Report Title: The Effects of Dietary Iron Supplementation on the Toxicity of Octopirox in the Young Growing Rat

Test Type: Supplemental 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: 10 females, 10 males per group

Test Conditions: 10 female and 10 male Charles River CD rats placed on feed providing a dose of 300 mg/kg/day of G0539.02.

Results: Adding supplemental iron to the diet at 3 levels completely prevented the effects of Octopirox on growth for both sexes. In either sex there were no significant differences in body weights, or in the gain in body weight, during the six-week period between the iron supplemented Octopirox treated rats and the controls. It was concluded that the mechanism of OP toxicity was the prevention of dietary iron absorption by in situ chelation.

Study #: B86-0272
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To File ✓

APPROVAL

APR 20 1987
Section Head

Associate Director

4/27/87
Director

RESEARCH AND DEVELOPMENT DEPARTMENT REPORT
Human and Environmental Safety Division

G. A. Nolen

Date: March 27, 1987
Work Done: 6/12/86-7/31/86
Notebook: YB-994

The Effects of Dietary Iron Supplementation on the
Toxicity of Octopirox in the Young Growing Rat (886-0272)

Summary

Groups of 10 Charles River CD rats of each sex were fed 300 mg/kg/day of Octopirox and were supplemented with 0, 50, 100 or 200 ppm dietary iron as $FeSO_4 \cdot 7H_2O$ for six weeks. The rats fed 300 mg/kg of Octopirox alone gained significantly less body weight and ate significantly less feed, with the effect being more pronounced in males than in females. Two of the males died in the sixth week. They also developed severe microcytic, hypochromic anemia.

The rats supplemented with all three levels of iron grew similar to controls, but the rats supplemented with 50 ppm iron had a mild case of anemia with all of the hematological iron-associated factors being significantly depressed. The 100 ppm supplement restored all factors to normal in the females, but there was still slight reductions in the male. The 200 ppm supplement of iron restored all characteristics to values similar to the controls. Thus, it was concluded that the mechanism of Octopirox toxicity was the prevention of dietary iron absorption by *in situ* chelation.

Report

Introduction

Octopirox (G0539.02), an anti-bacterial agent, was toxic to young growing rats at 300 mg/kg/day in a long-term reproduction study (B85-0460). The males were more affected than the females, with the primary symptom in both sexes being pale, colorless eyes indicating anemia. Because of its anti-bacterial properties we supposed that it might be interfering with the intestinal synthesis of water-soluble vitamins, and indeed some of the rats exhibited symptoms of vitamin B complex deficiencies, such as chromodacryorrhea and "greasy" dermititis. However, a study whereby the diet was fortified with additional water-soluble vitamins showed no amelioration of the toxicity of Octopirox (1).

Octopirox also has strong chelating properties; therefore, we further postulated that it was binding to and preventing intestinal iron absorption and thereby leading to the severely anemic state. This situation would be especially significant for the young rat, since iron uptake decreases after weaning when body stores are very low because of the rapid growth (2).

This study was done to determine the effects of various graded doses of supplemental dietary iron on the toxicity of a 300 mg/kg/day dosage of Octopirox.

Methods and Materials

Seventy weanling Charles River CD rats of each sex were obtained from Charles River Breeding Laboratories, Portage, MI. Upon arrival they were inspected for disease, weighed, ear-tagged and placed in individual stainless steel suspended wire cages. They were given Purina Chow and tap water ad libitum. The environmental conditions and animal care conformed to the Standard Operating Procedures of the Biological Testing Facility at Miami Valley Laboratories.

After a seven-day acclimation period, the rats were weighed and randomly distributed into five groups of 10 males and 10 females per group. The extra animals were then discarded.

The various groups, separated by sex, were then placed on ground Purina Chow as follows:

Group	Octopirox, mg/kg/day	Fe, ppm in diet[a]
1	0	0
2	300	0
3	300	50
4	300	100
5	300	200

a. As $FeSO_4.7H_2O$

These diets were fed for six weeks, with body weights and feed intakes being recorded weekly. After six weeks the rats were sacrificed by excessive ethyl ether, and blood was obtained from the posterior vena cava for hematology and serum chemistries (See Appendix 1 for a complete listing and the results).

The growth data were analyzed by Analysis of Variance using the Reproduction/ Teratology computer system. The hematology and clinical chemistry values were analyzed by R. D. Bruce.

Results and Discussion

The pattern of toxicity from a 300 mg/kg dose of Octopirox was similar to that observed in the long-term reproduction study and the effects were again more pronounced in the male than in the female. Two of the male rats died during the sixth week of the study. In addition, the body weights of the males were affected during the first week of feeding, while in the female, the effects on body weight were not evident until the third week (Tables 1 and 2). The feed consumed followed a similar pattern.

Adding supplemental iron to the diet at three levels completely prevented the effects of Octopirox on growth for both sexes. In either sex there were no significant differences in body weights, or in the gain in body weight, during the six week period between the iron supplemented Octopirox treated rats and the controls.

The rats treated with Octopirox alone had severe microcytic, hypochromic anemia indicating a simple iron deficiency. The number of red blood cells, hemoglobin levels, hematocrit, mean corpuscular volume and hemoglobin were all highly significantly reduced in these animals (Tables 3 and 4). However, adding the supplemental iron reversed these trends in a dose-responsive fashion. The animals supplemented with 50 ppm iron had significantly lower values for these characteristics, although they were restored to near normal values. At the 100 ppm supplemented level of iron the mean corpuscular volume and hemoglobin were still significantly lower in males, but not in females. At the 200 ppm supplemented iron level, all of the hematological characteristics were restored to normal values, although the hemoglobin level was still significantly lower in males than in the controls.

In both sexes platelets and reticulocytes were significantly elevated in the Octopirox treated rats without supplementation and supplemented with 50 ppm iron. Both of these groups also had significantly reduced total iron and significantly increased total iron binding capacity.

The rats treated with Octopirox alone had significantly elevated BUNs and significantly reduced serum proteins. Total bilirubin was also significantly increased (Tables 5 and 6). There were some other isolated significant differences in serum lipids, but these and some other characteristics are not shown in the tables. See Appendix 1 for these and other details. These blood characteristics are indicative of nutritional perturbation brought on by the inanition secondary to the severe iron-deficiency-anemia in the rats treated with Octopirox at high doses.

Since Octopirox is a strong chelating agent, it appears that it is sequestering dietary iron and preventing its absorption leading to the severe anemia. Purina Rat Chow contains 197 ppm iron, while the rats daily requirement is only 0.25 mg, which is equivalent to a diet containing 25 ppm iron (3). Purina Chow contains, therefore, 19.7 mg iron/100 g of diet, which evidently is being entirely sequestered by the Octopirox. Another 20 mg/100 g supplemental iron is needed

to allow the rat normal iron nutrition. The male is more affected than the female because of its larger body size and faster growth rate.

Prior studies done by Hoescht, the supplier of Octopirox, indicated that Sprague-Dawley rats of both sexes could tolerate Octopirox at doses up to 800 mg/kg in a 30 day study given by intubation. It is probable that the bolus of intubed Octopirox did not mix thoroughly with the chyme, and was not able to chelate the dietary iron as completely as it can when mixed thoroughly with the bation is less toxic than dosing in the diet.

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GAN405:cw

Subjects for Indexing

Anemia
Iron Deficiency
Octopirox
Rats
Toxicity

References

1. G. A. Nolen. R&DD Experimental Summary, The Effects of Supplementary Water-Soluble Vitamins on the Toxicity of Octopriox, March 20, 1987.

2. Gallagher, N. D., Mason, R. and Toley, K. E. Mechanisms of Iron Absorption and Transport in Neonatal Rat Intestine. Gastroenterology 64: 438-444 (1973).

3. Warner, R. G. Nutrient Requirements in the Rat, NAS/NPC Publication 990 (1966).

TABLE 1

The Effects of Dietary Iron Supplementation on the Toxicity of Octopirox (G0539.02) in the Growing Male Rat
Body Weights and Feed Consumption (Means±SD)

Group No.	1	2	3	4	5
Octopirox, mg/kg/day	0	300	300	300	300
Supplemental Iron, ppm[1]	0	0	50	100	200
Body Weights, g					
Week 1	151±8	143±11*	150±9	149±6	150±8
2	201±10	154±20**	200±11	199±10	200±13
3	246±9	162±26**	252±18	244±12	249±17
4	291±11	164±33**	287±17	287±15	290±18
5	329±16	160±36**	325±18	322±18	329±23
6	360±18	159±31**	353±32	353±22	358±27
6-Weeks Gain	271±19	69±29**(8)[2]	264±31	264±20	274±30
Feed Consumption, g/day					
Week 1	18.5±1.1	16.9±1.6*	18.0±1.3	18.0±0.9	18.5±1.2
2	22.1±1.5	16.3±2.8**	22.3±1.6	21.3±1.2	22.1±1.9
3	23.4±1.2	16.1±1.6**	23.7±2.1	23.5±1.6	23.6±2.1
4	25.2±1.5	15.8±1.7**	26.1±1.8	25.9±1.4	25.2±1.9
5	25.5±1.7	13.9±2.3**	27.5±1.9*	26.3±1.4	25.9±2.2
6	27.0±1.5	14.2±2.5*	27.7±3.2	27.8±2.6	26.3±2.4
Feed Consumption, g/kg/day					
Week 1	154±6	146±5**	151±5	151±5	159±13
2	125±5	110±20**	127±6	122±4	127±6
3	105±4	103±14	105±7	106±4	105±4
4	94±4	99±16	97±4	97±3	94±2
5	82±4	88±16	90±3**	86±3*	84±4
6	78±4	90±25	82±7	83±8	77±3

1. Added to Purina Chow as $FeSO_4.7H_2O$.
2. Two deaths occurred in the sixth week.

* Significantly different from controls; $P<.05$.
** Significantly different from controls; $P\leq.01$.

