRESSION	0.000+++
	SE	5.1	5.2	2.6		
	N	25	25	25		
	PROB		0.283	0.000		
TG (MG/DL)	AVG	89.0	98.8	60.1	LINEAR REGRESSION	0.040* ?
	SE	11.2	11.5	5.3		
	N	25	25	25		
	PROB		0.452	0.057		
VIT.B12 (PG/ML)	AVG	842.8	913.4	855.2	LINEAR REGRESSION	0.898
	SE	42.6	69.5	59.4		
	N	5	5	5		
	PROB		0.690	1.000		

SYMBOLS APPEARING BY GROUP AVERAGES/MEDIANS INDICATE DIFFERENCES FROM GROUP 1 M  
 \*, \*\*, \*\*\* DENOTE SIGNIFICANCE BY NORMAL DISTN. METHODS WITH P<.05, .01, .001 RESPECTIVELY  
 +, ++, +++ DENOTE SIGNIFICANCE BY DISTN.-FREE METHODS WITH P<.05, .01, .001 RESPECTIVELY  
 ? DENOTES SIGNIFICANT LACK-OF-FIT TEST AT P<.05

CLINICAL PATHOLOGY TABLE 2 2

STUDY 6530460 - MALES  
SUMMARY OF STATISTICAL ANALYSES

4/13/87

		GROUP 1	GROUP 2	GROUP 3		
		M	M	M	OTHER TESTS	PROB
FOLIC.A.	AVG	79.4	81.2	89.4	LINEAR REGRESSION	0.152
(NG/ML)	SE	4.7	4.2	4.9		
	N	5	5	5		
	PROB		1.000	0.310		

NO SIGNIFICANT DIFFERENCES AT THE 5% LEVEL

CLINICAL PATHOLOGY TABLE 2 *R*

B090460 - NONPREGNANT FEMALES  
SUMMARY OF STATISTICAL ANALYSES

4/13/87

		GROUP 1	GROUP 2	GROUP 3	OTHER TESTS	PROB
		F	F	F		
GLUC (MG/DL)	AVG	204.3	180.4	184.0	LINEAR REGRESSION	0.773
	SE	22.0	11.1	23.9		
	N	6	8	8		
	PROB		0.414	0.755		
BUN (MG/DL)	AVG	18.15	16.39	18.16	LINEAR REGRESSION	0.892
	SE	1.28	0.84	0.91		
	N	6	8	8		
	PROB		0.142	1.000		
CREAT. (MG/DL)	AVG	0.73	0.77	0.71	LINEAR REGRESSION	0.383
	SE	0.02	0.02	0.02		
	N	6	8	8		
	PROB		0.228	0.662		
TP (GM/DL)	AVG	7.52	7.40	8.07	LINEAR REGRESSION	0.095
	SE	0.27	0.13	0.29		
	N	6	8	8		
	PROB		0.662	0.282		
ALB (GM/DL)	AVG	4.63	4.84	5.20	LINEAR REGRESSION	0.053
	SE	0.16	0.08	0.14		
	N	6	8	8		
	PROB		0.852	0.181		
GLOB (GM/DL)	AVG	2.68	2.56	2.87	LINEAR REGRESSION	0.276
	SE	0.11	0.08	0.17		
	N	6	8	8		
	PROB		0.282	0.491		
A/G	AVG	1.807	1.888	1.842	LINEAR REGRESSION	0.768
	SE	0.032	0.050	0.086		
	N	6	8	8		
	PROB		0.059	0.282		
ALK (IU/L)	AVG	62.3	57.8	62.9	LINEAR REGRESSION	0.936
	SE	5.4	5.3	12.3		
	N	6	8	8		
	PROB		0.491	0.414		
AST (IU/L)	AVG	180.2	252.0	287.0	LINEAR REGRESSION	0.244
	SE	48.3	44.3	76.8		
	N	6	8	8		
	PROB		0.181	0.414		
ALT (IU/L)	AVG	89.7	112.2	137.7	LINEAR REGRESSION	0.294
	SE	29.8	21.5	23.9		
	N	6	8	8		
	PROB		0.573	0.282		

NO SIGNIFICANT DIFFERENCES AT THE 5% LEVEL

CLINICAL PATHOLOGY TABLE 2 *g*

B850460 - NONPREGNANT FEMALES  
SUMMARY OF STATISTICAL ANALYSES

4/13/87

		GROUP 1	GROUP 2	GROUP 3	OTHER TESTS	PROB
		F	F	F		
TBILI (MG/DL)	AVG	0.15	0.19	0.16	LINEAR REGRESSION	0.818
	SE	0.02	0.04	0.02		
	N	8	8	8		
	PROB		0.662	0.755		
NA (MEQ/L)	AVG	145.5	144.9	144.7	LINEAR REGRESSION	0.607
	SE	0.8	1.1	0.8		
	N	6	8	8		
	PROB		0.852	0.414		
K (MEQ/L)	AVG	5.95	5.44	5.79	LINEAR REGRESSION	0.821
	SE	0.46	0.28	0.34		
	N	6	8	8		
	PROB		0.345	0.573		
CA (MG/DL)	AVG	11.55	11.16	12.05	LINEAR REGRESSION	0.219
	SE	0.24	0.19	0.41		
	N	6	8	8		
	PROB		0.414	0.282		
PHOS (MG/DL)	AVG	6.25	5.81	6.12	LINEAR REGRESSION	0.893
	SE	0.40	0.40	0.46		
	N	6	8	8		
	PROB		0.573	1.000		
FE (MG/DL)	AVG	250.3	251.7	256.0	LINEAR REGRESSION	0.886
	SE	17.0	8.7	40.4		
	N	6	8	8		
	PROB		0.852	0.755		
CHOL (MG/DL)	AVG	89.3	82.5	105.6	LINEAR REGRESSION	0.066
	SE	6.9	5.5	6.5		
	N	6	8	8		
	PROB		0.414	0.345		
TG (MG/DL)	AVG	100.7	114.9	135.1	LINEAR REGRESSION	0.132
	SE	13.9	13.1	17.2		
	N	6	8	8		
	PROB		0.491	0.282		
VIT. B12 (PG/ML)	AVG	1161.0	998.0	916.5	LINEAR REGRESSION	0.443
	SE	0.0	28.0	203.5		
	N	1	2	2		
	PROB		0.667	0.667		

NO SIGNIFICANT DIFFERENCES AT THE 5% LEVEL

CLINICAL PATHOLOGY TABLE 2 *L*

**B850460 - NONPREGNANT FEMALES  
SUMMARY OF STATISTICAL ANALYSES**

4/13/87

		GROUP 1	GROUP 2	GROUP 3		
		F	F	F	OTHER TESTS	PROB
FOLIC A.	AVG	105.0	79.5	86.5	LINEAR REGRESSION	0.311
(NG/ML)	SE	0.0	1.5	0.5		
	N	1	2	2		
	PROB		0.667	0.667		

NO SIGNIFICANT DIFFERENCES AT THE 5% LEVEL

CLINICAL PATHOLOGY TABLE 2

DATA LISTING

8850460 - FEMALES

PERIOD 1 VALUES

RESPONSE:	RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL.)	MCH (PG.)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)
NORM. RNG. -LO:	5.4	10.6	31.0	47	15.0	31.0	3.0	406	
HI:	10.2	17.2	52.0	66	23.0	38.0	17.3	1634	
GROUP ANIMAL									
GROUP 1 2722	6.04	11.3	34.0	57.	19.0	33.0	5.9	1116.	2.8
F 2723	5.83	11.5	34.0	58.	20.0	34.0	7.4	979.	3.6
2727	6.69	12.5	38.0	57.	19.0	33.0	6.7	865.	2.8
2729	5.97	11.2	35.0	58.	19.0	33.0	6.8	1088.	2.6
2739	5.63	11.4	35.0	62.	20.0	33.0	5.6	777.	3.5
2743	5.60	11.2	37.0	66.	20.0	30.0	7.3	984.	2.7
2744	6.16	12.0	36.0	59.	20.0	33.0	7.1	782.	3.2
2755	5.87	12.1	36.0	62.	21.0	33.0	7.2	987.	3.7
2769	5.63	10.3	36.0	63.	18.0	29.0	8.5	957.	3.1
2770	6.16	11.6	34.0	55.	19.0	34.0	6.5	948.	2.1
2776	7.63	14.6	44.0	57.	19.0	34.0	6.4	802.	2.9
2781	5.90	11.4	36.0	60.	19.0	32.0	5.9	1049.	4.0
2787	5.29	10.2	31.0	58.	19.0	33.0	10.3	1205.	3.1
2795	6.07	12.0	37.0	60.	20.0	33.0	4.2	1021.	2.7
2804	6.51	12.3	38.0	58.	19.0	33.0	4.2	1092.	2.9
2805	5.77	11.1	35.0	61.	19.0	32.0	5.4	942.	2.9
2816	5.88	11.4	35.0	60.	19.0	32.0	5.5	1154.	4.0
2817	5.74	11.1	32.0	55.	19.0	35.0	7.3	970.	3.5
2839	5.79	11.1	35.0	60.	19.0	32.0	6.2	1018.	2.6
AVERAGE	6.008	11.59	35.68	59.3	19.32	32.68	6.55	986.1	3.09
STD. ERR.	0.116	0.22	0.62	0.6	0.15	0.32	0.32	27.5	0.12
GROUP 2 2724	6.19	11.9	36.0	58.	19.0	33.0	6.5	1055.	3.5
F 2734	5.57	10.8	33.0	60.	19.0	33.0	6.0	803.	3.1
2737	5.79	10.8	36.0	62.	19.0	30.0	4.7	931.	2.4
2750	5.80	10.3	34.0	59.	18.0	30.0	7.9	1182.	1.5
2752	6.31	12.5	37.0	58.	20.0	34.0	4.9	917.	1.5
2765	5.78	10.8	33.0	58.	19.0	32.0	6.4	624.	2.3
2767	6.20	11.5	35.0	57.	19.0	33.0	5.4	856.	2.6
2782	5.63	11.5	29.0	52.	20.0	39.0	6.8	1079.	2.8
2788	5.84	11.2	34.0	58.	19.0	33.0	9.0	1097.	3.2
2789	5.81	10.9	33.0	57.	19.0	33.0	5.6	1118.	1.8
2784	6.37	11.7	34.0	54.	18.0	34.0	7.6	673.	2.1
2802	5.44	10.5	32.0	60.	19.0	32.0	6.1	873.	1.9
2810	6.63	13.0	36.0	54.	20.0	36.0	6.1	948.	2.0
2812	5.72	10.9	32.0	55.	19.0	34.0	6.9	1015.	2.2
2821	5.84	12.0	36.0	62.	21.0	33.0	10.2	922.	2.0
2826	6.03	14.9	45.0	56.	19.0	33.0	5.1	754.	2.2
2842	5.88	11.6	36.0	60.	20.0	33.0	5.3	916.	2.0
AVERAGE	6.049	11.58	34.76	57.6	19.24	33.24	6.63	927.3	2.30
STD. ERR.	0.145	0.27	0.81	0.7	0.18	0.50	0.38	37.8	0.14

CLINICAL PATHOLOGY APPENDIX 1a

DATA LISTING

8850460 - FEMALES

PERIOD 1 VALUES

RESPONSE:		RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL.)	MCH (PG.)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)
GROUP 3	2726	7.34	8.3	26.0	35.	11.0	32.0	7.5	1157.	2.2
F	2738	6.85	9.5	27.0	39.	14.0	35.0	3.6	930.	2.1
	2741	6.92	9.5	30.0	44.	14.0	32.0	4.5	1062.	1.6
	2747	6.28	8.1	25.0	40.	13.0	32.0	8.0	998.	1.2
	2751	8.75	13.9	40.0	45.	16.0	35.0	6.3	749.	2.1
	2754	6.84	10.8	34.0	49.	16.0	32.0	5.5	1033.	1.6
	2762	6.64	6.9	21.0	31.	10.0	33.0	7.9	1351.	1.5
	2768	6.42	6.7	25.0	40.	14.0	34.0	6.0	1170.	1.6
	2771	6.07	7.2	23.0	38.	12.0	31.0	7.6	980.	1.7
	2780	7.52	12.3	37.0	49.	16.0	34.0	7.9	857.	2.1
	2800	6.09	10.1	32.0	52.	17.0	32.0	5.8	977.	1.2
	2801	8.28	11.2	32.0	39.	14.0	35.0	4.1	1182.	2.0
	2806	7.05	9.8	30.0	42.	14.0	33.0	7.3	1114.	1.1
	2814	6.09	6.8	21.0	35.	11.0	32.0	5.3	1407.	1.9
	2825	6.28	8.4	25.0	40.	13.0	34.0	9.0	1298.	2.4
	2845	7.03	10.8	31.0	44.	15.0	35.0	5.2	902.	1.0
AVERAGE		6.900	9.52	28.69	41.4	13.75	33.19	6.34	1072.9	1.71
STD. ERR.		0.185	0.49	1.38	1.4	0.50	0.34	0.40	45.5	0.11