TABLE 2

The Effects of Dietary Iron Supplementation on the Toxicity of Octopirox (G0539.02) in the Growing Female Rat
Body Weights and Feed Consumption (Means±SD)

Group No.	1	2	3	4	5
Octopirox, mg/kg/day	0	300	300	300	300
Supplemental Iron, ppm[1]	0	0	50	100	200
Body Weights, g					
Week 1	138±11	141±7	136±5	140±10	136±12
2	172±8	169±10	172±8	175±8	167±15
3	194±8	181±14*	198±9	200±9	191±17
4	214±11	192±17**	220±11	219±10	215±17
5	232±13	201±22**	239±14	239±11	237±21
6	248±16	202±22**	255±13	255±13	251±22
6-Weeks Gain	164±18	118±17**	170±19	170±14	166±20
Feed Consumption, g/day					
Week 1	17.6±1.5	18.1±1.3	17.3±0.7	18.0±1.1	18.3±1.6
2	19.8±1.5	19.0±1.6	19.7±1.0	20.0±0.8	20.0±1.7
3	19.9±2.0	17.4±1.8**	19.9±1.1	19.9±1.1	20.5±1.8
4	20.7±2.8	18.5±2.0**	20.7±1.7	19.9±1.1	21.3±2.0
5	20.8±2.7	18.3±2.6*	21.0±1.4	21.6±2.2	21.7±2.2
6	20.9±2.5	16.3±2.0**	22.8±1.6*	22.4±1.5	21.2±1.8
Feed Consumption, g/kg/day					
Week 1	158±9	161±8	156±8	160±8	166±9
2	128±11	122±5	128±6	129±7	133±10
3	109±11	99±6*	108±6	106±4	116±10
4	102±12	99±4	99±8	95±6	105±9
5	93±11	93±7	92±5	94±10	96±8
6	87±8	81±8	92±6	91±6	87±6

1. Added to Purina Chow as $FeSO_4.7H_2O$.
* Significantly different from controls; $P<.05$.
** Significantly different from controls; $P\leq.01$.

TABLE 3

The Effects of Dietary Iron Supplementation on the Toxicity of Octopirox (G0539.02) in the Growing Male Rat Hematology (Means±SE)

Group No.	1	2	3	4	5
Octopirox, mg/kg/day	0	300	300	300	300
Supplemental Iron, ppm[1]	0	0	50	100	200
RBC (millions)	8.0±0.1	1.9±0.2***	7.8±0.3	8.1±0.2	7.6±0.1
Hemoglobin (g/dl)	15.7±0.2	2.9±0.4***	12.5±0.8***	14.8±0.5	14.8±0.2**
Hematocrit (%)	43.2±0.6	7.6±1.0***	33.2±2.1***	40.8±1.2	40.7±0.8
Mean Corpuscular Volume (fl)	54.3±0.6	38.9±1.1***	42.3±1.4***	50.8±0.8*	53.9±0.8
Mean Corpuscular Hemoglobin (pg)	19.7±0.2	14.9±0.4***	15.9±0.4***	18.3±0.2**	19.5±0.2
MCHC (%)	36.4±0.2	38.4±0.4***	37.8±0.4**	36.3±0.4	36.4±0.5
WBC (thousands)	8.1±0.7	8.1±0.5	8.4±0.8	9.3±0.8	10.6±1.1*
Platelets (thousands)	1016±36	2500±352***	1320±134*	982±44	1025±35
Reticulocytes (%)	3.1±0.2	33.2±1.3***	6.9±1.1***	3.5±0.4	3.4±0.2

1. Added to Purina Chow as $FeSO_4.7H_2O$.
* Significantly different from controls; $P<.05$.
** Significantly different from controls; $P\leq.01$.
*** Significantly different from controls; $P\leq.001$.

TABLE 4

The Effects of Dietary Iron Supplementation on the Toxicity of Octopirox (G0539.02) in the Growing Female Rat
Hematology (Means±SE)

Group No.	1	2	3	4	5
Octopirox, mg/kg/day	0	300	300	300	300
Supplemental Iron, ppm[1]	0	0	50	100	200
RBC (millions)	7.6±0.1	1.7±0.1***	7.7±0.1	7.5±0.1	7.7±0.1
Hemoglobin (g/dl)	14.9±0.1	2.5±0.2***	14.0±0.3**	14.7±0.2	15.0±0.2
Hematocrit (%)	41.7±0.4	6.9±0.5***	39.0±0.8***	41.2±0.5	42.1±0.5
Mean Corpuscular Volume (fl)	54.8±0.4	39.7±1.0***	51.1±0.6***	54.8±0.8	54.8±0.5
Mean Corpuscular Hemoglobin (pg)	19.5±0.2	14.5±0.3***	18.3±0.3**	19.6±0.3	19.5±0.2
MCHC (%)	35.6±0.2	36.5±0.4*	35.9±0.2	35.8±0.1	35.6±0.2
WBC (thousands)	6.3±0.3	6.6±0.4	6.5±0.4	6.4±0.5	6.1±0.5
Platelets (thousands)	938±19	1947±129***	919±24	962±24	857±24*
Reticulocytes (%)	2.9±0.3	24.1±1.3***	2.9±0.2	2.9±0.2	3.1±0.2

1. Added to Purina Chow as $FeSO_4.7H_2O$.
* Significantly different form controls; $P<.05$.
** Significantly different from controls; $P\leq.01$.
*** Significantly different from controls; $P\leq.001$.

TABLE 5

The Effects of Dietary Iron Supplementation on the Toxicity of Octopirox (G0539.02) in the Growing Male Rat
Serum Chemistries (Means±SE)

Group No.	1	2	3	4	5
Octopirox, mg/kg/day	0	300	300	300	300
Supplemental Iron, ppm[1]	0	0	50	100	200
BUN (mg/dl)	16.8±1.1	26.9±3.5*	19.7±0.7	17.4±1.0	17.6±0.7
Creatinine (mg/dl	0.7±.02	0.5±.03***	0.7±.02	0.7±.02	0.7±.02
Total Protein (g/dl)	6.3±0.1	5.1±0.1***	6.2±0.1	6.2±0.1	6.2±0.1
Albumin (g/dl)	4.3±.04	3.9±0.1**	4.3±.05	4.3±.03	4.3±.03
Globulin (g/dl)	2.1±0.1	1.2±.05***	2.0±0.1	1.9±0.1	2.0±.05
A/G Ratio	2.1±0.1	3.3±0.1***	2.2±0.1	2.2±0.1	2.2±0.1
Total Bilirubin (mg/dl)	0.11±.01	0.21±.02***	0.16±.02	0.08±.01	0.11±.01
Na (meq/l)	145±0.4	140±1.4***	145±0.5	145±0.8	143±0.4*
Total Fe (mcg/dl)	208±22	24±3***	80±23**	168±33	153±36*
Total Iron Binding Cap. (mcg/dl)	541±24	759±31***	646±34**	553±15	575±22

1. Added to Purina Chow as $FeSO_4.7H_2O$.
* Significantly different from controls; $P \leq .05$.
** Significantly different from controls; $P \leq .01$.
*** Significantly different from controls; $P \leq .001$.

TABLE 6

The Effects of Dietary Iron Suppplementation on the Toxicity of Octopirox (G0539.02) in the Groving Female Rat
Serum Chemistries (Means±SE)

Group No.	1	2	3	4	5
Octopirox, mg/kg/day	0	300	300	300	300
Supplemental Iron, ppm[1]	0	0	50	100	200
BUN (mg/dl)	17.9±0.8	28.8±1.9***	18.8±0.6	18.1±0.8	17.6±1.7
Creatinine (mg/dl)	0.64±.02	0.58±.01*	0.63±.02	0.64±.02	0.67±.02
Total Protein (g/dl)	6.4±0.1	5.7±0.1***	6.3±0.1	6.4±0.1	6.3±0.1
Albumin (g/dl)	4.5±.05	4.3±.07*	4.5±.05	4.5±.04	4.5±.04
Globulin (g/dl)	1.9±0.1	1.4±0.1***	1.8±0.1	1.9±.04	1.9±.05
A/G Ratio	2.4±0.1	3.1±0.1***	2.5±0.1	2.4±.05	2.4±.06
Total Bilirubin (mg/dl)	0.11±.01	0.22±.02**	0.12±.01	0.13±.02	0.11±.01
Na (meq/l)	145±1.0	141±1.1**	146±1.0	145±1.0	145±.05
Total Fe (mcg/dl)	234±20	12±2***	146±22**	194±32	218±24
Total Iron Binding Cap. (mcg/dl)	517±18	892±78***	563±43	590±34	539±26

1. Added to Purina Chow as $FeSO_4.7H_2O$.
* Significantly different from controls; $P \leq .05$.
** Significantly different from controls; $P \leq .01$.
*** Significantly different from controls; $P \leq .001$.

APPENDIX 1

Hematology and Serum Chemistries

INTERDEPARTMENTAL CORRESPONDENCE

FROM: K. A. Stitzel, J. S. Englehart, D. L. Rothacker

DATE: February 3, 1987

TO: G. A. Nolen

R/L: NON-DISCRETIONARY

SUBJECT: Pathology Report B86-0272, TSIN G0539.02, DRD BY0428-52

CONCLUSIONS

CLINICAL PATHOLOGY

This study showed that the microcytic, hypochromic, anemia demonstrated in Group 2 males and females dosed with the test substance was due to iron deficiency. Groups 3, 4, and 5, dosed with the test substance and supplemented with 50, 100, and 200 ppm of iron, respectively, demonstrated iron supplementation prevented or lessened the anemia.

ANATOMIC PATHOLOGY

Gross necropsy was performed on fifty male and fifty female rats. There was macroscopic evidence of anemia noted as pale eyes and tissues and enlarged heart in Group 2 animals at terminal sacrifice. Fifty ppm or more of dietary iron supplement prevented macroscopic observation of anemia in Groups 3, 4, and 5 at necropsy.

INTRODUCTION

The purpose of this study was to determine if dietary supplemental iron would prevent Octopirox (G0539.02) induced anemia in rats.

MATERIALS AND METHODS

EXPERIMENTAL MODEL

TYPE OF STUDY:	Feeding
SPECIES:	Rat
STRAIN (SOURCE):	Sprague Dawley, Charles River
SEX:	Male and Female
TEST SUBSTANCE:	Octopirox and Iron
CONTROL SUBSTANCE:	Certified Purina Chow
ROUTE OF EXPOSURE:	Diet
DOSING REGIMEN:	Daily
OBSERVATION:	6 weeks

ANIMAL GROUP ASSIGNMENT

Refer to the report submitted by Experimental Pathology Laboratories, Inc. for a description of Animal Group Assignment (Anatomic Pathology Appendix I).

CLINICAL PATHOLOGY

Blood for hematology and chemistry analyses was collected at necropsy (Period 1) from the vena cava. Blood for hematology analyses was collected into tubes containing an appropriate amount of EDTA anticoagulant. Blood for chemistry analyses was collected into serum separator tubes for chemistry analyses. Hematology and chemistry analyses were performed at the Clinical Pathology Laboratory (MVL).