DATA LISTING

8850460 - FEMALES

PERIOD 1 VALUES

RESPONSE: BANDS BASO EOS LYMPH MONO SEGS NUC.RBC \*  
 THOUSAND THOUSAND THOUSAND THOUSAND THOUSAND THOUSAND #/100WBC

NORM. RNG. -LO:

HI:

GROUP	ANIMAL	BANDS	BASO	EOS	LYMPH	MONO	SEGS	NUC.RBC
GROUP 1	2722	0.0	0.0	0.0	3.89	0.06	1.95	0.0
	2723	0.0	0.0	0.07	4.00	0.44	2.89	0.0
	2727	0.0	0.0	0.0	5.36	0.27	1.07	0.0
	2728	0.0	0.0	0.14	4.76	0.41	1.90	2.00
	2738	0.0	0.0	0.06	3.53	0.34	1.68	0.0
	2743	0.0	0.0	0.07	5.33	0.36	1.53	1.00
	2744	0.0	0.0	0.28	4.54	0.43	1.85	0.0
	2755	0.0	0.0	0.0	5.33	0.29	1.58	0.0
	2769	0.0	0.0	0.0	4.42	1.02	3.06	0.0
	2770	0.0	0.0	0.13	3.96	0.45	1.95	0.0
	2776	0.0	0.0	0.0	5.76	0.32	0.32	0.0
	2781	0.0	0.0	0.06	4.07	0.28	1.47	0.0
	2787	0.0	0.0	0.10	6.49	0.82	2.88	0.0
	2798	0.0	0.0	0.04	2.48	0.21	1.47	0.0
	2804	0.0	0.0	0.06	2.73	0.25	1.13	0.0
	2805	0.0	0.0	0.0	3.46	0.22	1.73	0.0
	2815	0.0	0.0	0.11	4.29	0.16	0.93	0.0
	2817	0.0	0.0	0.0	4.67	0.58	2.04	0.0
	2839	0.0	0.0	0.0	4.28	0.06	1.86	0.0

\* -M- equals 0 NRBC's counted.

AVERAGE 0.0 0.0 0.061 4.387 0.368 1.732 0.158  
 STD. ERR. 0.0 0.0 0.017 0.229 0.054 0.156 0.115

GROUP	ANIMAL	BANDS	BASO	EOS	LYMPH	MONO	SEGS	NUC.RBC
GROUP 2	2724	0.0	0.0	0.0	5.12	0.76	1.61	0.0
	2734	0.0	0.0	0.0	3.78	0.24	1.98	0.0
	2737	0.0	0.0	0.0	2.87	0.28	1.55	0.0
	2750	0.0	0.0	0.0	5.08	0.39	2.45	0.0
	2752	0.0	0.0	0.05	2.89	0.24	1.71	0.0
	2765	0.0	0.0	0.06	3.26	0.80	2.18	0.0
	2767	0.0	0.0	0.05	3.24	0.27	1.84	0.0
	2782	0.0	0.0	0.07	4.49	0.34	1.90	0.0
	2788	0.0	0.0	0.0	5.57	0.36	2.07	0.0
	2789	0.0	0.0	0.0	4.12	0.12	1.57	0.0
	2794	0.0	0.0	0.0	4.48	0.30	2.81	0.0
	2802	0.0	0.0	0.0	4.15	0.12	1.83	0.0
	2810	0.0	0.0	0.0	4.45	0.49	1.16	0.0
	2812	0.0	0.0	0.0	4.48	0.48	1.93	0.0
	2821	0.0	0.0	0.10	5.00	0.41	4.69	0.0
	2826	0.0	0.0	0.0	3.93	0.46	0.71	0.0
	2842	0.0	0.0	0.05	3.29	0.16	1.80	0.0

AVERAGE 0.0 0.0 0.023 4.246 0.372 1.988 0.0  
 STD. ERR. 0.0 0.0 0.008 0.252 0.051 0.203 0.0

DATA LISTING

BB50460 - FEMALES

PERIOD 1 VALUES

RESPONSE:		BANDS THOUSAND	BA50 THOUSAND	EOS THOUSAND	LYMPH THOUSAND	MONO THOUSAND	SEGS THOUSAND	NUC.RBC #/100WBC
GROUP 3	2726	0.0	0.0	0.0	4.97	0.30	2.63	0.0
. F	2738	0.0	0.0	0.0	2.23	0.22	1.15	0.0
	2741	0.0	0.0	0.0	2.43	0.09	1.98	0.0
	2747	0.0	0.0	0.0	5.38	0.08	2.56	0.0
	2751	0.0	0.0	0.13	4.47	0.38	1.32	0.0
	2754	0.0	0.0	0.11	3.35	0.27	1.76	0.0
	2762	0.0	0.0	0.08	5.69	0.32	1.82	0.0
	2768	0.0	0.0	0.0	3.48	0.06	2.46	0.0
	2771	0.0	0.0	0.0	5.40	0.23	1.98	0.0
	2780	0.0	0.0	0.0	5.13	0.32	2.45	0.0
	2800	0.0	0.0	0.0	4.06	0.12	1.62	0.0
	2801	0.0	0.0	0.0	2.91	0.20	0.98	0.0
	2806	0.0	0.0	0.07	4.60	0.07	2.55	0.0
	2814	0.0	0.0	0.0	3.07	0.05	2.17	0.0
	2825	0.0	0.0	0.0	5.22	0.18	3.60	0.0
	2848	0.0	0.0	0.0	4.16	0.21	0.83	0.0
AVERAGE		0.0	0.0	0.024	4.134	0.193	1.992	0.0
STD.ERR.		0.0	0.0	0.011	0.277	0.026	0.181	0.0

\* -H- equals 0 NRBC's counted.

DATA LISTING

8850460 - MALES

PERIOD 1 VALUES

RESPONSE:	RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL.)	MCH (PG.)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)
NORM. RNG. -LO:	8.4	10.6	31.0	47	15.0	31.0	3.0	406	
HI:	10.2	17.2	52.0	66	23.0	38.0	17.3	1634	
GROUP ANIMAL									
GROUP 1									
M									
2596	8.75	16.6	51.0	58.	19.0	33.0	7.7	1007.	2.0
2603	8.80	15.4	46.0	52.	18.0	34.0	5.2	1036.	1.6
2608	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-
2611	8.24	14.2	48.0	59.	17.0	29.0	9.9	719.	2.2
2619	8.39	15.8	48.0	58.	19.0	33.0	8.5	907.	1.6
2620	8.48	15.2	49.0	57.	18.0	31.0	6.2	866.	2.2
2623	8.81	15.1	46.0	52.	17.0	33.0	4.8	863.	2.5
2625	8.67	14.8	44.0	51.	17.0	34.0	6.9	1068.	2.1
2631	8.43	16.0	45.0	53.	19.0	36.0	9.9	851.	1.3
2639	8.63	15.7	45.0	52.	18.0	35.0	8.1	1159.	1.6
2637	8.97	16.0	47.0	52.	18.0	34.0	11.6	899.	2.8
2646	8.30	13.9	42.0	51.	17.0	33.0	8.7	1125.	3.2
2653	9.25	16.8	44.0	48.	18.0	38.0	7.8	987.	2.2
2654	9.93	17.9	51.0	52.	18.0	35.0	7.6	1020.	2.4
2660	9.44	16.6	44.0	46.	18.0	38.0	8.2	950.	1.6
2675	8.72	15.8	46.0	53.	18.0	35.0	7.7	923.	3.4
2680	9.09	16.4	46.0	50.	18.0	36.0	12.3	1174.	2.0
2681	8.68	15.0	44.0	50.	17.0	35.0	9.8	1011.	3.2
2682	8.95	15.8	44.0	49.	18.0	36.0	11.5	1119.	3.8
2690	8.92	16.3	46.0	52.	18.0	35.0	6.8	994.	2.0
2689	9.33	16.5	47.0	50.	18.0	35.0	16.5	1150.	2.4
2701	9.85	16.2	46.0	46.	16.0	35.0	10.9	1021.	2.6
2710	9.16	16.4	47.0	52.	18.0	35.0	8.7	950.	2.1
2711	8.99	15.2	45.0	49.	17.0	34.0	10.8	1088.	2.3
2718	8.20	15.8	46.0	50.	17.0	34.0	9.1	1185.	2.6
AVERAGE	8.916	15.81	46.13	51.8	17.78	34.42	8.87	1003.0	2.32
STD. ERR.	0.080	0.18	0.44	0.7	0.15	0.39	0.52	24.2	0.13

DATA LISTING

8850460 - MALES

PERIOD 1 VALUES

RESPONSE:	RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL.)	MCH (PG.)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)	
GROUP 2	2597	9.25	16.6	49.0	53.	18.0	34.0	5.6	1011.	2.0
M	2602	9.78	15.9	47.0	48.	16.0	34.0	8.6	1309.	2.1
	2606	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-
	2613	8.39	14.6	47.0	56.	17.0	31.0	8.8	914.	1.7
	2617	8.66	15.3	48.0	56.	18.0	32.0	7.3	959.	2.2
	2618	8.02	12.8	45.0	56.	16.0	29.0	7.3	872.	2.0
	2632	9.04	16.0	48.0	53.	18.0	34.0	8.8	1203.	2.1
	2636	8.98	15.6	48.0	54.	17.0	32.0	6.1	869.	2.9
	2638	8.92	16.7	48.0	54.	19.0	35.0	8.3	1176.	1.9
	2648	8.35	14.3	41.0	49.	17.0	35.0	10.6	1162.	2.8
	2650	9.86	17.2	50.0	50.	17.0	35.0	7.9	1292.	2.2
	2652	8.84	16.2	48.0	54.	18.0	34.0	8.2	1015.	2.0
	2657	9.67	16.3	45.0	46.	17.0	37.0	8.0	829.	2.0
	2662	8.75	15.7	44.0	51.	18.0	35.0	7.6	1022.	2.6
	2674	9.50	16.9	47.0	50.	18.0	36.0	8.0	881.	2.6
	2676	8.57	15.9	43.0	51.	19.0	37.0	9.7	854.	3.0
	2678	8.41	14.4	37.0	44.	17.0	39.0	7.8	827.	1.1
	2685	8.68	15.0	43.0	49.	17.0	35.0	8.6	1081.	5.4
	2689	9.82	16.5	45.0	46.	17.0	37.0	8.7	1012.	2.0
	2695	8.78	16.0	45.0	51.	18.0	36.0	11.0	1092.	2.4
	2696	8.62	15.0	44.0	51.	17.0	34.0	10.7	1294.	2.4
	2703	9.10	15.8	47.0	51.	17.0	34.0	13.1	960.	3.2
	2706	10.13	17.4	48.0	48.	17.0	36.0	11.2	1000.	2.2
	2708	9.19	16.6	45.0	49.	18.0	37.0	5.3	880.	3.0
	2714	9.92	16.8	49.0	50.	17.0	34.0	10.0	1161.	1.6
AVERAGE	9.050	15.81	45.88	50.8	17.42	34.67	8.63	1028.1	2.39	
STD. ERR.	0.118	0.22	0.60	0.7	0.16	0.45	0.37	31.3	0.16	

DATA LISTING

B050460 - MALES

PERIOD 1 VALUES

RESPONSE:	BANDS	BASO	EOS	LYMPH	MONO	SEGS	NUC.RBC *
	THOUSAND	THOUSAND	THOUSAND	THOUSAND	THOUSAND	THOUSAND	#/100WBC
NORM. RNG. -LO:							
HI:							
GROUP ANIMAL							
GROUP 1 2586	0.0	0.0	0.0	8.39	0.46	0.85	0.0
M 2603	0.0	0.0	0.05	3.85	0.10	1.20	0.0
2608	-M-						
2611	0.0	0.0	0.0	8.02	0.59	1.29	0.0
2615	0.0	0.0	0.08	7.22	0.68	0.51	0.0
2620	0.0	0.0	0.0	4.96	0.19	1.05	0.0
2623	0.0	0.0	0.0	3.31	0.10	1.39	0.0
2625	0.0	0.0	0.28	5.52	0.21	0.90	0.0
2631	0.0	0.0	0.0	8.81	0.69	0.40	0.0
2635	0.0	0.0	0.16	6.48	0.57	0.89	0.0
2637	0.0	0.0	0.0	10.67	0.35	0.58	0.0
2648	0.0	0.0	0.0	8.00	0.26	0.43	0.0
2653	0.0	0.0	0.08	6.08	0.78	0.66	0.0
2654	0.0	0.0	0.0	7.18	0.47	0.16	0.0
2680	0.0	0.0	0.18	6.07	0.49	1.48	0.0
2675	0.0	0.0	0.08	6.54	0.31	0.77	0.0
2680	0.0	0.0	0.12	9.72	0.25	2.21	0.0
2681	0.0	0.0	0.20	8.13	0.49	0.98	0.0
2682	0.0	0.0	0.0	10.00	0.57	0.92	0.0
2690	0.0	0.0	0.14	5.44	0.54	0.68	0.0
2699	0.0	0.0	0.16	13.20	0.99	2.14	0.0
2701	0.0	0.0	0.22	9.48	0.11	1.09	0.0
2710	0.0	0.0	0.0	7.83	0.35	0.52	0.0
2711	0.0	0.0	0.0	9.50	0.32	0.97	0.0
2718	0.0	0.0	0.0	7.28	0.36	1.46	0.0
AVERAGE	0.0	0.0	0.072	7.488	0.426	0.888	0.0
STD. ERR.	0.0	0.0	0.018	0.461	0.046	0.102	0.0

\* -M- equals 0 NRBC's counted.

DATA LISTING

B850460 - MALES

PERIOD 1 VALUES

RESPONSE:		BANDS	BASO	EOS	LYMPH	MONO	SEGS	MJC.RBC *
		THOUSAND	THOUSAND	THOUSAND	THOUSAND	THOUSAND	THOUSAND	#/100WBC
GROUP 2	2597	0.0	0.0	0.0	4.31	0.22	1.06	0.0
M	2602	0.0	0.0	0.0	7.57	0.34	0.69	0.0
	2606	-M-						
	2613	0.0	0.0	0.09	7.13	0.35	1.23	0.0
	2617	0.0	0.0	0.0	6.42	0.29	0.58	0.0
	2618	0.0	0.0	0.07	6.20	0.51	0.51	0.0
	2632	0.0	0.0	0.18	6.78	0.44	1.41	0.0
	2638	0.0	0.0	0.06	4.82	0.37	0.85	0.0
	2638	0.0	0.0	0.06	6.56	0.41	1.24	0.0
	2648	0.0	0.0	0.11	6.80	0.85	0.85	0.0
	2650	0.0	0.0	0.0	6.24	0.55	1.11	0.0
	2652	0.0	0.0	0.0	7.22	0.25	0.74	0.0
	2657	0.0	0.0	0.06	6.64	0.56	0.72	0.0
	2662	0.0	0.0	0.06	6.46	0.53	0.53	0.0
	2674	0.0	0.0	0.16	6.88	0.24	0.72	0.0
	2676	0.0	0.0	0.10	6.34	0.76	0.48	0.0
	2678	0.0	0.0	0.06	6.32	0.23	1.17	0.0
	2685	0.0	0.0	0.09	7.22	0.34	0.95	0.0
	2689	0.0	0.0	0.17	6.87	0.26	1.39	0.0
	2695	0.0	0.0	0.11	6.91	0.44	1.54	0.0
	2696	0.0	0.0	0.11	6.20	0.64	0.75	0.0
	2703	0.0	0.0	0.13	11.00	0.65	1.31	0.0
	2706	0.0	0.0	0.0	6.52	0.45	1.23	0.0
	2708	0.0	0.0	0.11	4.61	0.21	0.37	0.0
	2714	0.0	0.0	0.20	7.60	0.50	1.70	0.0
	AVERAGE	0.0	0.0	0.063	7.151	0.435	0.964	0.0
	STD. ERR.	0.0	0.0	0.012	0.320	0.036	0.075	0.0

\* -M- equals 0 NRBC's counted.

DATA LISTING

8850460 - MALES

PERIOD 1 VALUES

RESPONSE:	RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL.)	MCH (PG.)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)	
GROUP 3	2598	8.43	8.4	14.0	22.	8.0	38.0	6.6	2161.	8.5
M	2604	5.68	6.2	20.0	34.	11.0	32.0	1.8	63.	3.6
	2609	7.12	8.4	17.0	24.	9.0	37.0	23.9	2585.	8.3
	2612	9.10	15.4	46.0	51.	17.0	33.0	5.1	946.	2.0
	2619	8.38	12.2	34.0	41.	15.0	36.0	5.4	977.	3.6
	2621	7.30	6.1	17.0	23.	8.0	36.0	4.5	1398.	5.0
	2634	8.82	8.9	24.0	27.	10.0	36.0	5.2	1620.	5.0
	2640	8.20	11.6	35.0	43.	14.0	33.0	9.0	1039.	3.3
	2641	9.38	10.4	27.0	28.	11.0	39.0	5.7	1759.	6.7
	2645	9.09	10.5	27.0	30.	12.0	39.0	7.6	1706.	4.8
	2647	9.08	9.9	24.0	27.	11.0	41.0	16.1	2072.	8.0
	2649	5.94	6.9	16.0	27.	12.0	42.0	15.3	3909.	7.2
	2655	8.38	9.3	22.0	26.	11.0	43.0	6.0	3518.	9.2
	2656	8.45	8.8	22.0	25.	10.0	41.0	6.8	2946.	6.6
	2661	8.29	12.7	36.0	43.	15.0	36.0	12.1	1052.	3.0
	2665	9.34	12.5	32.0	34.	13.0	39.0	8.9	1275.	4.0
	2671	10.27	12.9	34.0	33.	13.0	36.0	6.0	1198.	4.0
	2672	6.87	7.5	18.0	26.	11.0	43.0	8.5	4410.	11.2
	2679	6.80	7.3	18.0	26.	11.0	42.0	8.2	3788.	7.6
	2683	9.64	13.4	36.0	39.	14.0	36.0	5.0	1231.	4.2
	2686	2.74	3.3	8.0	28.	12.0	43.0	6.8	3248.	14.8
	2694	8.15	11.8	30.0	32.	13.0	40.0	9.0	1167.	5.0
	2697	8.67	12.7	37.0	42.	15.0	35.0	9.8	1048.	2.2
	2705	5.58	6.6	15.0	27.	12.0	44.0	9.4	4283.	12.0
	2715	5.41	5.9	14.0	26.	11.0	42.0	9.7	3703.	12.7
AVERAGE	7.764	9.37	25.00	31.4	11.96	38.56	8.58	2124.1	6.38	
STD. ERR.	0.349	0.63	1.92	1.5	0.45	0.70	0.91	249.2	0.69	
GROUP 4	2658	2.48	1.8	6.0	24.	8.0	32.0	7.9	623.	2.4
AVERAGE	2.480	1.90	6.00	24.0	8.00	32.00	7.90	623.0	2.35	
STD. ERR.	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-	

DATA LISTING

8850460 - MALES

PERIOD 1 VALUES

RESPONSE:		BANDS	BASO	EOS	LYMPH	MONO	SEGS	NUC.RBC *
		THOUSAND	THOUSAND	THOUSAND	THOUSAND	THOUSAND	THOUSAND	#/100WBC
GROUP 3	2588	0.0	0.0	0.0	4.62	0.33	1.65	0.0
M	2604	0.0	0.0	0.02	1.60	0.05	0.13	0.0
	2609	0.0	0.0	0.24	9.58	0.72	13.38	0.0
	2612	0.0	0.0	0.0	3.77	0.36	0.97	0.0
	2619	0.0	0.0	0.08	4.75	0.11	0.49	0.0
	2621	0.0	0.0	0.0	3.64	0.13	0.72	0.0
	2634	0.0	0.0	0.0	4.47	0.16	0.57	0.0
	2640	0.0	0.0	0.0	7.29	0.27	1.44	0.0
	2641	0.0	0.0	0.0	4.84	0.0	0.85	0.0
	2645	0.0	0.0	0.08	6.08	0.30	1.14	0.0
	2647	0.0	0.0	0.0	10.14	0.81	5.15	0.0
	2649	0.0	0.0	0.31	9.64	0.61	4.74	1.00
	2655	0.0	0.0	0.0	5.10	0.18	0.72	0.0
	2658	0.0	0.0	0.0	6.86	0.18	1.78	0.0
	2661	0.0	0.0	0.12	10.53	0.73	0.73	0.0
	2665	0.0	0.0	0.0	8.28	0.0	0.62	0.0
	2671	0.0	0.0	0.08	5.46	0.18	0.30	0.0
	2672	0.0	0.0	0.0	7.14	0.68	0.68	0.0
	2679	0.0	0.0	0.08	7.05	0.25	0.82	0.0
	2683	0.0	0.0	0.0	4.25	0.30	0.45	0.0
	2686	0.0	0.0	0.07	5.58	0.41	0.75	0.0
	2694	0.0	0.0	0.27	7.47	0.36	0.90	1.00
	2697	0.0	0.0	0.10	6.62	0.49	0.59	0.0
	2705	0.0	0.0	0.09	7.90	0.28	1.13	0.0
	2715	0.0	0.0	0.0	8.15	0.48	1.07	1.00
	AVERAGE	0.0	0.0	0.059	6.512	0.334	1.670	0.120
	STD.ERR.	0.0	0.0	0.018	0.458	0.046	0.544	0.066
GROUP 4	2689	0.0	0.0	0.08	3.32	0.83	3.87	5.00
	AVERAGE	0.0	0.0	0.079	3.318	0.632	3.871	5.000
	STD.ERR.	-M-						

\* -M- equals 0 NRBC's counted.

DATA LISTING

8850460 - NON-PREGNANT FEMALES

PERIOD 1 VALUES

RESPONSE:	RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL.)	MCH (PG.)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)
NORM. RNG. -LO:	8.4	10.6	31.0	47	15.0	31.0	3.0	408	
HI:	10.2	17.2	52.0	66	23.0	38.0	17.3	1634	
GROUP 1									
ANIMAL									
F 2746	7.29	14.2	45.0	62.	20.0	31.0	11.9	843.	1.5
2759	7.77	15.0	46.0	59.	19.0	33.0	5.7	897.	1.4
2764	7.43	15.0	46.0	62.	20.0	33.0	6.0	729.	2.6
2778	7.69	14.6	44.0	58.	19.0	33.0	4.1	784.	2.4
2791	7.33	14.1	42.0	59.	19.0	33.0	4.3	910.	3.9
2835	7.42	13.8	44.0	59.	19.0	32.0	6.2	1013.	2.4
AVERAGE	7.488	14.45	44.80	59.7	19.33	32.50	6.37	862.7	2.37
STD. ERR.	0.080	0.20	0.62	0.8	0.21	0.34	1.16	41.0	0.37
GROUP 2									
F 2730	7.25	14.1	44.0	61.	19.0	32.0	4.6	981.	2.7
2732	7.88	15.6	47.0	60.	20.0	33.0	5.0	770.	2.9
2740	7.32	13.6	43.0	59.	19.0	31.0	3.9	989.	2.8
2742	7.23	14.6	45.0	63.	20.0	32.0	3.3	827.	1.8
2753	7.06	14.6	44.0	62.	21.0	34.0	7.7	613.	1.6
2773	7.75	14.6	45.0	57.	19.0	33.0	4.1	760.	2.1
2778	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-
2822	7.65	15.0	47.0	61.	20.0	32.0	8.3	665.	2.8
AVERAGE	7.448	14.59	45.00	60.4	19.71	32.43	5.27	800.7	2.39
STD. ERR.	0.117	0.24	0.58	0.8	0.29	0.37	0.74	54.5	0.20
GROUP 3									
F 2725	8.52	11.4	33.0	38.	13.0	35.0	3.8	756.	4.0
2733	7.50	14.0	42.0	56.	19.0	33.0	7.9	746.	3.2
2779	7.49	14.3	43.0	58.	19.0	33.0	4.3	827.	2.7
2783	7.62	14.1	42.0	55.	18.0	33.0	3.6	818.	2.2
2784	8.62	13.0	39.0	45.	15.0	33.0	4.8	998.	2.5
2807	7.92	12.7	40.0	54.	17.0	31.0	4.6	1169.	2.1
2813	8.31	12.6	39.0	47.	15.0	32.0	3.2	1038.	1.1
2828	8.46	12.1	34.0	40.	14.0	35.0	5.6	955.	1.0
AVERAGE	8.005	13.02	39.00	49.1	16.38	33.13	4.72	913.4	2.35
STD. ERR.	0.182	0.37	1.31	2.7	0.86	0.48	0.83	53.3	0.36