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

Alanine Aminotransferase (ALT, formally SGPT
Albumin (ALB)
Albumin/Globulin Ratio (A/G ratio)
Alkaline Phosphatase (ALK)
Aspartate Aminotransferase (AST, formally SGOT)
Blood Urea Nitrogen (BUN)
Calcium (CA)
Cholesterol (CHOL)
Creatinine (CREAT)
Globulin (GLOB)
Glucose (GLUC)
Phosphorus (PHOS)
Potassium (K)
Sodium (NA)
Total Bilirubin (TBILI)
Total Protein (TP)
Triglycerides (TG)
Total Iron (FE)
Total Iron Binding Capacity (TIBC)

Hematology and chemistry results were statistically analyzed by R. D. Bruce using Procter and Gamble Computer Program #B8944. All test groups (2, 3, 4, and 5) were compared to the control group (1). In addition, Groups 3, 4, and 5 were compared to Group 2. Finally, linear regression was applied to Groups 2, 3, 4, and 5, respectively.

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 J. S. Englehart.

ANATOMIC PATHOLOGY

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

RESULTS

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 and II, respectively. Data from the study can be located in notebook YE-967 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.

Several values are missing (see table below) and are noted as -M- on the hematology and chemistry data tables. The amount of missing data was small and did not affect the overall evaluation of the data.

Table of Missing Data

Group	Animal #	Sex	Test(s)	Reason*
1	2941	M	RETIC	A
1	3061	F	RETIC	A
2	2933	M	All tests	B
2	2937	M	All tests	B
2	3026	F	RETIC	C
4	2972	M	RETIC	A
5	2938	M	CBC, WBC Differential, and RETIC	D
5	2943	M	RETIC	A

*A - Quantity insufficient for analysis.
B - No specimen received.
C - A reticulocyte count was performed. However, the results were incompatible with the results of the CBC and WBC differential analyses.
D - EDTA specimen clotted.

Many statistically significant differences were noted in the males and females when hematology and chemistry parameters from the treated groups were compared to Group 1. Differences were also noted when Groups 3, 4, and 5 were compared to Group 2. In addition, several differences in the hematology and chemistry parameters were noted when linear regression was applied to Groups 2, 3, 4, and 5.

The normal ranges established are designed to include only 95% of the population for each of the parameters, so occasional slight outliers are expected.

The values from the spun capillary HCT's do not match the instrument HCT values. This is due to overlapping between RBC's and platelets as seen by the laser cell counter. This overlapping was a result of the small size of the RBC's in the anemic animals and the lack of hemoglobin. Therefore, numbers generated for RBC, hematocrit and platelets are inaccurate and should be used for comparisons between groups but not as definitive values. Because of the severity of the anemia, this inaccuracy does not affect the interpretation of the data.

Two statistical comparisons were made with the study data. One, treatment Groups 2, 3, 4, and 5 were compared to Group 1 (Comparison I). And two, treatment groups supplemented with iron (Groups 3, 4, and 5) were compared to treatment Group 2, no supplement (Comparison II). Each comparison will be discussed separately.

COMPARISON I

Hematology

Males

Statistically significant changes were noted in all test groups (Groups 2, 3, 4, and 5) when compared to Group 1. Two or more parameters were effected in each group.

1. The average Group 2 (treated, nonsupplemented) RBC value was statistically significantly depressed when compared to Group 1. Group 2 RBC values were 3.01 x 10^6/ul or less compared to a control mean of 7.97.

2. Hemoglobin and hematocrit values for Groups 2, 3 and 5 (treated, low and high supplemented, respectively) were statistically significant when compared to the control group. Group 2 values for both parameters were severally depressed, i.e., hemoglobin values ranged from 1.6 to 5.0 g/dl, while hematocrit values ranged from 4.4 to 12.9%. Groups 3 and 5 hemoglobin values ranged from 8.7 to 14.8 and 14.1 to 15.3, respectively. Hematocrit values for the same groups ranged from 21.3 to 40.3 and 35.6 to 43.5, respectively. The control mean value for hemoglobin was 15.71, while the control hematocrit mean was 43.1.

3. The RBC indices (MCV, MCH, and MCHC) for Groups 2, 3, and 4 were statistically significant. Group 2 mean values for these parameters were ≤43 fl, ≤16.6 pg, and ≤40.0%, respectively. Group 3 mean values for the same parameters were ≤48, ≤17.5, and ≤40.8, respectively. Group 4 mean values for MCV and MCH were ≤54 and ≤19.7, respectively. No statistically significant difference occurred in the Group 4 MCHC parameter. Control group mean values for MCV, MCH, and MCHC were 54.3, 19.72, and 36.37, respectively.

4. The only statistically significant occurrence in the WBC parameter was in Group 5. The WBC value was slightly elevated with values ranging from 6.1 to 16.3 x 10^3/ul compared to a control mean of 8.13.

5. Platelet values for Groups 2 and 3 were statistically significant with values 3685 x 10^3/ul or less and 2216 or less, respectively, compared to a control mean of 1016.

6. Reticulocyte values for Groups 2 and 3 were statistically significant. Group 2's values of 39.0% or less were greatly elevated compared to the control mean of 3.08. While Groups 3's values were only slightly elevated (13.6 or less) when the same comparison was made.

7. Monocyte and segmented neutrophil values for Group 2 were statistically significant. Both were increased with monocyte values 1.17 x 10^3/ul or less and segmented neutrophil values 2.67 x 10^3/ul or less when compared to a control means of 0.395 and 0.598, respectively. In addition, monocyte values for Groups 3 and 5 were statistically significant with values 0.45 or less and 0.98 or less, respectively.

Females

1. Group 2 RBC, HGB, and HCT values were severally depressed and statistically significant when compared to control group values. Group 2 RBC values were ≤2.16 x 10^6/ul, HGB values were ≤3.3 g/dl, and HCT values were ≤9.1% compared to control mean values for RBC, HGB, and HCT of 7.615, 14.85, and 41.72, respectively.

2. Group 2 RBC indices were also depressed and statistically significant. MCV values were 45 fl or less, MCH values were 15.6 pg or less, and MCHC values were 37.5% or less compared to mean values of 39.7, 14.48, and 36.51 for MCV, MCH, and MCHC, respectively.

3. Group 3 HGB, HCT, MCV, and MCH values were slightly depressed and statistically significant. Group 3 values were 14.9 g/dl or less, 43.1% or less, 53 fl or less, and 19.2 pg or less for HGB, HCT, MCV, and MCH, respectively.

4. Group 2 platelet values were statistically significant and greatly elevated, 2379 x 10^3/ul or less, when compared to a control mean of 938.

5. Reticulocyte and monocyte values for Group 2 were statistically significant. Reticulocyte values were greatly increased, ranging from 19.1 to 25.6%, compared to a control mean value of 2.91. Monocyte values were moderately elevated, 1.00 x 10^3/ul or less, when compared to a control mean of 0.298.

Chemistry

Males

1. Group 2 glucose values were moderately depressed and statistically significant when compared to the control group. Group 2 values ranged from 186 to 385 mg/dl while the control group mean was 369.3.

2. BUN, creatinine, total protein, albumin, globulin, and A/G ratio values for Group 2 were also statistically significant. BUN values were moderately elevated, 42.2 mg/dl or less, when compared to the control group mean of 16.82. Creatinine, total protein, albumin, and globulin mean values (0.52 mg/dl, 5.06 g/dl, 3.89 g/dl, and 1.17 g/dl, respectively) were slightly depressed when compared to the control group mean values of 0.65, 6.33, 4.28, and 2.05, respectively. The A/G ratio was slightly elevated, mean value of 3.33 compared to a control mean of 2.113.

3. Alkaline phosphatase, AST, total bilirubin, and cholesterol values for Group 2 were also statistically significant when compared to the control group values. Alkaline phosphatase values ranged from 80 to 263 IU/l for Group 2 animals while the control mean was 278.6. AST values were slightly elevated for Group 2 with a mean of 126.6 IU/l vs a control mean of 103.2. Total bilirubin values were elevated for Group 2, a mean of 0.21 mg/dl vs a control mean of 0.11. Finally, cholesterol values were slightly depressed for Group 2 when compared to the control, 54.3 vs 67.2 mg/dl.

4. Group 2 calcium and sodium values were slightly depressed and statistically significant when compared to the control group. The mean for Group 2 calcium values was 11.07 mg/dl compared to a control mean of 11.98. As for the sodium values, the Group 2 mean was 140.2 mEq/l compared to a control mean of 145.0.

5. Total iron and total iron binding capacity values were statistically significant when compared to the control group. Group 2 total iron values were markedly depressed when compared to the control mean, 23.5 vs 208.1 mcg/dl, respectively. The total iron binding capacity for Group 2 was moderately elevated when compared to the control mean, 759.4 vs 541.4 mcg/dl, respectively.

6. Group 3 values for total bilirubin, total iron, and total iron binding capacity were statistically significant when compared to the control group values. Total bilirubin values were slightly elevated when compared to the control mean, 0.16 vs 0.11 mg/dl, respectively. Total iron values were severely depressed when compared to the control mean, 80.4 vs 208.1 mcg/dl, respectively. Total iron binding capacity values were slightly elevated when compared to the control group mean, 646.4 vs 541.4 mcg/dl, respectively.

7. Group 5 values for sodium and total iron were statistically significant when compared to the control group. The depression of sodium values was slight, a mean of 143.4 mEq/l vs a control mean of 145.0. The Group 2 total iron values were slightly depressed when compared to the control mean, 153.2 vs 208.1 mcg/dl.

Females

1. Group 2 BUN and creatinine values were statistically significant when compared to the control group. Group 2 BUN values were moderately elevated when compared to control mean, 28.76 vs 17.92 mg/dl, respectively. While creatinine values were slightly depressed when the same comparison was made, 0.58 vs 0.64 mg/dl, respectively.

2. Statistical significance occurred when Group 2 total protein, albumin, globulin, and A/G ratio values were compared to the control group. Total protein, albumin, and globulin mean values were slightly depressed when compared to the control group means for the same parameters, 5.71, 4.31, and 1.40 vs 6.38 g/dl, 4.47 g/dl, and 1.91 g/dl, respectively.

3. Group 2 alkaline phosphatase, AST, total bilirubin, and triglyceride values were statistically significant when compared to the control group. The alkaline phosphatase mean value was moderately depressed, 144.7 IU/l compared to the control mean of 238.4. The AST mean value was slightly elevated when compared to the control, 131.6 vs 87.5 IU/l, respectively. Both the total bilirubin and triglyceride mean values were moderately elevated compared to the control mean, 0.22 and 167.4 vs 0.11 mg/dl and 78.9 mg/dl, respectively.

4. Group 2 sodium and phosphorous values were also statistically significant. The sodium mean value was slightly depressed compared to the control mean value, 141.3 vs 144.6 mEq/l, respectively. While the phosphorous mean value was slightly elevated when the same comparison was made, 9.37 vs 8.36 mEq/l, respectively.

5. Group 2 total iron and iron binding capacity values were also statistically significant when compared to the control group values. Total iron values were markedly depressed, a mean of 12.5 mcg/dl vs a control mean of 234.3. Total iron binding capacity values were greatly increased under the same comparison, 891.7 vs 517.0 mcg/dl.

6. Finally, Group 3 phosphorous, triglyceride, and total iron values were statistically significant when compared to the control values. Phosphorous values were slightly elevated, 9.55 mg/dl compared to 8.36. Triglyceride and total iron values were moderately depressed, 58.5 and 145.8 vs 78.9 mg/dl and 234.3 mcg/dl, respectively.

COMPARISON II

The only comparisons to be discussed in this section are those that meet the following: (1) if statistical significance occurred in an individual parameter when the treated, but not supplemented group (Group 2) was compared to the control group (Group 1); and (2), if iron supplementation in the treated groups (Groups 3, 4, and 5) did not result in a statistically significant change when compared to the treated, but not supplemented group (Group 2).

Hematology

Statistically significant change did not occur in the MCH and MCHC parameters when a treatment group supplemented with 50 ppm iron (Group 3, males) was compared to the treated but not supplemented group (Group 2, males). The Group 3 mean MCH value was 15.94 pg compared to the Group 2 mean value of 14.91, while the Group 3 mean MCHC value was 37.77% compared to the Group 2 mean value of 38.44. For reference, the control (Group 1, males) mean MCH value was 19.72 and the MCHC mean value was 36.37.

When linear regression was applied to Test Groups 2, 3, 4, and 5, the following was noted: a positive dose regression occurred in the males in the WBC parameter but not in the females. In addition, positive dose regression occurred in the males in the monocyte and segmented neutrophil parameters, but again not in the females. Finally, positive dose regression occurred in the females in the MCHC parameter, but not in the males,

Chemistry

Statistically significant change did not occur in the phosphorus parameter when a treatment group supplemented with 50 ppm iron (Group 3, females) was compared to the treated but not supplemented group (Group 2, females). The Group 3 mean phosphorus value was 9.55 mg/dl compared to the Group 2 mean value of 9.37. For reference, the control (Group 1, females) mean phosphorus value was 8.36.

When linear regression was applied to Test Groups 2, 3, 4, and 5, the following was noted: a positive dose regression occurred in the total iron parameter for males, but not in the females. In addition, positive dose regression occurred in the creatinine, albumin, calcium, phosphorus, and cholesterol parameters in females, but not in males.

ANATOMIC PATHOLOGY

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

DISCUSSION

CLINICAL PATHOLOGY

A microcytic, hypochromic anemia was demonstrated in Group 2 males and females dosed with the test substance. A similar anemia was demonstrated in previous studies (B85-0460 and B86-0224) with this test compound. This anemia was compatible with iron deficiency. Simple iron deficiency is difficult to prove conclusively with laboratory tests. The classic method of proving an anemia is caused by iron deficiency is to prevent or cure the anemia with supplemental iron.

Supplementation with 50, 100, or 200 ppm of iron prevented or lessened the anemia is a dose related fashion. Thus, this study provides very strong evidence that the cause of the anemia associated with administration of this test substance is simple iron deficiency.

Test substance administration alone caused a microcytic, hypochromic anemia as shown by the decrease in red cell numbers, hemoglobin, hematocrit, red cell volume, and mean corpuscular hemoglobin. The MCHC increased slightly, it is believed this is due to machine error in counting some of the very small red cells as platelets, thus increasing the percent of hemoglobin in the remaining cells. Reticulocytes increased in response to the anemia. The increase in platelet numbers was spurious, caused by interference of the small red cells in the platelet counting. In this study there was also a slight increase in the number of monocytes in both sexes with test substance administration. The changes were slight, and may be due to normal biological variation or test substance administration. Segmented neutrophils also increased in the males only, again the change is small and may be due to biological variation.

Associated with the severe iron deficiency anemia were changes in clinical chemistry parameters. The serum iron levels decreased significantly and the serum iron binding capacity increased. These two changes are expected with iron deficiency anemia. The other changes are secondary to the debilitation and anoxia caused by the iron deficiency. Decreased perfusion of the kidneys and liver resulted in increases in BUN, serum bilirubin, and liver enzymes and a decrease in serum proteins; decreased muscle mass was associated with a decrease in creatinine. Other nonspecific changes in metabolism were reflected in changes in the serum electrolytes, glucose, alkaline phosphatase, and lipids.

Supplementation with 50 ppm of iron (Group 3) reduced the degree of anemia, although these rats were still anemic compared to the controls. In this group the females were less affected than the males, possibly because of their smaller body size. In the females the MCV increased to nearly normal range, thus the spurious change in platelet count was not seen. The reticulocyte count was also not elevated in the females. The more severe effect in the males is reflected in the MCV and the significantly elevated reticulocyte count. The decrease in monocyte counts in the males is probably due to normal variation, since it did not occur in the females and was the opposite of the effect seen in the Group 2 animals.

Serum iron was still affected in Group 3 rats but the increased iron binding capacity was only seen in the males. The other secondary changes in clinical chemistry parameters were not seen, with the exception of a continued slight increase in total bilirubin in the males and possibly phosphorus in the females. Serum triglyceride levels were decreased in the females, a change which appears to be fortuitous since it does not occur in the males or any other dose group including Group 2.

Supplementation with 100 ppm of iron (Group 4) completely prevented anemia in the females. In the males there was a continued slight decrease in MCV and MCH. No statistically significant changes were reported in the clinical chemistry values, but examination of the individual results shows a few rats with low serum iron values.

Supplementation with 200 ppm of iron (Group 5) increased the MCV and MCH in the males to normal. The HCT and HGB fell very slightly compared with Group 4 and were significantly different from Group 1. In addition there was a slight increase in WBC and absolute monocyte numbers in Group 5 males. Clinical chemistry parameters were unaffected except for a continued slight and statistically significant decrease in serum iron in the males. A decrease in serum sodium in the males if probably due to biological variation since it did not occur in the females nor in a dose related fashion.

In summary, supplementation with 100 ppm of iron or greater returned the female rats to normal. Supplementation with either 50 or 100 ppm of iron in the males continued to be associated with a decrease in red cell size and serum iron. At 200 ppm supplementation in the males red cell size had returned to normal, but hemoglobin levels were still slightly decreased, and serum iron levels were still significantly lower than the controls.

ANATOMIC PATHOLOGY

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

Kathe G. Stitzel

CLINCAL PATHOLOGIST

REVIEWING ANATOMIC PATHOLOGIST

STATISTICAL ANALYSIS SUMMARY

B860272 - MALES PERIOD 1 VALUES

RESPONSE:		RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL)	MCH (PG)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)
GROUP										
GROUP 1	AVG.	7.972	15 71	43 21	54 3	19 72	36 37	8 13	1016 1	3 08
M	S.E.	0.100	0 20	0 63	0 6	0 20	0 23	0 68	35 7	0.15
GROUP 2	AVG	1 921	2 91	7.57	38 9	14 91	38 44	8 14	2499 9	33 21
M	S E.	0.210	0 38	1.00	1 1	0 42	0 38	0 50	352 0	1.34
	P(C)	0 000***	0 000***	0 000***	0 0 ***	0 000***	0 000***	0 995	0 000***	0 000***
GROUP 3	AVG	7 786	12 50	33.20	42 3	15 94	37 77	8 36	1320 5	6.94
M	S E.	0.296	0 75	2 10	1 4	0 42	0 40	0 75	133 8	1.05
	P(C)	0 796	0 000***	0 000***	0 0 ***	0 000***	0 010**	0 836	0 019*	0 000***
GROUP 4	AVG	8 062	14 81	40 83	50 8	18 34	36 25	9 33	981 6	3 50
M	S E	0 225	0 46	1 16	0 8	0 22	0 39	0 81	43 9	0 37
	P(C)	0 247	0 165	0 165	0 013*	0 001**	0 817	0 282	0 912	0 730
GROUP 5	AVG	7 570	14 78	40 71	53 9	19 54	36 40	10 56	1024 8	3.36
M	S E	0 105	0 18	0 82	0 8	0 16	0 46	1 11	35 4	0 20
	P(C)	0 065	0 001**	0 043*	0 769	0 549	0 955	0 038*	0 780	0 370
GRPS 283	P(O)	0 000***	0 000***	0 000***	0 022*	0 083	0 229	0 850	0 004**	0 000***
GRPS 284	P(O)	0 000***	0 000***	0 000***	0 0 ***	0 000***	0 000***	0 313	0 000***	0 000***
GRPS 285	P(O)	0 000***	0 000***	0 000***	0 0 ***	0 000***	0 001***	0 050*	0 000***	0 000***
FE REGR.	P(O)	0 0 ?	0 0 ?	0 0 ?	0 0 ?	0 0 ?	0 0007	0 030*	0 0007	0 0 ?

P(C) DENOTES P-VALUE FOR COMPARISON OF OTHER GROUPS WITH CONTROL, GROUP 1 M .
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

CLINICAL PATHOLOGY TABLE I a

STATISTICAL ANALYSIS SUMMARY

B860272 - MALES PERIOD 1 VALUES

RESPONSE:		BANDS THOUSAND	BASO THOUSAND	EOS THOUSAND	LYMPH THOUSAND	MONO THOUSAND	SEGS THOUSAND
GROUP							
GROUP 1	AVG.	0 0	0.0	0.045	7 092	0 395	0 598
M	S.E.	0 0	0.0	0.021	0 676	0 036	0 051
GROUP 2	AVG	0 0	0 0	0 023	6 056	0 687	1 372
M	S E.	0 0	0 0	0 015	0 332	0 098	0 262
	P(C)	-M-	-M-	0 504	0 347	0 009**	0 006**
GROUP 3	AVG	0 0	0 0	0 052	7 117	0 279	0 912
M	S E	0 0	0 0	0 018	0 740	0 029	0 175
	P(C)	-M-	-M-	0 807	0 981	0 023*	0 247
GROUP 4	AVG	0 0	0 0	0 036	7 849	0 466	0 980
M	S E	0 0	0 0	0 024	0 150	0 051	0 225
	P(C)	-M-	-M-	0 769	0 465	0 315	0 247
GROUP 5	AVG	0 0	0 0	0 028	9 211	0 587	0 730
M	S E	0 0	0 0	0 028	1 015	0 073	0 080
	P(C)	-M-	-M-	0 593	0 051	0 043*	0 182
GRPS 283	P(O)	-M-	-M-	0 370	0 136	0 000***	0 203
GRPS 284	P(O)	-M-	-M-	0 694	0 107	0 083	0 203
GRPS 285	P(O)	-M-	-M-	0 882	0 007**	0 541	0 027*
FE REGR	P(O)	-M-	-M-	0 911	0 005**	0 8887	0 030*

P(C) DENOTES P-VALUE FOR COMPARISON OF OTHER GROUPS WITH CONTROL, GROUP 1 M .
P(O) DENOTES P-VALUE FOR LINEAR REGRESSION OR FOR A CONTRAST.
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+,++,+++ DENOTE SIGNIFICANCE BY DISTRIBUTION-FREE METHODS WITH P<.05, .01 OR 001 RESPECTIVELY.
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-M- INDICATES A STATISTICAL TEST NOT PERFORMED BECAUSE OF NO DATA OR WITHIN-GROUP VARIANCE = 0.