CLINICAL PATHOLOGY APPENDIX I K

DATA LISTING

B650460 - NON-PREGNANT FEMALES

PERIOD 1 VALUES

RESPONSE:	RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL.)	MCH (PG.)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)	
GROUP 4	2728	2.13	1.8	8.0	23.	9.0	38.0	8.7	1740.	2.2
F	2735	1.98	1.8	8.0	23.	9.0	40.0	6.8	1533.	2.4
	2745	1.94	1.5	4.0	23.	8.0	34.0	5.2	874.	2.4
	2756	1.78	1.5	4.0	23.	8.0	37.0	5.2	911.	2.7
	2758	1.82	1.7	4.0	24.	9.0	40.0	7.1	1636.	2.3
	2761	1.94	1.6	8.0	24.	8.0	35.0	7.8	1323.	2.1
	2772	1.72	1.4	4.0	23.	8.0	35.0	9.8	774.	2.0
	2792	2.48	1.9	8.0	22.	8.0	35.0	3.8	1454.	1.9
	2793	1.92	1.6	8.0	23.	8.0	36.0	4.0	1656.	1.6
	2811	1.71	1.7	4.0	24.	10.0	42.0	4.0	1903.	2.0
	2820	2.23	1.8	8.0	24.	8.0	34.0	3.3	1128.	1.6
	2824	2.48	2.3	8.0	23.	9.0	40.0	5.4	2485.	2.0
	2843	1.84	1.6	8.0	23.	8.0	36.0	3.8	1448.	2.1
AVERAGE	2.004	1.71	4.69	23.2	8.46	37.08	5.76	1451.2	2.10	
STD. ERR.	0.070	0.06	0.17	0.2	0.18	0.74	0.58	130.2	0.08	

DATA LISTING

8850460 - NON-PREGNANT FEMALES

PERIOD 1 VALUES

RESPONSE:	BANDS	BA50	EOS	LYMPH	MONO	SEGS	NUC.RBC	*
	THOUSAND	THOUSAND	THOUSAND	THOUSAND	THOUSAND	THOUSAND	#/100WBC	
NORM. RNG. -LO:								
HI:								
GROUP	ANIMAL							
GROUP 1	2746	0.0	0.0	0.0	10.11	0.83	0.95	0.0
F	2759	0.0	0.0	0.0	4.86	0.23	0.51	0.0
	2764	0.0	0.0	0.0	5.04	0.12	0.84	0.0
	2775	0.0	0.0	0.0	3.53	0.12	0.45	0.0
	2791	0.0	0.0	0.04	3.70	0.13	0.43	0.0
	2835	0.0	0.0	0.0	5.27	0.25	0.68	0.0
	AVERAGE	0.0	0.0	0.007	5.435	0.280	0.645	0.0
	STD. ERR.	0.0	0.0	0.007	0.983	0.113	0.088	0.0
GROUP 2	2730	0.0	0.0	0.05	4.14	0.18	0.23	0.0
F	2732	0.0	0.0	0.0	4.20	0.25	0.55	0.0
	2740	0.0	0.0	0.0	3.00	0.27	0.62	0.0
	2742	0.0	0.0	0.03	2.84	0.23	0.20	0.0
	2753	0.0	0.0	0.08	6.62	0.23	0.77	0.0
	2773	0.0	0.0	0.04	3.57	0.12	0.37	0.0
	2776	-M-	-M-	-M-	-M-	-M-	-M-	-M-
	2822	0.0	0.0	0.0	7.55	0.33	0.41	0.0
	AVERAGE	0.0	0.0	0.028	4.560	0.232	0.451	0.0
	STD. ERR.	0.0	0.0	0.011	0.688	0.025	0.079	0.0
GROUP 3	2725	0.0	0.0	0.04	3.08	0.19	0.49	0.0
F	2733	0.0	0.0	0.08	6.71	0.39	0.71	0.0
	2779	0.0	0.0	0.0	3.22	0.13	0.95	0.0
	2783	0.0	0.0	0.04	2.85	0.11	0.50	0.0
	2784	0.0	0.0	0.0	4.08	0.10	0.82	0.0
	2807	0.0	0.0	0.05	3.59	0.28	0.69	0.0
	2813	0.0	0.0	0.03	2.94	0.06	0.16	0.0
	2828	0.0	0.0	0.11	4.42	0.22	0.84	0.0
	AVERAGE	0.0	0.0	0.043	3.878	0.185	0.621	0.0
	STD. ERR.	0.0	0.0	0.013	0.449	0.039	0.085	0.0

‡ -M- equals 0 NRBC's counted.

DATA LISTING

0850460 - NON-PREGNANT FEMALES

PERIOD 1 VALUES

RESPONSE:		BANDS	BASO	EOS	LYMPH	MONO	SEGS	NUC.RBC *
		THOUSAND	THOUSAND	THOUSAND	THOUSAND	THOUSAND	THOUSAND	#/100WBC
GROUP 4	2728	0.0	0.0	0.0	5.65	1.39	1.65	3.00
F	2735	0.0	0.0	0.0	4.90	0.46	1.43	2.00
	2748	0.0	0.0	0.10	3.99	0.42	1.09	3.00
	2758	0.0	0.0	0.0	2.81	0.89	1.30	2.00
	2758	0.0	0.0	0.0	4.28	0.71	2.13	0.0
	2761	0.0	0.0	0.0	5.77	0.84	1.09	2.00
	2772	0.0	0.0	0.0	5.49	0.78	3.53	2.00
	2792	0.0	0.0	0.0	2.74	0.38	0.68	0.0
	2793	0.0	0.0	0.0	2.92	0.68	0.40	0.0
	2811	0.0	0.0	0.0	2.76	0.36	0.88	0.0
	2820	0.0	0.0	0.03	2.14	0.40	0.73	1.00
	2824	0.0	0.0	0.0	3.40	0.59	1.40	0.0
	2843	0.0	0.0	0.0	2.93	0.49	0.38	0.0
	AVERAGE	0.0	0.0	0.011	3.805	0.662	1.284	1.154
	STD. ERR.	0.0	0.0	0.008	0.350	0.084	0.232	0.337

\* -M- equals 0 NRBC's counted.

DATA LISTING

STUDY B050460 - FEMALES

PERIOD 1 VALUES

RESPONSE:	GLUC (MG/DL)	BUN (MG/DL)	CREAT. (MG/DL)	TP (GM/DL)	ALB (GM/DL)	GLOB (GM/DL)	A/G	ALK (IU/L)	AST (IU/L)	ALT (IU/L)	TBILI (MG/DL)
NORM. RNG. -LO:	53	10	0.5	4.0	2.9			33	58	18	0.0
HI:	110	21	0.9	7.1	4.3			221	202	70	0.33
GROUP 1 ANIMAL											
F 2722	48.	13.4	0.6	5.5	3.6	1.9	1.89	105.	158.	51.	0.1
2723	95.	21.3	0.7	6.1	3.7	2.4	1.54	42.	254.	74.	0.2
2727	87.	16.7	0.6	5.9	4.0	1.9	2.11	70.	168.	59.	0.2
2729	116.	17.2	0.7	5.6	3.8	1.8	2.11	95.	106.	39.	0.1
2739	93.	21.7	0.6	5.8	3.7	2.1	1.76	128.	227.	82.	0.1
2743	124.	22.5	0.7	6.0	3.9	2.1	1.86	106.	154.	42.	0.4
2744	94.	16.3	0.5	5.9	4.1	1.8	2.28	103.	215.	79.	0.1
2755	103.	15.8	0.7	5.7	3.9	1.9	2.00	54.	139.	89.	0.1
2769	112.	18.1	0.7	6.1	4.0	2.1	1.90	141.	285.	101.	0.1
2770	125.	9.4	0.6	6.0	4.0	2.0	2.00	72.	82.	31.	0.1
2776	145.	21.4	0.7	7.6	4.9	2.7	1.81	208.	315.	137.	0.1
2781	74.	16.9	0.5	5.8	3.8	2.0	1.90	66.	152.	43.	0.1
2787	120.	16.1	0.6	5.0	3.4	1.6	2.13	58.	86.	39.	0.1
2795	102.	16.7	0.5	5.9	3.8	2.1	1.81	134.	145.	45.	0.1
2804	147.	19.4	0.7	6.9	4.5	2.4	1.88	99.	171.	70.	0.1
2805	109.	13.0	0.6	6.0	3.9	2.1	1.86	70.	136.	51.	0.1
2815	108.	17.1	0.7	6.3	4.2	2.1	2.00	107.	109.	54.	0.1
2817	156.	13.6	0.6	5.5	3.8	1.7	2.24	44.	81.	53.	0.1
2839	90.	20.6	0.6	5.6	3.7	1.9	1.95	70.	103.	30.	0.1
AVERAGE	107.8	17.22	0.63	5.86	3.93	2.03	1.949	93.3	162.9	61.5	0.13
STD. ERR.	6.0	0.78	0.02	0.13	0.08	0.06	0.040	9.3	15.9	6.2	0.02
GROUP 2 ANIMAL											
F 2724	100.	15.2	0.6	5.8	3.8	2.0	1.90	58.	300.	78.	0.1
2734	120.	18.7	0.6	5.5	2.6	1.8	1.89	65.	212.	58.	0.1
2737	92.	14.8	0.6	5.1	3.3	1.8	1.83	38.	128.	39.	0.2
2750	82.	16.4	0.6	5.3	3.6	1.7	2.12	43.	124.	46.	0.1
2752	99.	16.2	0.6	5.8	3.8	2.0	1.90	55.	132.	34.	0.1
2765	95.	6.5	0.5	5.3	3.6	1.7	2.12	79.	303.	68.	0.1
2767	94.	13.0	0.6	5.7	3.8	1.8	2.00	80.	119.	38.	0.0
2782	108.	18.0	0.6	5.5	3.5	2.0	1.75	46.	98.	39.	0.1
2788	109.	15.3	0.6	5.4	3.7	1.7	2.18	93.	150.	40.	0.1
2789	108.	8.9	0.6	6.0	3.9	2.1	1.86	94.	212.	51.	0.1
2794	110.	20.7	0.7	5.2	3.6	1.6	2.25	62.	71.	35.	0.1
2802	149.	14.6	0.6	5.7	3.9	1.8	2.17	103.	103.	35.	0.1
2810	126.	14.1	0.7	6.7	4.6	2.1	2.19	49.	68.	47.	0.1
2812	89.	11.5	0.6	6.0	3.9	2.1	1.86	69.	86.	34.	0.1
2821	98.	19.8	0.6	6.7	4.3	2.4	1.79	50.	179.	38.	0.1
2826	121.	16.8	0.7	6.8	4.6	2.2	2.09	71.	135.	51.	0.2
2842	123.	11.8	0.7	6.6	4.4	2.2	2.00	122.	96.	37.	0.1
AVERAGE	107.6	14.72	0.62	5.83	3.88	1.95	1.994	69.2	147.9	45.2	0.11
STD. ERR.	3.9	0.88	0.01	0.14	0.09	0.05	0.038	5.7	17.4	3.1	0.01

CLINICAL PATHOLOGY APPENDIX II

DATA LISTING

STUDY B850460 - FEMALES

PERIOD 1 VALUES

RESPONSE:	GLUC (MG/DL)	BUN (MG/DL)	CREAT. (MG/DL)	TP (GM/DL)	ALB (GM/DL)	GLOB (GM/DL)	A/G	ALK (IU/L)	AST (IU/L)	ALT (IU/L)	TBILI (MG/DL)
GROUP 3											
2726	82.	12.7	0.6	8.6	4.1	2.5	1.64	164.	106.	41.	0.2
F											
2738	102.	16.5	0.7	8.0	3.4	1.6	2.13	48.	87.	34.	0.1
2741	94.	16.9	0.6	5.4	3.6	1.8	2.00	87.	105.	35.	0.1
2747	85.	19.3	0.5	5.7	3.7	2.0	1.85	124.	164.	51.	0.0
2751	233.	19.1	0.8	6.7	4.6	2.1	2.19	58.	106.	56.	0.2
2754	103.	16.5	0.6	5.7	3.6	2.1	1.71	54.	159.	55.	0.1
2762	113.	12.5	0.6	6.1	3.8	2.3	1.65	50.	168.	39.	0.2
2768	144.	13.4	0.6	5.6	3.7	1.9	1.95	85.	77.	28.	0.1
2771	98.	20.2	0.7	5.2	3.6	1.6	2.25	55.	161.	24.	0.1
2780	89.	13.5	0.7	5.8	4.1	1.7	2.41	28.	200.	27.	0.1
2800	92.	15.8	0.5	5.8	4.1	1.7	2.41	100.	143.	52.	0.1
2801	163.	15.0	0.7	8.1	5.1	3.0	1.70	152.	211.	67.	0.2
2808	151.	11.2	0.5	6.1	4.0	2.1	1.90	43.	158.	48.	0.1
2814	138.	19.3	0.7	6.0	4.1	1.9	2.16	117.	137.	38.	0.1
2825	95.	14.8	0.7	6.0	3.8	2.2	1.73	113.	121.	34.	0.0
2845	100.	17.8	0.6	6.0	3.9	2.1	1.86	109.	69.	29.	0.0
AVERAGE	118.2	15.91	0.63	6.88	3.95	2.04	1.971	86.7	135.7	41.1	0.11
STD. ERR.	9.8	0.69	0.02	0.18	0.11	0.09	0.065	10.2	10.5	3.1	0.02