CLINICAL PATHOLOGY TABLE 1 b

STATISTICAL ANALYSIS SUMMARY

B860272 - FEMALES

PERIOD 1 VALUES

RESPONSE:		RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL)	MCH (PG)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)
GROUP										
GROUP 1	AVG.	7.615	14.85	41.72	54.8	19.51	35.60	6.27	938.0	2.91
F	S.E.	0.058	0.11	0.36	0.4	0.18	0.16	0.31	19.2	0.31
GROUP 2	AVG	1.739	2.53	6.92	39.7	14.48	36.51	6.60	1946.8	24.09
F	S.E.	0.108	0.19	0.50	1.0	0.32	0.40	0.40	128.9	1.29
	P(C)	0.0 ***	0.0 ***	0.0 ***	0.0 ***	0.0 ***	0.035*	0.599	0.000***	0.000***
GROUP 3	AVG	7.655	13.98	38.98	51.1	18.28	35.87	6.49	918.7	2.92
F	S.E.	0.138	0.28	0.76	0.6	0.25	0.21	0.42	24.0	0.23
	P(C)	0.817	0.003**	0.001***	0.000***	0.001**	0.280	0.726	0.631	0.720
GROUP 4	AVG	7.537	14.74	41.16	54.8	19.58	35.82	6.42	962.0	2.86
F	S.E.	0.142	0.15	0.45	0.8	0.26	0.14	0.54	24.4	0.23
	P(C)	0.652	0.693	0.462	1.000	0.844	0.481	0.811	0.631	0.905
GROUP 5	AVG	7.705	15.01	42.14	54.8	19.51	35.62	6.10	857.0	3.14
F	S.E.	0.140	0.21	0.51	0.5	0.23	0.18	0.48	24.4	0.22
	P(C)	0.603	0.986	0.580	1.000	1.000	1.000	0.786	0.029*	0.315
GRPS 2&3	P(O)	0.0 ***	0.0 ***	0.0 ***	0.0 ***	0.0 ***	0.123	0.861	0.000***	0.000***
GRPS 2&4	P(O)	0.0 ***	0.0 ***	0.0 ***	0.0 ***	0.0 ***	0.063	0.774	0.000***	0.000***
GRPS 2&5	P(O)	0.0 ***	0.0 ***	0.0 ***	0.0 ***	0.0 ***	0.029*	0.427	0.000***	0.000***
FE REGR.	P(O)	0.0 ?	0.0 ?	0.0 ?	0.0 ?	0.0 ?	0.019*	0.409	0.0 ?	0.0 ?

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.

CLINICAL PATHOLOGY TABLE T C

STATISTICAL ANALYSIS SUMMARY

8860272 - FEMALES PERIOD 1 VALUES

RESPONSE:		BANDS THOUSAND	BASO THOUSAND	EOS THOUSAND	LYMPH THOUSAND	MONO THOUSAND	SEGS THOUSAND
GROUP							
GROUP 1	AVG	0.0	0 0	0.017	5 521	0 298	0 433
F	S.E.	0.0	0.0	0.009	0 284	0 039	0 071
GROUP 2	AVG	0 0	0 0	0.007	5 414	0 515	0 663
F	S E.	0 0	0 0	0.007	0 298	0 067	0 098
	P(C)	-M-	-M-	0 579	0 837	0 005**	0 071
GROUP 3	AVG	0 0	0 0	0 073	5 980	0 341	0 486
F	S E.	0 0	0 0	0 032	0 349	0 030	0 071
	P(C)	-M-	-M-	0 247	0 909	0 353	0 616
GROUP 4	AVG	0 0	0 0	0 017	5 590	0 263	0 549
F	S E	0 0	0 0	0 012	0 528	0 050	0 072
	P(C)	-M-	-M-	0 853	0 891	0 353	0 356
GROUP 5	AVG	0 0	0 0	0 041	5 096	0 425	0 538
F	S E	0 0	0 0	0.025	0 301	0 111	0 117
	P(C)	-M-	-M-	0 853	0 412	0 481	0 404
GRPS 283	P(O)	-M-	-M-	0 123	0 748	0 043*	0 185
GRPS 284	P(O)	-M-	-M-	0 739	0 733	0 005**	0 363
GRPS 285	P(O)	-M-	-M-	0 481	0 538	0 052	0 318
FE REGR.	P(O)	-M-	-M-	0.617	0 462	0 4927	0 479

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 DISTRIBUTION-FREE METHODS WITH P<.05, .01 OR 001 RESPECTIVELY.
? INDICATES A "LACK OF FIT" IN LINEAR REGRESSION OR IN A CONTRAST.
-M- INDICATES A STATISTICAL TEST NOT PERFORMED BECAUSE OF NO DATA OR WITHIN-GROUP VARIANCE = 0.

CLINICAL PATHOLOGY TABLE 1D

STATISTICAL ANALYSIS SUMMARY

STUDY B860272 - 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)	NA (MEQ/L)
GROUP													
GROUP 1	AVG	369 3	16.82	0.65	6 33	4 28	2 05	2 113	278 6	103 2	53 9	0.11	145.0
M	S E	20.3	1.07	0.02	0 10	0 04	0 08	0.077	17 1	5 6	4.6	0.01	0 4
GROUP 2	AVG	276 9	26 92	0 52	5 06	3 89	1 17	3 330	163 2	126 8	54.1	0.21	140.2
M	S E	27 3	3 47	0 03	0 14	0 10	0 05	0 093	24 1	12 9	8.8	0.02	1.4
	P(C)	0 024*	0 034*	0 000***	0 0 ***	0 003**	0 0 ***	0 0 ***	0 000***	0 046*	0 460	0.0 ***	0.000***
GROUP 3	AVG	313 6	19 73	0 65	6 23	4 27	1 96	2 213	278 0	106 2	52.0	0.16	145.0
M	S E	31 2	0 73	0 02	0 13	0 05	0 09	0 089	23 0	6 1	2.5	0.02	0.5
	P(C)	0 141	0 083	1 000	0 486	0 971	0 346	0 356	0 982	0.781	0.739	0.017*	1.000
GROUP 4	AVG	350 8	17 41	0 67	6 16	4 25	1 91	2 244	232 1	109 3	53 0	0.08	144 7
M	S E	21 8	1 02	0 02	0 07	0 03	0 06	0 070	15 5	6 1	2 6	0 01	0 8
	P(C)	0 615	0 971	0 482	0 238	0 912	0 146	0 228	0 093	0.573	0 796	0 143	1 000
GROUP 5	AVG	327 9	17 63	0 65	6 20	4 25	1 95	2 191	231 3	106.7	49.9	0.11	143 4
M	S E	31 2	0 70	0 02	0 07	0 03	0 05	0 056	18 2	8 2	3.4	0.01	0.4
	P(C)	0 271	0 739	1 000	0 366	0 912	0 296	0 471	0 088	0 746	0.579	1.000	0.023*
GRPS 283	P(O)	0 356	0 274	0 000***	0 0 ***	0 004**	0 0 ***	0 0 ***	0 000***	0.080	0 515	0 018*	0 001***
GRPS 284	P(O)	0 068	0 027*	0 000***	0 0 ***	0 004**	0 0 ***	0 0 ***	0 021*	0 135	0.315	0.0 ***	0 009**
GRPS 285	P(O)	0 202	0 068	0 000***	0 0 ***	0 004**	0 0 ***	0 0 ***	0 022*	0 087	0.965	0.0 ***	0.016*
FE REGR.	P(O)	0.189	0.0007	0.0017	0.0 ?	0 0007	0 0 ?	0.0 ?	0.1617	0.156	0.551	0.0 ?	0.0417

P(C) DENOTES P-VALUE FOR COMPARISON OF OTHER GROUPS WITH CONTROL, GROUP 1 M .
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.

CLINICAL PATHOLOGY TABLE 2 2

STATISTICAL ANALYSIS SUMMARY

STUDY B860272 - MALES PERIOD 1 VALUES

RESPONSE:		K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	TOT FE (MCG/DL)	TIBC (MCG/DL)
GROUP								
GROUP 1	AVG.	7 49	11.88	9 15	67 2	112 3	208 1	541 4
M	S E	0 31	0.21	0.28	3 7	17 8	22 0	24 3
GROUP 2	AVG.	6 90	11 07	8 29	54 3	223 0	23 5	759 4
M	S E	0 38	0.23	0 47	4 4	77 8	3 2	31 2
	P(C)	0 247	0 008**	0 083	0 019*	0 515	0 000***	0 0 ***
GROUP 3	AVG	7 01	11 96	9 49	60 6	85 8	80 4	646 4
M	S E	0 37	0.21	0 25	3 3	12 2	22 8	34 0
	P(C)	0.317	0 948	0 462	0 195	0 280	0 002**	0 005**
GROUP 4	AVG	7 26	11 70	8 92	66 1	100 9	168 0	553 8
M	S E	0 31	0 21	0 29	2 9	9 3	33 2	15 2
	P(C)	0 630	0 365	0 618	0 827	0 684	0 190	0 731
GROUP 5	AVG	6 86	11 39	8 69	59 8	116 4	153 2	575 1
M	S E	0 34	0 24	0 37	3 8	21 0	35 5	22 0
	P(C)	0 191	0 081	0 321	0 147	0 971	0 015*	0 352
GRPS 283	P(O)	0 828	0 009**	0 017*	0 239	0 274	0 000***	0 005**
GRPS 284	P(O)	0 478	0 061	0 200	0 031*	0 633	0 000***	0 0 ***
GRPS 285	P(O)	0 937	0 337	0 412	0 302	0 633	0 000***	0 000***
FE REGR	P(O)	0.937	0.7657	0.8727	0 334	0 0937	0 001**	0.0 ?