CLINICAL PATHOLOGY APPENDIX II A

DATA LISTING

STUDY B850460 - FEMALES

PERIOD 1 VALUES

RESPONSE:	NA (MEQ/L)	K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	FE (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	VIT. B12 (PG/ML)	FOLIC A. (NG/ML)
NORM. RNG. -LO:	141	3.8	10.2	6.8		19	6		
HI:	159	7.1	12.2	9.0		122	30		
GROUP ANIMAL									
GROUP 1									
F 2722	140.	7.7	8.7	4.3	63.	88.	707.	-M-	-M-
2723	138.	8.0	9.6	4.5	118.	110.	905.	617.	69.
2727	140.	6.2	10.2	5.8	166.	111.	255.	-M-	-M-
2729	138.	7.3	9.7	2.5	20.	77.	231.	-M-	-M-
2739	141.	7.0	10.1	5.5	121.	90.	460.	-M-	-M-
2743	142.	6.6	11.7	4.8	135.	105.	558.	-M-	-M-
2744	139.	5.4	9.9	5.1	224.	83.	452.	602.	79.
2755	142.	5.8	10.3	4.6	138.	81.	434.	-M-	-M-
2769	143.	6.3	11.1	3.7	68.	79.	416.	566.	41.
2770	138.	5.9	9.4	2.3	55.	89.	588.	-M-	-M-
2776	142.	7.2	12.0	6.9	344.	90.	281.	-M-	-M-
2781	142.	6.7	7.7	3.7	88.	80.	504.	-M-	-M-
2787	141.	5.7	8.7	4.6	94.	110.	824.	-M-	-M-
2795	142.	6.3	8.5	5.3	119.	104.	629.	-M-	-M-
2804	146.	6.6	12.0	6.8	121.	109.	207.	907.	76.
2805	142.	7.2	10.6	4.9	161.	126.	491.	-M-	-M-
2815	143.	7.2	10.6	3.5	166.	94.	632.	-M-	-M-
2817	140.	4.2	9.4	3.2	47.	101.	891.	-M-	-M-
2839	142.	4.8	9.6	4.4	42.	72.	381.	-M-	-M-
AVERAGE	141.1	6.43	9.89	4.55	120.5	95.2	518.2	673.0	66.3
STD. ERR.	0.5	0.22	0.27	0.29	17.2	3.3	48.3	78.7	8.7
GROUP 2									
F 2724	138.	5.6	9.9	3.2	62.	108.	867.	-M-	-M-
2734	141.	4.8	9.9	3.5	24.	107.	840.	-M-	-M-
2737	141.	5.3	8.7	2.2	51.	114.	795.	-M-	-M-
2750	140.	6.0	9.9	2.8	3.	83.	684.	-M-	-M-
2752	140.	6.0	9.5	2.5	75.	82.	612.	-M-	-M-
2765	143.	5.1	8.1	3.5	11.	44.	160.	369.	41.
2767	143.	4.9	9.1	2.9	16.	83.	683.	-M-	-M-
2782	137.	4.9	9.3	3.0	83.	116.	982.	-M-	-M-
2788	139.	5.0	9.1	5.3	40.	95.	792.	557.	52.
2789	142.	5.9	9.1	2.9	33.	91.	617.	-M-	-M-
2794	143.	5.5	9.3	2.9	73.	71.	462.	-M-	-M-
2802	145.	6.0	11.1	4.7	17.	80.	174.	-M-	-M-
2810	144.	4.4	11.0	4.4	178.	88.	422.	637.	73.
2812	141.	5.1	9.3	1.8	5.	100.	962.	-M-	-M-
2821	141.	4.5	9.9	4.2	102.	66.	225.	-M-	-M-
2826	146.	4.3	9.8	3.9	287.	91.	87.	-M-	-M-
2842	143.	6.3	11.0	5.6	100.	91.	345.	-M-	-M-
AVERAGE	141.6	5.27	9.65	3.49	68.2	89.4	571.1	521.0	55.3
STD. ERR.	0.6	0.15	0.20	0.26	17.5	4.4	71.1	79.4	9.4

DATA LISTING

STUDY B850480 - FEMALES

PERIOD 1 VALUES

RESPONSE:	NA (MEQ/L)	K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	FE (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	VIT. B12 (PG/ML)	FOLIC A. (NG/ML)
GROUP 3									
F									
2728	141.	7.0	10.5	4.3	4.	76.	221.	-M-	-M-
2738	138.	6.2	9.4	3.8	1.	81.	355.	-M-	-M-
2741	144.	5.4	10.0	2.5	4.	87.	691.	-M-	-M-
2747	143.	4.8	9.6	3.1	0.	63.	407.	-M-	-M-
2751	144.	4.3	10.8	5.1	445.	72.	73.	-M-	-M-
2754	140.	8.0	10.7	3.3	18.	93.	687.	-M-	-M-
2762	142.	5.2	10.1	5.2	3.	51.	374.	-M-	-M-
2768	138.	5.3	10.2	5.4	14.	61.	298.	-M-	-M-
2771	143.	4.9	9.8	4.3	0.	57.	287.	-M-	-M-
2780	141.	4.4	8.9	5.3	45.	74.	57.	-M-	-M-
2800	141.	6.3	9.8	4.5	20.	60.	282.	529.	42.
2801	143.	6.3	11.8	5.2	29.	102.	137.	-M-	-M-
2806	141.	5.9	9.3	7.1	9.	62.	357.	580.	58.
2814	138.	4.4	10.1	5.2	0.	70.	416.	473.	44.
2825	141.	4.4	9.4	3.5	9.	91.	360.	-M-	-M-
2845	142.	7.1	10.5	4.4	2.	81.	190.	-M-	-M-
AVERAGE	141.2	5.62	10.06	4.51	37.7	73.8	324.5	527.3	48.0
STD. ERR.	0.5	0.28	0.18	0.28	27.3	3.6	45.2	30.9	5.0

DATA LISTING

STUDY B850460 - MALES

PERIOD 1 VALUES

RESPONSE:	GLUC (MG/DL)	BUN (MG/DL)	CREAT. (MG/DL)	TP (GM/DL)	ALB (GM/DL)	GLOB (GM/DL)	A/G	ALK (IU/L)	AST (IU/L)	ALT (IU/L)	TBILI (MG/DL)
NORM. RNG. -LO:	53	10	0.5	4.0	2.9			33	58	18	0.0
HI:	110	21	0.9	7.1	4.3			221	202	70	0.33
GROUP ANIMAL											
GROUP 1											
M											
2596	257.	17.2	0.6	6.8	4.4	2.4	1.83	107.	181.	77.	0.2
2603	334.	18.3	0.8	6.7	4.4	2.3	1.81	78.	98.	44.	0.1
2608	278.	12.0	0.6	6.5	4.0	2.8	1.60	315.	178.	144.	0.1
2611	183.	16.0	0.7	6.3	3.9	2.4	1.63	135.	272.	135.	0.2
2615	173.	11.7	0.7	6.3	3.8	2.5	1.52	132.	130.	50.	0.2
2620	183.	12.8	0.7	6.7	4.1	3.0	1.40	87.	13.	42.	0.2
2623	332.	13.6	0.6	7.2	4.2	3.0	1.40	201.	133.	120.	0.1
2625	129.	9.5	0.6	6.2	4.3	1.9	2.26	120.	136.	54.	0.1
2631	230.	14.8	0.7	6.6	4.1	2.8	1.64	172.	104.	59.	0.3
2635	177.	15.6	0.7	6.4	4.2	2.2	1.91	112.	137.	132.	0.3
2637	284.	14.2	0.7	6.7	4.3	2.4	1.79	125.	169.	33.	0.3
2646	225.	11.0	0.6	6.5	4.2	2.3	1.83	100.	66.	30.	0.3
2653	228.	15.7	0.7	6.8	4.3	2.5	1.72	86.	120.	47.	0.2
2654	270.	16.4	0.7	6.8	4.2	2.6	1.62	144.	102.	57.	0.3
2660	208.	12.8	0.8	6.6	3.9	2.7	1.44	57.	136.	54.	0.3
2675	225.	17.0	0.6	6.7	4.2	2.5	1.68	132.	106.	32.	0.2
2680	163.	13.6	0.7	6.9	4.1	2.8	1.46	68.	61.	20.	0.3
2681	200.	7.9	0.6	6.4	3.8	2.6	1.46	91.	104.	40.	0.3
2682	358.	14.2	0.7	6.2	3.9	2.3	1.70	70.	81.	40.	0.4
2690	285.	12.6	0.7	6.6	4.0	2.6	1.54	68.	97.	33.	0.3
2699	194.	16.5	0.8	6.8	4.3	2.5	1.72	108.	1157.	936.	0.4
2701	277.	15.7	0.7	6.8	4.3	2.5	1.72	109.	83.	47.	0.3
2710	227.	17.8	0.8	6.7	4.3	2.4	1.79	95.	97.	37.	0.2
2711	228.	14.5	0.7	6.8	4.3	2.5	1.72	88.	66.	35.	0.3
2718	187.	23.4	0.7	7.1	4.1	3.0	1.37	127.	85.	28.	0.3
AVERAGE	232.2	14.58	0.70	6.64	4.14	2.50	1.677	117.1	155.3	93.0	0.25
STD. ERR.	11.8	0.63	0.01	0.05	0.04	0.05	0.041	10.8	42.8	35.8	0.02

CLINICAL PATHOLOGY APPENDIX III

DATA LISTING

STUDY B850460 - MALES

PERIOD 1 VALUES

RESPONSE:	GLUC (MG/DL)	BUN (MG/DL)	CREAT. (MG/DL)	TP (GM/DL)	ALB (GM/DL)	GLOB (GM/DL)	A/G	ALK (IU/L)	AST (IU/L)	ALT (IU/L)	TBILI (MG/DL)
GROUP 2											
M											
2597	212.	14.4	0.7	7.3	4.4	2.9	1.52	104.	130.	63.	0.1
2602	260.	20.4	0.7	7.0	4.1	2.9	1.41	106.	116.	68.	0.1
2608	78.	17.6	0.6	6.6	3.7	2.9	1.28	185.	625.	268.	0.1
2613	180.	14.0	0.7	5.9	3.9	2.0	1.95	96.	180.	64.	0.1
2617	131.	15.8	0.7	6.8	4.3	2.5	1.72	129.	221.	71.	0.1
2618	152.	11.4	0.7	6.5	4.1	2.4	1.71	83.	214.	102.	0.1
2632	168.	15.6	0.7	6.6	4.3	2.3	1.87	136.	91.	43.	0.1
2636	250.	17.1	0.7	7.0	4.5	2.5	1.80	151.	211.	124.	0.1
2638	192.	14.8	0.7	6.2	3.9	2.3	1.70	100.	84.	38.	0.3
2648	197.	12.8	0.6	6.3	3.9	2.4	1.63	85.	114.	40.	0.3
2650	173.	13.1	0.6	6.7	4.0	2.6	1.48	170.	164.	84.	0.3
2652	317.	13.6	0.7	6.6	4.3	2.3	1.87	82.	138.	42.	0.3
2657	250.	13.6	0.7	6.8	4.5	2.3	1.96	59.	123.	36.	0.2
2662	384.	19.4	0.8	7.0	4.7	2.3	2.04	252.	105.	66.	0.3
2674	257.	18.1	0.7	6.8	4.4	2.4	1.83	133.	126.	65.	0.3
2676	180.	13.0	0.7	6.4	4.1	2.3	1.78	48.	105.	40.	0.3
2678	148.	16.7	0.7	6.1	3.8	2.3	1.65	46.	128.	26.	0.2
2685	226.	12.2	0.7	6.8	3.9	2.9	1.34	65.	106.	41.	0.3
2689	406.	15.5	0.6	7.2	4.4	2.6	1.57	79.	89.	47.	0.3
2695	316.	13.3	0.7	6.6	4.3	2.3	1.87	127.	144.	55.	0.3
2698	185.	14.8	0.7	6.7	4.4	2.3	1.91	62.	110.	35.	0.3
2703	204.	13.6	0.7	6.6	4.1	2.5	1.54	70.	277.	111.	0.3
2708	296.	15.6	0.8	7.0	4.3	2.7	1.59	80.	95.	31.	0.3
2708	214.	22.1	0.7	6.7	4.1	2.6	1.53	125.	275.	88.	0.3
2714	167.	17.1	0.6	6.7	4.1	2.6	1.58	50.	84.	28.	0.3
AVERAGE	221.7	15.42	0.68	6.68	4.18	2.49	1.691	104.9	162.6	67.1	0.23
STD. ERR.	15.4	0.83	0.01	0.07	0.05	0.05	0.040	9.7	22.3	9.9	0.02