P(C) DENOTES P-VALUE FOR COMPARISON OF OTHER GROUPS WITH CONTROL, GROUP 1 M .
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

CLINICAL PATHOLOGY TABLE 2D

STATISTICAL ANALYSIS SUMMARY

STUDY 8860272 - 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)	NA (MEQ/L)
GROUP													
GROUP 1	AVG	355.4	17.92	0.64	6.38	4.47	1.91	2.385	238.4	87.5	44.9	0.11	144.6
F	S.E.	20.9	0.77	0.02	0.12	0.05	0.09	0.110	19.0	1.9	1.8	0.01	0.9
GROUP 2	AVG	313.5	28.78	0.58	5.71	4.31	1.40	3.125	144.7	131.6	52.6	0.22	141.3
F	S.E.	19.4	1.91	0.01	0.13	0.07	0.07	0.110	20.3	14.6	6.4	0.02	1.1
	P(C)	0.131	0.000***	0.015*	0.000***	0.028*	0.0 ***	0.0 ***	0.001**	0.001***	0.684	0.001**	0.007**
GROUP 3	AVG.	317.4	18.78	0.63	6.27	4.48	1.79	2.523	229.4	91.1	48.0	0.12	145.9
F	S.E.	18.7	0.64	0.02	0.09	0.05	0.06	0.071	16.7	4.3	2.7	0.01	0.8
	P(C)	0.170	0.280	0.675	0.443	0.888	0.184	0.251	0.740	0.971	0.884	0.739	0.270
GROUP 4	AVG	333.0	18.11	0.64	6.38	4.50	1.88	2.403	198.4	88.5	48.8	0.13	145.1
F	S.E.	16.6	0.78	0.02	0.06	0.04	0.04	0.052	22.8	2.9	2.9	0.02	0.8
	P(C)	0.415	0.739	1.000	1.000	0.672	0.737	0.880	0.144	0.631	0.684	0.481	0.670
GROUP 5	AVG	359.0	17.61	0.67	6.14	4.49	1.85	2.443	227.1	91.2	47.6	0.11	145.1
F	S.E.	20.3	1.73	0.02	0.09	0.04	0.05	0.057	15.4	4.2	3.5	0.01	0.5
	P(C)	0.895	0.280	0.211	0.780	0.778	0.503	0.627	0.677	0.393	0.796	1.000	0.670
GRPS 283	P(O)	0.887	0.000***	0.040*	0.000***	0.020*	0.000***	0.000***	0.003**	0.003**	0.853	0.004**	0.000***
GRPS 284	P(O)	0.478	0.000***	0.015*	0.000***	0.010**	0.0 ***	0.000***	0.052	0.001**	0.739	0.011*	0.002**
GRPS 285	P(O)	0.102	0.000***	0.000***	0.000***	0.014*	0.000***	0.000***	0.004**	0.005**	0.796	0.001**	0.002**
FE REGR	P(O)	0.074	0.0 ?	0.001***	0.000?	0.032*	0.000?	0.000?	0.020?	0.002?	0.440	0.000?	0.017?

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.

CLINICAL PATHOLOGY TABLE 2C

STATISTICAL ANALYSIS SUMMARY

STUDY 8860272 - FEMALES PERIOD 1 VALUES

RESPONSE:		K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	TOT FE (MCG/DL)	TIBC (MCG/DL)
GROUP								
GROUP 1	AVG.	7.21	12 02	8 36	69 0	78 9	234 3	517 0
F	S E	0 41	0 17	0.26	5 1	7 0	19 9	18 4
GROUP 2	AVG	6 94	12.38	9 37	58 7	167 4	12 5	891 7
F	S.E	0 27	0 19	0.32	3 6	22 0	2 2	78 2
	P(C)	0 538	0 187	0 018*	0 073	0 000***	0 000***	0 000***
GROUP 3	AVG	6 48	12 28	9 55	65 8	58 5	145 8	562 8
F	S E.	0 38	0 27	0 27	3 6	4 8	21 7	42 6
	P(C)	0 100	0 338	0 006**	0 572	0 043*	0 009**	0 529
GROUP 4	AVG	6 81	12 05	8 60	76 1	78 7	194 3	589 6
F	S E	0 21	0 16	0 28	4 2	9 7	31 6	33 7
	P(C)	0 363	0 912	0 562	0 213	0 853	0 143	0 089
GROUP 5	AVG	7 23	11 88	8 31	72 8	66 3	217 8	538 6
F	S E	0 21	0 14	0 31	3 0	6 7	23 7	26 4
	P(C)	0 984	0 605	0 904	0 502	0 165	0 481	0 436
GRPS 283	P(O)	0 296	0 711	0 663	0 213	0 000***	0 000***	0 002**
GRPS 284	P(O)	0 766	0 226	0 067	0 003**	0 001***	0 000***	0 000***
GRPS 285	P(O)	0.508	0 069	0.013*	0 016*	0 000***	0 000***	0 000***
FE REGR.	P(O)	0.294	0 050*	0 003**	0 012*	0 000?	0 000?	0 000?

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.

CLINICAL PATHOLOGY TABLE 2d

DATA LISTING

B860272 - MALES

PERIOD 1 VALUES

RESPONSE		RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL)	MCH (PG)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)	SPUN HCT (%)
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	2934	7 64	15 8	43 0	56	20 7	36 7	6 0	1097	3 8	-M-
M	2936	7 60	14 8	39 9	53	19 5	37 1	8 6	993	2 8	-M-
	2941	7 71	15 1	40 8	53	19 6	37 0	5 9	1016	-M-	-M-
	2944	7 82	15 7	44 9	57	20 1	35 0	9 7	990	3 0	-M-
	2946	8 18	15 4	42 9	52	18 8	35 9	12 8	903	2 1	-M-
	2948	8 44	16 4	46 1	55	19 4	35 6	9 7	1005.	3 4	-M-
	2952	8 34	17 0	45 7	55	20 4	37 2	7 0	959	3 1	-M-
	2969	7 86	15 7	43 7	56	20 0	35 9	6 2	914	3 2	-M-
	2994	8 33	15 6	42 3	51	18 7	36 9	7 3	986	3 2	-M-
	2996	7 80	15 6	42 8	55	20 0	36 4	8 1	1298	3 1	-M-
AVERAGE		7 972	15 71	43 21	54 3	19 72	36 37	8 13	1016 1	3 08	-M-
STD ERR		0 100	0 20	0 63	0 6	0 20	0 23	0 68	35 7	0.15	-M-
GROUP 2	2935	1 17	1 6	4 4	38	13 7	36 4	7 8	1194.	34 6	6.
M	2953	1 27	1 8	4 5	35	14 2	40 0	6 2	1395	30.6	6.
	2964	2 00	3 1	8 2	41	15 5	37 8	7 4	3221	36.6	12.
	2967	3 01	5 0	12 9	43	16 6	38 8	8 0	3423	30.0	18.
	2974	1 89	2 5	6.4	34	13 2	39 1	7 0	1729	35 2	10.
	2981	1.64	2 4	6 2	38	14 6	38 7	9 0	2138	39.0	9.
	2997	2.04	3 3	8 5	42	16 2	38 8	9 0	3214	32 1	13.
	3001	2.35	3.6	9.5	40.	15 3	37 9	10.7	3685.	27.6	14.
AVERAGE		1.921	2.81	7.57	38 9	14 91	38 44	8 14	2499 9	33.21	11.0
STD ERR		0.210	0.39	1.00	1 1	0 42	0 38	0 50	352 0	1.34	1.5
GROUP 3	2949	6.45	8 9	23.4	36	13 8	38 0	6 7	1965	13 6	29.
M	2951	7.12	11 4	31.7	45	16 0	36 0	11 2	1134	5 5	-M-
	2955	6.30	8 7	21.3	34	13 8	40 8	8.2	2216	11 4	30
	2956	8.47	14 8	40.3	48	17 5	36 7	9 0	1057	4 0	-M-
	2970	8.22	13.7	36.1	44	16 7	38 0	6 0	1095	7 5	42.
	2980	8.68	14.8	38.9	45.	16 8	37 5	13 2	896.	4 0	-M-
	2983	8 65	14.6	38.1	44	16 9	38.3	8 9	1150	3 8	-M-
	2986	7.14	11.2	30.2	42	15 7	37 1	6 8	1226	6 4	36.
	3000	8.24	12.5	33 0	40	15 2	37 9	7 9	1290	8 1	40.
	3004	8.59	14 6	39.0	45	17 0	37 4	5 7	1176	5 1	-M-
AVERAGE		7.786	12 50	33 20	42 3	15 94	37.77	8.36	1320 5	6 94	35 4
STD.ERR.		0.296	0.75	2.10	1 4	0 42	0.40	0.75	133 8	1 05	2 6

DATA LISTING

B860272 - MALES

PERIOD 1 VALUES

RESPONSE:		RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL)	MCH (PG.)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)	SPUN HCT (%)
GROUP 4	2932	8.42	15.1	41.8	50	17 9	36 1	6 4	1024	2.4	-M-
M	2950	6 18	11 0	32 6	53	17 8	33 7	7 4	665.	2.8	-M-
	2959	8.34	15 8	44 3	53	18 9	35 7	7 3	1017.	2.8	-M-
	2961	7 80	14 3	39.2	50	18 3	36 5	14 8	956.	4.5	-M-
	2965	8 27	16 0	44 6	54	19 3	35 9	10 3	1027	2 3	-M-
	2971	8 11	16 0	43 6	54	19 7	36 7	7 8	893	3 4	-M-
	2972	8 37	15 0	39 8	48	17 8	37 6	11 4	1148	-M-	-M-
	2978	8 80	15.6	43 3	49	17 7	36 0	7 6	900	4 7	-M-
	2982	8 03	14 5	37 9	47	18 1	38 3	11 0	1098	5 4	-M-
	2995	8 30	14 8	41 1	50	17 8	36 0	9 3	1088	3 2	-M-
AVERAGE		8 062	14 81	40 83	50 8	18 34	36 25	9 33	981 6	3 50	-M-
STD ERR		0 225	0 46	1 16	0 8	0 22	0 39	0 81	43 9	0 37	-M-
GROUP 6	2938	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-	-M-
M	2939	7 82	14 5	40 8	52	18 5	35 5	16 3	1097	4 0	-M-
	2942	7 16	14 2	38 1	51	19 8	37 3	8 2	913	2 7	-M-
	2943	7 28	14 1	35 6	49	19 4	39 6	8 8	977	-M-	-M-
	2947	7 93	15 3	43 0	54	19 3	35 6	6 1	925	3 9	-M-
	2962	7 27	14 6	41 1	57	20 1	35 5	12 3	1200	3 9	-M-
	2968	7 80	15 3	41 8	54	19 6	36 6	13 6	1159	2 6	-M-
	2989	7 80	15 3	43 5	56	19 6	35 2	12 6	1012	3 0	-M-
	2999	7 81	15.2	41.8	54	19 5	36 4	7 3	1022	3 4	-M-
	3003	7.26	14.6	40.7	56	20 1	35 9	9 8	918	3.4	-M-
AVERAGE		7.570	14.79	40.71	53 9	19 54	36 40	10.56	1024.8	3.36	-M-
STD ERR.		0.105	0.16	0.82	0 8	0 16	0 46	1 11	35.4	0.20	-M-