CLINICAL PATHOLOGY APPENDIX II *R*

DATA LISTING

STUDY B850480 - MALES

PERIOD 1 VALUES

RESPONSE:	GLUC (MG/DL)	BUN (MG/DL)	CREAT. (MG/DL)	TP (GM/DL)	ALB (GM/DL)	GLOB (GM/DL)	A/G	ALK (IU/L)	AST (IU/L)	ALT (IU/L)	TBILI (MG/DL)
GROUP 3											
2598	256.	11.7	0.7	6.0	4.2	1.8	2.33	73.	133.	40.	0.1
M 2604	184.	15.5	0.8	6.3	4.2	2.1	2.00	129.	232.	85.	0.1
2608	219.	19.6	0.7	6.3	3.5	2.8	1.25	205.	203.	104.	0.1
2612	200.	14.9	0.7	6.4	4.2	2.2	1.91	118.	99.	45.	0.2
2619	138.	19.0	0.7	5.8	4.1	1.7	2.41	78.	132.	33.	0.1
2621	186.	15.9	0.7	5.9	3.9	2.0	1.95	137.	168.	43.	0.1
2634	211.	15.4	0.6	6.5	4.1	2.4	1.71	100.	122.	64.	0.1
2640	139.	13.1	0.6	6.8	4.1	2.7	1.52	180.	215.	45.	0.1
2641	156.	19.3	0.8	6.6	4.3	2.3	1.87	75.	158.	35.	0.3
2645	207.	16.7	0.6	5.9	4.0	1.9	2.11	159.	166.	35.	0.2
2647	187.	11.6	0.6	6.3	4.0	2.3	1.74	87.	147.	38.	0.2
2649	221.	12.0	0.7	5.8	3.9	1.9	2.05	115.	-M-	-M-	0.2
2655	202.	16.2	0.7	6.3	4.3	2.0	2.15	101.	126.	55.	0.3
2656	269.	13.6	0.7	6.0	4.2	1.8	2.33	66.	88.	35.	0.3
2661	195.	15.1	0.7	6.7	3.8	1.9	2.00	123.	111.	44.	0.3
2665	274.	13.4	0.7	6.2	4.1	2.1	1.95	76.	98.	38.	0.2
2671	394.	18.2	0.8	6.3	4.2	2.1	2.00	131.	97.	41.	0.3
2672	367.	11.8	0.7	6.4	4.0	2.4	1.67	118.	104.	41.	0.3
2679	489.	11.4	0.6	6.2	4.1	2.1	1.95	45.	123.	40.	0.4
2683	249.	14.6	0.7	6.3	4.2	2.1	2.00	84.	90.	34.	0.3
2686	278.	15.8	0.7	6.3	4.1	2.2	1.86	136.	83.	40.	0.3
2694	193.	18.2	0.7	6.2	4.2	2.0	2.10	106.	130.	65.	0.3
2697	280.	13.1	0.8	6.4	4.1	2.3	1.78	76.	124.	35.	0.3
2705	159.	13.8	0.7	5.8	3.9	1.9	2.05	108.	339.	201.	0.4
2715	249.	16.5	0.7	6.3	4.1	2.2	1.86	66.	96.	35.	0.3
AVERAGE	236.1	15.06	0.70	6.20	4.07	2.13	1.942	107.7	141.0	53.0	0.23
STD. ERR.	16.3	0.50	0.01	0.05	0.03	0.05	0.050	7.5	11.9	7.3	0.02
GROUP 4											
2659	138.	27.1	0.5	5.7	3.9	1.8	2.17	325.	186.	135.	-M-
AVERAGE	138.0	27.10	0.50	5.70	3.90	1.80	2.170	325.0	196.0	135.0	-M-
STD. ERR.	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-

DATA LISTING

STUDY 8850460 - MALES

PERIOD 1 VALUES

RESPONSE:	NA (MEQ/L)	K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	FE (MG/DL)	CHOL. (MG/DL)	TG (MG/DL)	VIT. B12 (PG/ML)	FOLIC A. (NG/ML)
NORM. RNG. -LO:	141	3.9	10.2	6.8		18	6		
HI:	189	7.1	12.2	9.0		122	30		
GROUP ANIMAL									
GROUP 1									
M									
2598	147.	7.4	11.6	6.9	182.	86.	81.	-M-	-M-
2603	144.	8.2	11.1	6.9	121.	59.	25.	-M-	-M-
2608	145.	8.3	11.8	8.1	258.	78.	82.	-M-	-M-
2611	144.	4.8	10.0	5.4	231.	78.	97.	819.	65.
2615	147.	7.2	11.1	7.1	283.	52.	160.	-M-	-M-
2620	145.	4.2	9.7	4.8	184.	87.	43.	-M-	-M-
2623	143.	7.7	11.9	6.7	261.	87.	92.	931.	90.
2625	146.	5.7	9.8	5.1	141.	83.	53.	-M-	-M-
2631	145.	5.8	11.0	5.0	168.	82.	165.	-M-	-M-
2635	146.	5.7	10.6	5.0	149.	95.	56.	-M-	-M-
2637	145.	4.9	10.4	5.5	132.	75.	70.	-M-	-M-
2646	147.	7.6	11.9	7.8	131.	105.	75.	-M-	-M-
2653	145.	8.4	11.0	7.1	173.	79.	67.	-M-	-M-
2664	147.	7.9	12.3	7.4	163.	68.	137.	-M-	-M-
2660	143.	8.7	10.7	6.8	119.	107.	30.	-M-	-M-
2675	147.	7.7	11.7	6.6	171.	143.	279.	-M-	-M-
2680	145.	7.2	11.1	5.7	127.	145.	102.	840.	72.
2681	148.	5.1	10.2	6.6	137.	76.	30.	-M-	-M-
2682	147.	5.3	10.7	6.6	114.	99.	82.	-M-	-M-
2690	146.	7.1	10.8	6.3	147.	78.	35.	-M-	-M-
2699	146.	7.5	11.4	7.6	102.	117.	38.	-M-	-M-
2701	147.	8.0	11.7	6.4	147.	89.	136.	926.	87.
2710	149.	5.2	11.5	6.8	189.	112.	86.	698.	83.
2711	148.	7.2	11.6	6.8	194.	108.	121.	-M-	-M-
2718	145.	9.1	11.8	6.5	141.	154.	82.	-M-	-M-
AVERAGE	145.9	6.88	11.08	6.47	166.6	93.7	89.0	842.8	79.4
STD. ERR.	0.3	0.28	0.14	0.18	9.6	5.1	11.2	42.6	4.7

DATA LISTING

STUDY B850460 - MALES

PERIOD 1 VALUES

RESPONSE:	NA (MEQ/L)	K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	FE (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	VIT. B12 (PG/ML)	FOLIC A. (NG/ML)
GROUP 2 2597	144.	8.7	11.0	8.9	159.	87.	47.	-M-	-M-
M 2602	144.	7.4	12.3	8.1	135.	67.	65.	-M-	-M-
2606	145.	7.8	9.7	8.8	225.	53.	155.	-M-	-M-
2613	144.	4.7	9.8	6.2	282.	47.	70.	-M-	-M-
2617	145.	6.8	10.4	8.4	255.	78.	81.	-M-	-M-
2618	145.	4.8	9.4	4.0	222.	84.	105.	-M-	-M-
2632	144.	5.8	10.8	4.9	188.	70.	71.	985.	72.
2636	143.	9.3	11.2	7.5	149.	72.	130.	-M-	-M-
2638	144.	8.2	11.2	6.5	115.	143.	63.	-M-	-M-
2648	142.	7.4	11.1	6.9	88.	74.	84.	-M-	-M-
2650	148.	6.5	10.8	7.3	<del>88</del> 231 60.	38.	-M-	-M-	
2652	147.	6.9	11.8	7.1	214.	119.	115.	-M-	-M-
2657	146.	7.3	11.3	6.1	132.	99.	91.	-M-	-M-
2662	147.	7.8	12.9	7.9	188.	97.	128.	-M-	-M-
2674	146.	7.8	12.0	6.4	210.	123.	307.	-M-	-M-
2678	143.	8.1	10.8	6.8	145.	72.	114.	-M-	-M-
2678	143.	4.5	9.4	4.6	121.	63.	131.	705.	95.
2685	146.	7.6	11.1	7.3	80.	55.	36.	-M-	-M-
2689	148.	7.3	12.4	7.5	221.	97.	194.	1222.	81.
2695	145.	5.5	11.1	5.5	139.	89.	77.	-M-	-M-
2696	146.	9.3	11.0	7.5	119.	126.	86.	-M-	-M-
2703	145.	7.2	11.1	7.2	143.	121.	51.	857.	85.
2706	147.	7.8	11.7	6.8	138.	108.	89.	798.	73.
2708	146.	8.4	10.8	7.5	174.	68.	86.	-M-	-M-
2714	146.	8.2	11.1	8.2	113.	81.	55.	-M-	-M-
AVERAGE	145.2	7.32	11.03	6.70	164.8	86.5	98.8	913.4	81.2
STD. ERR.	0.3	0.28	0.18	0.23	10.8	5.2	11.5	89.5	4.2

DATA LISTING

STUDY B850460 - MALES

PERIOD 1 VALUES

RESPONSE:	NA (MEQ/L)	K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	FE (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	VIT.B12 (PG/ML)	FOLIC A. (NG/ML)
GROUP 3									
M 2598	145.	7.5	11.5	8.2	16.	61.	40.	-M-	-M-
2604	143.	8.1	9.9	6.0	60.	48.	88.	1042.	92.
2609	145.	7.6	11.5	8.2	28.	32.	89.	-M-	-M-
2612	143.	8.1	11.3	8.6	94.	67.	26.	-M-	-M-
2618	147.	4.8	9.6	4.4	33.	66.	39.	-M-	-M-
2621	145.	6.0	10.3	7.1	34.	55.	40.	-M-	-M-
2634	144.	6.5	11.2	7.4	61.	63.	66.	-M-	-M-
2640	145.	5.1	10.1	6.0	47.	67.	59.	-M-	-M-
2641	142.	7.2	10.5	7.6	19.	75.	31.	893.	87.
2645	145.	5.2	9.4	4.8	24.	58.	46.	-M-	-M-
2647	144.	5.3	10.2	6.2	81.	48.	45.	-M-	-M-
2649	147.	7.2	11.3	7.9	24.	50.	46.	-M-	-M-
2655	147.	7.4	11.3	7.9	80.	57.	27.	766.	76.
2656	146.	7.2	11.4	8.8	25.	52.	37.	-M-	-M-
2661	143.	4.8	9.7	6.8	148.	55.	58.	-M-	-M-
2665	147.	6.9	11.1	6.7	63.	60.	30.	-M-	-M-
2671	143.	7.0	12.4	7.1	122.	95.	118.	-M-	-M-
2672	146.	8.9	12.2	9.4	14.	87.	84.	-M-	-M-
2679	145.	9.0	12.3	9.0	19.	65.	79.	-M-	-M-
2683	148.	7.0	10.3	6.8	182.	68.	56.	880.	86.
2686	144.	6.9	10.9	6.8	9.	58.	77.	-M-	-M-
2684	146.	6.7	10.2	6.9	113.	54.	56.	695.	106.
2697	143.	5.4	10.8	5.9	136.	64.	117.	-M-	-M-
2705	147.	6.3	10.6	6.9	100.	76.	60.	-M-	-M-
2715	146.	7.0	11.4	7.9	14.	68.	89.	-M-	-M-
AVERAGE	145.0	6.76	10.86	7.17	61.8	61.9	60.1	855.2	89.4
STD.ERR.	0.3	0.24	0.17	0.25	9.8	2.6	5.3	59.4	4.9
GROUP 4									
2659	150.	5.2	10.4	7.4	78.	83.	334.	-M-	-M-
AVERAGE	150.0	5.20	10.40	7.40	78.0	83.0	334.0	-M-	-M-
STD.ERR.	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-

CLINICAL PATHOLOGY APPENDIX II 4

DATA LISTING

STUDY B85-0460 - NON-PREGNANT FEMALES

PERIOD 1 VALUES

RESPONSE:	GLUC (MG/DL)	BUN (MG/DL)	CREAT. (MG/DL)	TP (GM/DL)	ALB (GM/DL)	GLOB (GM/DL)	A/G	ALK (IU/L)	AST (IU/L)	ALT (IU/L)	TBILI (MG/DL)	
NORM. RNG. -LO:	89	10	0.8	4.0	2.9			33	58	18	0.0	
HI:	110	21	0.9	7.1	4.3			221	202	70	0.33	
GROUP 1	ANIMAL											
F	2746	151.	18.6	0.8	8.0	5.2	2.8	1.86	41.	401.	220.	0.2
	2788	167.	21.8	0.7	7.4	4.8	2.6	1.85	77.	156.	63.	0.2
	2764	297.	12.5	0.7	6.4	4.2	2.2	1.91	53.	98.	36.	0.1
	2775	216.	20.3	0.8	7.7	4.9	2.8	1.75	64.	249.	156.	0.1
	2791	224.	17.2	0.7	7.3	4.6	2.7	1.70	71.	85.	43.	0.1
	2835	171.	18.8	0.7	8.3	5.3	3.0	1.77	68.	152.	80.	0.2
	AVERAGE	204.3	18.15	0.73	7.52	4.83	2.68	1.807	62.3	190.2	99.7	0.15
	STD. ERR.	22.0	1.28	0.02	0.27	0.16	0.11	0.032	5.4	48.3	29.8	0.02
GROUP 2	ANIMAL											
F	2730	169.	16.0	0.8	7.7	5.1	2.6	1.96	44.	324.	170.	0.2
	2732	201.	15.4	0.8	7.3	4.8	2.5	1.92	70.	158.	59.	0.1
	2740	222.	17.8	0.8	7.6	4.7	2.8	1.62	49.	163.	32.	0.2
	2742	198.	16.2	0.8	7.9	5.2	2.7	1.93	47.	183.	113.	0.1
	2753	151.	17.9	0.7	6.8	4.6	2.2	2.09	49.	246.	117.	0.2
	2773	209.	11.7	0.8	7.5	4.8	2.7	1.78	57.	532.	223.	0.1
	2778	134.	18.9	0.7	7.4	4.9	2.5	1.96	89.	198.	100.	0.2
	2822	159.	16.2	0.8	7.0	4.6	2.4	1.92	57.	212.	84.	0.4
	AVERAGE	180.4	16.39	0.77	7.40	4.84	2.56	1.898	57.8	252.0	112.2	0.19
	STD. ERR.	11.1	0.84	0.02	0.13	0.08	0.08	0.050	5.3	44.3	21.5	0.04
GROUP 3	ANIMAL											
F	2725	122.	18.9	0.7	6.8	4.7	2.1	2.24	46.	765.	250.	0.2
	2733	230.	15.4	0.7	7.3	4.8	2.5	1.92	59.	190.	98.	0.2
	2779	170.	18.7	0.7	8.1	5.3	2.8	1.89	120.	126.	63.	0.2
	2783	192.	21.4	0.7	8.9	5.8	3.1	1.87	36.	371.	180.	0.2
	2784	182.	21.6	0.8	9.2	5.4	3.8	1.42	35.	397.	184.	0.2
	2807	177.	15.4	0.7	7.8	4.8	3.0	1.60	62.	89.	56.	0.1
	2813	343.	18.6	0.8	8.6	5.6	3.0	1.87	113.	214.	164.	0.1
	2829	166.	15.3	0.6	7.9	5.2	2.7	1.93	32.	224.	107.	0.1
	AVERAGE	194.0	18.16	0.71	8.07	5.20	2.87	1.842	62.9	297.0	137.7	0.18
	STD. ERR.	23.8	0.91	0.02	0.28	0.14	0.17	0.086	12.3	76.8	23.9	0.02

DATA LISTING

STUDY 885-0480 - NON-PREGNANT FEMALES

PERIOD 1 VALUES

RESPONSE:	GLUC (MG/DL)	BUN (MG/DL)	CREAT. (MG/DL)	TP (GM/DL)	ALB (GM/DL)	GLOB (GM/DL)	A/G	ALK (IU/L)	AST (IU/L)	ALT (IU/L)	TBILI (MG/DL)
GROUP 4											
2728	134.	43.0	0.6	5.7	4.1	1.6	2.56	99.	164.	60.	-M-
F											
2735	121.	36.7	0.5	5.4	3.5	1.9	1.84	250.	154.	87.	-M-
2745	158.	30.8	0.5	5.5	3.7	1.8	2.06	278.	186.	113.	-M-
2756	154.	30.8	0.4	4.7	3.3	1.4	2.36	383.	226.	192.	-M-
2758	148.	32.8	0.5	5.4	3.7	1.7	2.18	360.	146.	113.	-M-
2761	138.	23.6	0.5	5.8	4.0	1.8	2.22	267.	178.	127.	-M-
2772	117.	31.7	0.5	4.8	3.3	1.5	2.20	246.	454.	244.	-M-
2792	215.	33.9	0.6	6.3	4.1	2.2	1.86	147.	128.	61.	-M-
2793	135.	39.7	0.5	5.6	4.1	1.5	2.73	114.	210.	107.	-M-
2811	129.	42.7	0.6	5.8	3.9	1.9	2.05	241.	179.	88.	-M-
2820	132.	29.2	0.6	6.2	4.1	2.1	1.95	157.	139.	80.	-M-
2824	195.	30.9	0.6	6.2	4.3	1.9	2.26	166.	144.	65.	-M-
2843	167.	43.3	0.6	5.9	4.2	1.7	2.47	211.	200.	151.	-M-
AVERAGE	149.5	34.55	0.54	5.64	3.87	1.77	2.211	224.5	192.9	114.5	-M-
STD.ERR.	8.0	1.69	0.02	0.14	0.09	0.07	0.074	24.2	23.2	15.0	-M-

DATA LISTING

STUDY B85-0460 - NON-PREGNANT FEMALES

PERIOD 1 VALUES

RESPONSE:	NA (MEQ/L)	K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	FE (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	VIT. B12 (PG/ML)	FOLIC A. (NG/ML)
NORM. RNG. -LO:	141	3.9	10.2	6.6		18	6		
HI:	159	7.1	12.2	9.0		122	30		
GROUP ANIMAL									
GROUP 1 2746	142.	4.1	11.5	5.4	281.	98.	86.	-M-	-M-
F 2759	147.	7.0	11.5	5.4	256.	72.	94.	-M-	-M-
2764	146.	6.2	10.7	7.0	276.	64.	63.	-M-	-M-
2775	145.	5.1	11.7	6.3	239.	98.	155.	1161.	105.
2791	147.	6.7	11.4	5.6	172.	103.	79.	-M-	-M-
2835	146.	6.6	12.5	7.8	278.	101.	127.	-M-	-M-
AVERAGE	145.5	5.95	11.55	6.25	250.3	89.3	100.7	1161.0	105.0
STD. ERR.	0.8	0.46	0.24	0.40	17.0	6.9	13.9	-M-	-M-
GROUP 2 2730	143.	6.3	11.9	5.5	251.	82.	143.	970.	81.
F 2732	147.	5.3	10.9	5.0	257.	95.	109.	1026.	78.
2740	143.	5.8	11.6	6.4	221.	103.	86.	-M-	-M-
2742	143.	5.8	11.5	4.7	238.	90.	91.	-M-	-M-
2753	145.	4.2	10.4	4.5	281.	56.	186.	-M-	-M-
2773	149.	6.3	11.5	7.5	250.	82.	69.	-M-	-M-
2778	140.	5.4	10.6	7.3	225.	73.	128.	-M-	-M-
2822	149.	4.4	10.9	5.6	291.	69.	107.	-M-	-M-
AVERAGE	144.9	5.44	11.16	5.81	251.7	82.5	114.9	998.0	79.5
STD. ERR.	1.1	0.28	0.19	0.40	6.7	5.5	13.1	28.0	1.5
GROUP 3 2725	143.	5.7	10.2	3.9	201.	97.	76.	-M-	-M-
F 2733	146.	4.9	10.9	4.9	481.	78.	77.	713.	78.
2779	149.	6.3	12.1	7.1	236.	96.	110.	-M-	-M-
2783	146.	5.2	12.6	6.3	285.	120.	203.	1120.	95.
2784	144.	5.8	12.4	6.9	356.	110.	132.	-M-	-M-
2807	145.	4.8	12.1	6.0	145.	139.	199.	-M-	-M-
2813	142.	7.8	14.1	8.1	173.	96.	154.	-M-	-M-
2829	143.	5.8	12.0	5.8	171.	109.	130.	-M-	-M-
AVERAGE	144.7	5.79	12.05	6.12	256.0	105.6	135.1	916.5	86.5
STD. ERR.	0.8	0.34	0.41	0.46	40.4	6.5	17.2	203.5	8.5

DATA LISTING

STUDY B85-0460 - NON-PREGNANT FEMALES

PERIOD 1 VALUES

RESPONSE:	NA (MEQ/L)	K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	FE (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	VIT. B12 (PG/ML)	FOLIC A. (NG/ML)
GROUP 4									
F									
2728	138.	5.7	11.0	7.4	51.	51.	344.	-M-	-M-
2735	137.	4.8	11.2	7.6	174.	132.	995.	-M-	-M-
2745	146.	5.6	10.8	8.0	70.	70.	370.	-M-	-M-
2756	137.	5.5	10.9	7.4	100.	82.	629.	-M-	-M-
2758	138.	5.8	11.2	7.3	154.	98.	928.	-M-	-M-
2761	142.	5.1	11.1	7.4	89.	90.	565.	-M-	-M-
2772	142.	4.3	10.0	5.2	97.	74.	503.	-M-	-M-
2782	145.	5.8	11.5	7.8	57.	60.	389.	-M-	-M-
2783	140.	5.6	11.0	8.2	96.	70.	558.	-M-	-M-
2811	141.	5.1	10.7	6.5	84.	75.	567.	-M-	-M-
2820	141.	4.4	10.4	6.7	67.	66.	503.	-M-	-M-
2824	139.	5.9	11.0	7.4	33.	52.	247.	-M-	-M-
2843	142.	6.0	10.5	7.0	78.	72.	598.	-M-	-M-
AVERAGE	140.6	5.35	10.87	7.22	88.5	76.3	553.6	-M-	-M-
STD. ERR.	0.8	0.16	0.11	0.21	10.8	5.9	59.2	-M-	-M-

Grp Id.	Animal Id.	Sex	Platelets	Polychromasia	Anisocytosis	Poikilocytosis	Rbc crenated	Smudge cells
0001	2722	F		1+	1+		OCC	
	2723			1+	1+		FEU	
	2727		PLTS NORM	1+	1+		MOD	
	2729		PLTS NORM	1+	1+		FEU	
	2739			1+	1+		OCC	
	2743			1+	1+		FEU	
	2744		PLTS NORM	1+	1+		OCC	
	*2746		PLTS NORM	NOTED	1+		RARE	
	2755		PLTS NORM	1+	1+		MOD	
	*2759		PLTS NORM	1+	1+		FEU	
	*2764			1+	1+		MOD	
	2769		PLTS NORM	1+	1+		MOD	
	2770			1+	1+		OCC	
	*2775			NOTED	1+		OCC	
	2776			1+	1+		MOD	
	2781			1+	1+		FEU	
	2787		PLTS NORM	NOTED	1+			
	*2791			NOTED	1+		OCC	
	2795			1+	1+		FEU	
	2804			1+	1+		MOD	
	2805			NOTED	1+		MOD	
	2815			NOTED	2+		MOD	
	2817			NOTED	1+			
	*2835			NOTED	1+		MANY	
	2839			NOTED	1+		FEU	
	2596	M		NOTED	1+		MANY	
	2603			NOTED	1+		MANY	
	2611			NOTED	1+		FEU	
	2615			NOTED	1+		MOD	
	2620		PLTS NORM	NOTED	1+		MOD	
	2623			NOTED	1+		MANY	
	2625			NOTED	3+		MOD	
	2631			NOTED	1+		OCC	
	2635		PLTS NORM	NOTED	1+		FEU	
	2637			NOTED	1+		MOD	
	2646			NOTED	1+		MANY	
	2653		PLTS NORM	NOTED	1+		FEU	
	2654			NOTED	1+		MOD	
	2660			NOTED	1+		FEU	
	2675			NOTED	1+		FEU	
	2680		PLTS NORM	NOTED	1+		RARE	
	2681			NOTED	1+		MOD	
	2682			NOTED	1+		FEU	
	2690			NOTED	1+		OCC	
	2699			NOTED	1+		FEU	
	2701		PLTS NORM	NOTED	1+		FEU	
	2710			NOTED	1+		MANY	
	2711			NOTED	1+		MOD	
	2718			NOTED	1+		MOD	
0002	2724	F		1+	1+		OCC	
	*2730			NOTED	2+		MOD	
	*2732			NOTED	1+		MANY	
	2734		PLTS NORM	1+	1+		OCC	

\* These are non-pregnant females.