DATA LISTING

B860272 - MALES PERIOD 1 VALUES

RESPONSE:		BANDS THOUSAND	BASO THOUSAND	EOS THOUSAND	LYMPH THOUSAND	MONO THOUSAND	SEGS THOUSAND
NORM.RNG -LO:							
HI:							
GROUP	ANIMAL						
GROUP 1	2934	0 0	0 0	0 0	4 92	0 42	0 66
M	2936	0 0	0 0	0 09	7 22	0 60	0 69
	2941	0 0	0 0	0 0	5 13	0 29	0 47
	2944	0 0	0 0	0 10	8 83	0 19	0 58
	2946	0 0	0 0	0 0	11 90	0 38	0 51
	2948	0 0	0 0	0 19	8 44	0 48	0 58
	2952	0 0	0 0	0 07	6 02	0 49	0 42
	2969	0 0	0 0	0 0	5 46	0 31	0 43
	2994	0 0	0 0	0 0	6 28	0 36	0 66
	2996	0 0	0 0	0 0	6 12	0 40	0 97
AVERAGE		0 0	0 0	0 045	7 092	0 395	0 598
STD ERR		0 0	0 0	0 021	0 676	0 036	0 051
GROUP 2	2939	0 0	0 0	0 08	6 32	0 39	1 01
M	2953	0 0	0 0	0 0	4 46	0 50	1 24
	2964	0 0	0 0	0 0	5 31	0 81	1 26
	2967	0 0	0 0	0 0	7 04	0 40	0 56
	2974	0 0	0 0	0 0	5 74	0 63	0 63
	2981	0 0	0 0	0 0	7 02	0 63	1 35
	2997	0.0	0.0	0.0	5 58	1 17	2 25
	3001	0.0	0 0	0.11	6 95	0 96	2 67
AVERAGE		0 0	0 0	0 023	6 056	0 687	1 372
STD.ERR		0.0	0.0	0.015	0 332	0 098	0 262
GROUP 3	2949	0.0	0.0	0.07	5.02	0.27	1.34
M	2951	0.0	0.0	0.0	9 41	0.45	1 34
	2955	0.0	0.0	0.0	7.46	0.16	0 57
	2956	0.0	0.0	0.18	7 83	0.36	0 63
	2970	0.0	0.0	0.06	5.40	0.24	0 30
	2980	0.0	0.0	0.0	12.28	0 40	0 53
	2983	0.0	0.0	0.09	6 50	0.18	2 14
	2986	0.0	0 0	0.07	5 85	0 27	0 61
	3000	0.0	0.0	0.0	7 03	0.24	0 63
	3004	0 0	0.0	0.06	4 39	0 23	1 03
AVERAGE		0.0	0.0	0.052	7 117	0 279	0 912
STD.ERR.		0.0	0.0	0.018	0 740	0 029	0 175

DATA LISTING

B860272 - MALES PERIOD 1 VALUES

RESPONSE:		BANDS THOUSAND	BASO THOUSAND	EOS THOUSAND	LYMPH THOUSAND	MONO THOUSAND	SEGS THOUSAND
GROUP 4	2932	0.0	0 0	0.0	5 44	0.26	0 70
M	2950	0 0	0 0	0 0	6.22	0 22	0 96
	2959	0.0	0 0	0.0	6 35	0 44	0 51
	2961	0 0	0 0	0 0	13 32	0 59	0 89
	2965	0 0	0 0	0.21	9 17	0 51	0 41
	2971	0 0	0 0	0 0	7 02	0 47	0 31
	2972	0 0	0 0	0 0	8 09	0 57	2 74
	2978	0 0	0 0	0 15	5 47	0 46	1 52
	2982	0 0	0 0	0 0	9 13	0 77	1 10
	2995	0 0	0 0	0 0	8 28	0 37	0 65
AVERAGE		0 0	0 0	0 036	7 849	0 466	0 980
STD ERR		0 0	0 0	0 024	0 750	0 051	0 225
GROUP 5	2938	-M-	-M	-M	-M	-M	-M-
M	2939	0 0	0 0	0 0	14 34	0 98	0 98
	2942	0 0	0 0	0 0	6 56	0 74	0 90
	2943	0 0	0 0	0 0	7 48	0 62	0 70
	2947	0 0	0 0	0 0	5 43	0 24	0 43
	2962	0 0	0 0	0 0	11 19	0 61	0 49
	2968	0 0	0 0	0 0	12 10	0 41	1 09
	2989	0 0	0 0	0 25	10 96	0 63	0 76
	2999	0 0	0 0	0 0	6 50	0 36	0 44
	3003	0.0	0.0	0.0	8 33	0 69	0 78
AVERAGE		0.0	0.0	0.028	9 211	0 587	0 730
STD ERR.		.0 0	0.0	0.028	1 015	0 073	0 080

DATA LISTING

B860272 - FEMALES

PERIOD 1 VALUES

RESPONSE:		RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL)	MCH (PG)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)	SPUN HCT (%)
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	3009	7 86	14 8	42 6	54	18 6	34 7	5 1	987	3 0	-M-
F	3012	7 39	14 7	40 5	55	19 9	36 3	6 7	877	2 3	-M-
	3021	7 68	14 8	42 1	55	19 3	35 2	5 4	872	2 8	-M-
	3045	7 64	14 7	41 4	54	19 2	35 5	4 8	890	2 6	-M-
	3048	7 61	14 3	39 7	52	18 8	36 0	7 0	1001	5 2	-M-
	3050	7 58	14 9	42 6	56	19 7	35 0	7 3	866	2 3	-M-
	3061	7 41	14 9	41 7	56	20 1	35 7	5 5	963	-M-	-M-
	3071	7 41	14 6	40 7	55	19 7	35 9	6 4	976	2 3	-M-
	3072	7 64	15 6	43 3	57	20 4	36 0	7 3	917	2 5	-M-
	3074	7 83	15 2	42 6	54	19 4	35 7	7 2	1031.	3 2	-M-
AVERAGE		7 615	14 85	41 72	54 8	19 51	35 60	6 27	938 0	2 91	-M-
STD ERR		0 058	0 11	0 36	0 4	0 18	0 16	0 31	19 2	0 31	-M-
GROUP 2	3010	2 11	3 3	9 1	41	15 6	36 3	6 6	2379	19 1	13
F	3026	1 42	1 8	4 9	35	12 7	36 7	7 3	1760	-M-	8
	3027	1 96	2 7	7 3	37	13 8	37 0	8 1	2119	20 0	10.
	3041	1 12	1 6	4.7	42	14 3	34 0	6 8	1087	23 4	5.
	3044	1 46	2 0	5 6	38	13 7	35 7	7 0	2170	30 4	8
	3051	1 89	3 0	8 0	40	15 1	37 5	4 8	1598.	25 6	12.
	3053	1 88	2 8	7.5	40	14 9	37 3	8 3	2253	22.3	10.
	3060	1.56	2 2	5.7	37	14 1	38 6	4 3	1664	24 0	8.
	3063	2 16	3 1	8.7	40	14 4	35 6	6 1	2292	22 4	11.
	3066	1.73	2 8	7.7	45	16.2	36 4	6 8	2146.	29.6	10.
AVERAGE		1.739	2 53	6 92	39 7	14 48	36 51	6 60	1946 8	24 09	9 5
STD.ERR		0 108	0 19	0.50	1.0	0.32	0 40	0 40	128 9	1.29	0.7
GROUP 3	3008	7.02	12.2	34.8	50	17.4	35 1	6 8	798.	3.3	-M-
F	3022	7.35	13.5	37.9	52	18.4	35.6	7.1	852.	2.0	-M-
	3030	7 75	14.4	39 6	51	18 6	36 4	6 1	763.	3.1	-M-
	3032	7.82	13.2	37 2	48	16 9	35 5	7 2	956.	2 7	-M-
	3035	7.75	14.7	40.8	53	19 0	36 0	5 0	951	2.9	-M-
	3056	8 06	14.9	43.1	53	18 5	34 6	8 7	951	2 4	-M-
	3059	7.33	14.0	38.7	53	19 1	36 2	5 2	964	2 1	-M-
	3065	7.33	13 4	36.7	50	18 3	36 5	7 9	947	3 7	-M-
	3067	8 54	14.9	40 6	48	17 4	36 7	6 5	911	2 7	-M-
	3073	7.60	14.6	40.4	53	19 2	36 1	4 4	994.	4 3	-M-
AVERAGE		7 655	13 98	38.98	51 1	18 28	35 87	6 49	918 7	2 92	-M-
STD ERR		0 138	0.28	0.76	0.6	0.25	0 21	0 42	24 0	0 23	-M-

DATA LISTING

8860272 - FEMALES

PERIOD 1 VALUES

RESPONSE:		RBC MILLION	HGB (GM/DL)	HCT (%)	MCV (FL)	MCH (PG)	MCHC (%)	WBC THOUSAND	PLATELET THOUSAND	RETIC (%)	SPUN HCT (%)
GROUP 4	3015	7.00	14.8	41.7	60	21.1	35.5	7.5	975	1.6	-M-
F	3017	7.66	14.5	39.5	52	18.9	36.7	4.7	843	2.6	-M-
	3033	7.38	14.5	40.4	55	19.6	35.9	6.7	950	2.2	-M-
	3039	7.10	14.0	39.7	56	19.7	35.3	4.6	985	3.6	-M-
	3040	7.40	14.4	39.9	54	19.5	36.1	5.3	965	3.6	-M-
	3054	7.54	14.7	41.8	55	19.5	35.2	5.6	1042	2.2	-M-
	3055	7.06	14.6	40.3	57	20.7	36.2	10.0	951	3.7	-M-
	3057	7.75	14.9	41.8	54	19.2	35.6	5.8	1115.	3.6	-M-
	3069	8.13	15.7	43.6	54	19.3	36.0	8.3	894.	2.7	-M-
	3070	8.35	15.3	42.9	51	18.3	35.7	5.7	900	2.8	-M-
AVERAGE		7.537	14.74	41.16	54.8	19.58	35.82	6.42	962.0	2.86	-M-
STD ERR		0.142	0.15	0.45	0.8	0.26	0.14	0.54	24.4	0.23	-M-
GROUP 5	3006	8.21	15.9	44.6	54	19.4	35.7	5.8	741	2.1	-M-
F	3019	7.15	14.5	40.0	56	20.3	36.3	6.0	857	3.8	-M-
	3028	7.04	13.9	39.5	56	19.7	35.2	5.6	790	3.7	-M-
	3037	7.48	14.7	41.4	55	19.7	35.5	5.5	801	4.3	-M-
	3038	8.10	14.7	42.7	53	18.1	34.4	6.4	997	2.8	-M-
	3043	7.50	14.7	41.3	55	19.6	35.6	5.2	938	3.1	-M-
	3058	7.54	14.8	42.0	56	19.8	35.5	8.0	892	2.9	-M-
	3075	8.26	15.3	42.8	52	18.5	35.7	5.5	809	3.2	-M-
	3076	8.11	15.8	43.8	54	19.6	36.3	9.3	837	2.2	-M-
	3077	7.68	15.6	43.3	57	20.4	36.0	3.7	908.	3.3	-M-
AVERAGE		7.705	15.01	42.14	54.8	19.51	35.62	6.10	857.0	3.14	-M-
STD ERR.		0.140	0.21	0.51	0.5	0.23	0.18	0.49	24.4	0.22	-M-