CLINICAL PATHOLOGY APPENDIX III

Grp Id.	Animal Id.	Sex	Platelets	Polychromasia	Anisocytosis	Poikilocytosis	Rbc crenated	Smudge cells
0002	2737	F	PLTS NORM	1+	1+			
	*2740			NOTED	1+		MOD	
	*2742			NOTED	1+		OCC	
	2750		PLTS NORM	1+	1+		RARE	
	2752		PLTS NORM	1+	1+		OCC	
	*2753		PLTS NORM	NOTED	1+		MOD	
	2765			1+	1+		OCC	
	2767			1+	1+		FEW	
	*2773		PLTS NORM	1+	1+		MANY	
	2782		PLTS NORM	NOTED	1+		OCC	
	2788		PLTS NORM	1+	1+		RARE	
	2789			1+	1+		RARE	
	2794			NOTED	1+		OCC	
	2802			1+	2+		MOD	
	2810			NOTED	1+		RARE	
	2812			NOTED	1+		RARE	
	2821			NOTED	1+		MANY	
	*2822			1+	1+		MOD	
	2826			NOTED	1+		MANY	
	2842			NOTED	1+		FEW	
	2597	M		NOTED	1+		MOD	
	2602			NOTED	1+		MANY	
	2613		PLTS NORM	NOTED	1+		FEW	
	2617		PLTS NORM	NOTED	1+		FEW	
	2618			NOTED			OCC	
	2632			NOTED	1+		MANY	
	2636			NOTED	1+		MANY	
	2638			NOTED	2+		FEW	
	2648			NOTED	1+		FEW	
	2650			NOTED	1+		FEW	
	2652			NOTED	1+		FEW	
	2657		PLTS NORM	NOTED	1+		MOD	
	2662			NOTED	1+		FEW	
	2674			NOTED	1+		MOD	
	2676		PLTS NORM	NOTED	1+		OCC	
	2678		PLTS NORM	NOTED	2+			
	2685			NOTED	1+		FEW	
	2689			NOTED	1+		FEW	
	2695			NOTED	1+		FEW	
	2696			NOTED	1+		MOD	
	2703			NOTED	1+		MOD	
	2706			NOTED	1+		MOD	
	2708			NOTED	1+		FEW	
	2714		PLTS NORM	NOTED	1+		MANY	
0003	*2725	F	PLTS NORM	1+	1+		FEW	
	2726		PLTS NORM	1+	1+		MANY	
	*2733			1+	1+		MANY	
	2738			1+	1+			
	2741		PLTS NORM	1+			FEW	
	2747		PLTS NORM	1+	1+		FEW	
	2751			1+	1+		MANY	
	2754			1+	1+			
	2762		PLTS NORM	1+	2+		OCC	

CLINICAL PATHOLOGY APPENDIX III

\* These are all pregnant females.

Grp	Animal	Sex	Platelets	Polychro	Aniso	Poikilo	Rbc	Smudge
d.	Id.			masia	cytosis	cytosis	crenated	cells
0003	2768	F	PLTS NORM	1+	1+			
	2771		PLTS NORM	1+	1+		FEW	
*	2779			1+	1+		MOD	
*	2780			1+	1+		MOD	
*	2783		PLTS NORM	NOTED	1+		FEW	
*	2784			NOTED	1+		FEW	
	2800			1+	1+		MOD	
	2801		PLTS NORM	1+	1+		MOD	
	2806		PLTS NORM	1+	1+		MOD	
*	2807		PLTS NORM	NOTED	1+		FEW	
*	2813			NOTED	1+		MOD	
	2814			NOTED	2+		FEW	
	2825			NOTED	1+		MOD	
*	2829		PLTS NORM	NOTED	1+		FEW	
	2845		PLTS NORM	NOTED	1+		OCC	
	2598	M		2+	2+	1+	FEW	
	2604			NOTED	3+	2+	MOD	
	2609			2+	2+		OCC	
	2612			NOTED	1+		MANY	
	2619		PLTS NORM	NOTED	1+			
	2621			2+	2+	1+	MOD	
	2634			1+	1+		MOD	
	2640			NOTED	1+		MANY	
	2641			1+	2+	1+	FEW	
	2645			1+	2+	2+	FEW	
	2647		PLTS NORM	1+	2+	2+	FEW	
	2649		PLTS NORM	1+	2+	2+	FEW	
	2655		PLTS NORM	1+	2+	2+	OCC	
	2656		PLTS NORM	1+	2+	2+	OCC	
	2661		PLTS NORM	NOTED	1+		OCC	
	2665			NOTED	1+		FEW	
	2671			NOTED	2+	1+	FEW	
	2672			1+	2+	2+	OCC	
	2679			1+	1+	3+	OCC	
	2683		PLTS NORM	NOTED	1+		MOD	
	2686		PLTS NORM	2+	2+	3+	OCC	
	2694		PLTS NORM	NOTED	2+	1+	FEW	
	2697			NOTED	1+	1+	OCC	
	2705		PLTS NORM	2+	2+	2+	OCC	
	2715		PLTS NORM	3+	2+	2+		

CLINICAL PATHOLOGY APPENDIX III C

0004	2728	F		3+	4+	1+		
	2735			3+	4+	1+		
	2745		PLTS NORM	3+	4+	1+		
	2756		PLTS NORM	3+	4+	1+		
	2758		PLTS NORM	3+	4+	1+		
*	2761		PLTS NORM	3+	4+	2+		
	2772		PLTS NORM	3+	4+	2+		
	2792		PLTS NORM	3+	4+	2+		
	2793			3+	4+	2+		
	2811		PLTS NORM	3+	4+	2+		
	2820		PLTS NORM	3+	4+	2+		
	2824		PLTS NORM	3+	4+	2+		
	2843			3+	4+	2+		

\* These are non-pregnant females.

Report: CLPXPRESS CLINICAL PATHOLOGY - HEMATOLOGY ALPHA RESULTS Run date: 07/22/86  
Study (Ref) no.: B85-0460 Run time: 08:20  
Period: 1 File no.: 85000452

Grp	Animal		Polychro	Aniso	Poikilo	Rbc	Smudge	
1.	Id.	Sex	Platelets	masia	cytosis	cytosis	crenated	cells
0004	2659	M	PLTS NORM	4+	4+			

CLINICAL PATHOLOGY APPENDIX III d

Grp d.	Animal Id.	Plt Sex	Plt Decrease	Plt Increase	Plt mkd Decrease	Plt mkd Increase	Plt clumped	Plt giant
0001	2722	F					MANY	
	2723						MANY	
	2727						OCC	
	2729						OCC	
	2739						MOD	
	2743						MOD	
	2744						OCC	RARE
	2755						OCC	
	*2764						MANY	OCC
	2769						OCC	
	2770						MANY	
	*2775						MOD	
	2776						MOD	
	2781						MOD	
	*2791						MANY	
	2795						MOD	
	2804						MANY	
	2805						MOD	
	2815						MANY	
	2817						MANY	
	*2835						MOD	
	2839						MOD	
	2596	M					MANY	
	2603						MANY	
	2611						MOD	
	2615						MANY	
	2623						MANY	
	2625						MOD	
	2631						MOD	
	2637						MANY	
	2646						MANY	
	2654						MOD	
	2660						MOD	
	2675						MANY	
	2681						MOD	
	2682						MOD	
	2690						MANY	
	2699						MANY	
	2710						MANY	
	2711						MOD	
	2718						MOD	
0002	2724	F					MOD	
	*2730						MOD	
	*2732						MANY	
	2734						OCC	
	2737						OCC	
	*2740						MOD	
	*2742						MOD	
	2752						RARE	
	2765						MOD	
	2767						MANY	
	*2773						FEW	
	2789						MOD	

CLINICAL PATHOLOGY APPENDIX III

\* These are non-pregnant females.

Grp Id.	Animal Id.	Pit Sex	Pit Decrease	Pit Increase	Pit mkd Decrease	Pit mkd Increase	Pit clumped	Pit giant
0002	2794	F					MANY	
	2802						MANY	
	2810						MOD	
	2812						MANY	
	2821						MOD	
	*2822						MOD	
	2826						MANY	
	2842						MOD	
	2597	M					MANY	
	2602						MANY	
	2618						MOD	
	2632						MOD	
	2636						MANY	
	2638						MOD	
	2648						MOD	
	2650						MANY	
	2652						MOD	
	2662						MANY	
	2674						MANY	
	2676						FEW	
	2685						MANY	
	2689						MANY	
	2695						MANY	
	2696						MOD	
	2703						MANY	
	2706						MANY	
	2708						MANY	
0003	2726	F					OCC	
	*2733						MANY	
	2738						MANY	
	2751						MOD	
	2754						MOD	
	2771						OCC	
	*2779						MANY	
	*2780						MOD	
	*2783						OCC	
	*2784						MOD	
	2800						MOD	
	*2813						MOD	
	2814						MOD	
	2825						MOD	
	2598	M					MOD	
	2604				PLT MKD D			
	2609						MANY	
	2612						MANY	
	2621						MOD	
	2634						MOD	
	2640						MANY	
	2641						MOD	
	2645			PLT INCRE				
	2661						OCC	
	2665						MOD	
	2671						MANY	

CLINICAL PATHOLOGY APPENDIX III

\* These are non-pregnant females.

Grp Id.	Animal Id.	Sex	Plt Decrease	Plt Increase	Plt mkd Decrease	Plt mkd Increase	Plt clumped	Plt giant
0003	2672 2679 2697 2715	M					MOD MANY MOD OCC	
0004	* { 2728 2735 2761 2792 2793 2811 2843	F		PLT INCRE		PLT MKD 1	2+ 1+ 2+ 1+ 1+ 1+	

CLINICAL PATHOLOGY APPENDIX III g

\* These are non-pregnant females.

Grp Id.	Animal Id.	Sex	Baso Stippling	Hypo Chromic	Micro cytes	Rbc dim orp pop	Rbc inclu sions
0001	2805	F		NOTED			
	2675	M		NOTED			
0002	2821	F		NOTED			
	2678	M		1+			
	2685			NOTED			
	2689			1+			
0003	2725	F		1+			
	2726			NOTED			
	2738			1+			
	2747			1+			
	2754			NOTED			
	2762			2+			
	2768			NOTED			
	2771			1+			
	2800			NOTED			
	2806			NOTED			
	*2813			1+			
	*2814			3+			
	2825			1+			
	2829			2+			
	2845			1+			
	2598	M		4+			
	2604			3+			
	2609			3+			
	2619			1+			
	2621			3+			
	2634			3+			
	2640			1+			
	2641			3+			
	2645			2+			
	2647			2+			
	2649			4+			
	2655			4+			
	2656			4+			
	2661			NOTED			
	2665			2+			
	2671			2+			
	2672			3+			
	2679			3+			
	2683			NOTED			
	2686			4+			
	2694			2+			
	2697			1+			
	2705			4+			
	2715			3+			

CLINICAL PATHOLOGY APPENDIX III X

0004	2728	F		3+	3+	2+	
	2735			2+	3+	2+	
	2745			2+	3+	2+	
*	2756			3+	2+	2+	
	2758		NOTED	3+	3+	2+	
	2761			3+	3+	2+	

1+

\* These are non-pregnant females.

Grp	Animal	Baso	Hypo	Micro	Rbc dia	Rbc inclu
Id.	Id.	Sex	Stippling	Chromic	orph pop	sions
0004	2772	F		3+	3+	2+
	2792			3+	3+	2+
	2793			2+	3+	2+
*	2811			2+	3+	2+
	2820			3+	3+	2+
	2824			3+	3+	2+
	2843			3+	3+	2+
	2659	M		3+	3+	2+

CLINICAL PATHOLOGY APPENDIX III

\* These are non-pregnant females.