DATA LISTING

BB60272 - FEMALES PERIOD 1 VALUES

RESPONSE		BANDS THOUSAND	BASO THOUSAND	EOS THOUSAND	LYMPH THOUSAND	MONO THOUSAND	SEGS THOUSAND
NORM.RNG.-LO:							
HI:							
GROUP	ANIMAL						
GROUP 1	3009	0 0	0 0	0 0	4 59	0 15	0 36
F	3012	0 0	0 0	0 0	5 96	0 54	0 20
	3021	0 0	0 0	0 05	4 64	0 32	0 38
	3045	0 0	0 0	0 0	4 22	0 47	0 14
	3048	0 0	0 0	0.0	5 95	0 21	0 84
	3050	0 0	0 0	0.0	6 50	0 15	0 66
	3061	0 0	0 0	0 05	4 78	0 27	0 38
	3071	0 0	0 0	0 06	5 50	0 26	0 58
	3072	0 0	0 0	0 0	6 72	0 36	0 22
	3074	0 0	0 0	0 0	6 34	0 29	0 58
	AVERAGE	0 0	0 0	0 017	5 521	0 298	0 433
	STD ERR	0 0	0 0	0 009	0 284	0 039	0 071
GROUP 2	3010	0 0	0 0	0 0	5 28	0 59	0 71
F	3026	0 0	0 0	0 0	6 28	0 44	0 58
	3027	0 0	0 0	0.0	6 88	0 49	0 73
	3041	0.0	0 0	0 07	5 37	0 54	0 82
	3044	0 0	0 0	0.0	5 32	0 70	0 98
	3051	0 0	0 0	0.0	4 46	0 29	0 15
	3053	0.0	0.0	0.0	6 14	1 00	1 16
	3060	0.0	0 0	0.0	3 65	0 34	0 30
	3063	0 0	0.0	0.0	4 88	0 43	0 79
	3066	0.0	0.0	0.0	5 87	0 33	0 40
	AVERAGE	0.0	0 0	0.007	5 414	0 518	0 683
	STD ERR.	0.0	0.0	0.007	0 298	0 067	0 098
GROUP 3	3008	0.0	0 0	0.27	5 64	0.48	0 41
F	3022	0.0	0 0	0.07	5 75	0 50	0 78
	3030	0.0	0.0	0.06	5.25	0.30	0 49
	3032	0.0	0.0	0.0	6 19	0.36	0 65
	3035	0.0	0.0	0.0	4 60	0.20	0 20
	3056	0.0	0.0	0.09	7 57	0 35	0 70
	3059	0 0	0.0	0.0	4 26	0 36	0 57
	3065	0 0	0 0	0.24	6 64	0.32	0 71
	3067	0 0	0 0	0.0	5 85	0 32	0 32
	3073	0.0	0 0	0 0	4 05	0 22	0 13
	AVERAGE	0 0	0 0	0 073	5 580	0 341	0 496
	STD.ERR	0.0	0 0	0 032	0 345	0 030	0 071

DATA LISTING

B860272 - FEMALES

PERIOD 1 VALUES

RESPONSE:		BANDS THOUSAND	BASO THOUSAND	EOS THOUSAND	LYMPH THOUSAND	MONO THOUSAND	SEGS THOUSAND
GROUP 4	3015	0 0	0.0	0.0	6 52	0 60	0 38
F	3017	0 0	0 0	0.0	4 23	0 23	0 23
	3033	0 0	0 0	0 0	5 63	0 13	0 94
	3039	0 0	0 0	0 0	3 77	0 18	0 64
	3040	0 0	0 0	0 0	4 61	0 16	0 53
	3054	0 0	0 0	0 06	4 48	0 28	0 78
	3055	0 0	0 0	0 0	9 10	0 20	0 70
	3057	0 0	0 0	0 0	5 05	0 17	0 58
	3069	0 0	0 0	0 0	7 55	0 50	0 25
	3070	0 0	0 0	0 11	4 96	0 17	0 46
	AVERAGE	0 0	0 0	0 017	5 590	0 263	0 549
	STD ERR	0 0	0 0	0 012	0 528	0 050	0 072
GROUP 5	3006	0 0	0 0	0 0	5 05	0 23	0 52
F	3019	0 0	0 0	0 0	5 22	0 36	0 42
	3028	0 0	0 0	0 11	4 65	0 22	0 62
	3037	0 0	0 0	0 05	4 13	0 27	0 44
	3038	0 0	0 0	0 0	5 82	0 26	0 32
	3043	0 0	0 0	0 0	4 47	0 47	0 26
	3058	0 0	0 0	0 24	6 12	0 40	1 04
	3075	0 0	0 0	0 0	4 73	0 38	0 38
	3076	0 0	0.0	0.0	6 60	1 39	1 30
	3077	0.0	0.0	0 0	3 37	0 26	0 07
	AVERAGE	0.0	0.0	0.041	5 096	0 425	0 538
	STD.ERR.	0.0	0.0	0.025	0 301	0.111	0 117

Report:CLPXPR55 CLINICAL PATHOLOGY - HEMATOLOGY ALPHA RESULTS Run date:09/12/
Study (Ref) no.:B86-0272 Run time: 14:13
Period: 1 File no.:8600078

Grp Id.	Animal Id.	Sex	Platelets	Polychromasia	Anisocytosis	Poikilocytosis	Rbc crenated	Smudge cells
0001	3009	F		NOTED	1+		MOD	
	3012			NOTED	1+		MOD	
	3021			NOTED	1+		MOD	
	3045			NOTED	1+		OCC	
	3048			NOTED	1+		MANY	
	3050			NOTED	1+		MANY	
	3061			NOTED	1+		MANY	
	3071			NOTED	1+		MANY	
	3072			NOTED	1+		MANY	
	3074			NOTED	1+		MANY	
	2934	M		NOTED	1+		MOD	
	2936			NOTED	1+		OCC	
	2941			NOTED	1+		FEW	
	2944			NOTED	1+		FEW	
	2946			NOTED	1+		FEW	
	2948			NOTED	1+		FEW	
	2952			NOTED	1+		MOD	
	2969			NOTED	1+		FEW	
	2994			NOTED	1+		OCC	
	2996			NOTED	1+		MANY	
0002	3010	F		3+	3+	2+	FEW	
	3026			3+	3+	1+	OCC	
	3027			3+	3+	1+	OCC	
	3041			2+	2+	1+	RARE	
	3044			3+	3+	2+	OCC	
	3051			3+	2+	1+	OCC	
	3053			3+	3+	1+	OCC	
	3060			2+	2+	1+	OCC	
	3063			3+	2+	2+	FEW	
	3066			2+	3+	1+	OCC	
	2935	M		3+	2+	2+	RARE	
	2953			3+	2+	1+	OCC	
	2964			3+	2+	2+	OCC	
	2967			3+	2+	1+	OCC	
	2974			3+	2+	2+	OCC	
	2981			3+	2+	2+	OCC	
	2997			3+	2+	2+	FEW	
	3001			3+	2+	2+	FEW	
0003	3008	F		1+	1+		MANY	
	3022			NOTED	1+		MANY	
	3030			NOTED	1+		MANY	
	3032			NOTED	1+		MOD	
	3035			NOTED	1+		MANY	
	3056			NOTED	1+		MANY	
	3059			NOTED	1+		MOD	
	3065			NOTED	1+		OCC	
	3067			NOTED	1+		MANY	
	3073			NOTED	1+		MANY	
	2949	M		2+	2+	2+	FEW	
	2951			1+	1+		FEW	
	2955			2+	2+	1+	FEW	
	2956			NOTED	1+		MOD	

Report:CLPXPR55 CLINICAL PATHOLOGY - HEMATOLOGY ALPHA RESULTS Run date:09/12/
Study (Ref) no.:B86-0272 Run time: 14:13
Period: 1 File no.:860007

Grp Id.	Animal Id.	Sex	Platelets	Polychromasia	Anisocytosis	Poikilocytosis	Rbc crenated	Smudge cells
0003	2970	M		NOTED	1+		MOD	
	2980			NOTED	1+		FEW	
	2983			NOTED	1+		MOD	
	2986			2+	2+		OCC	
	3000			NOTED	1+		FEW	
	3004			NOTED	2+	1+	MOD	
0004	3015	F		NOTED	1+		MANY	
	3017			NOTED	1+		MOD	
	3033			NOTED	1+		MOD	
	3039			NOTED	1+		MANY	
	3040			NOTED	1+		MANY	
	3054			NOTED	1+		MANY	
	3055			NOTED	1+		MANY	
	3057			NOTED	1+		MANY	
	3069			NOTED	1+		MANY	
	3070			NOTED	1+		MANY	
	2932	M		NOTED	1+		MOD	
	2950			NOTED	1+		OCC	
	2959			NOTED	1+		FEW	
	2961			NOTED	1+		FEW	
	2965			NOTED	1+		FEW	
	2971			NOTED	1+		OCC	
	2972		PLTS NORM	NOTED	1+	1+	RARE	
	2978			1+	1+		MOD	
	2982			NOTED	1+		OCC	
	2995			NOTED	1+		FEW	
0005	3006	F		NOTED	1+		MANY	
	3019			NOTED	1+		MOD	
	3028			NOTED	1+		MANY	
	3037			NOTED	1+		MANY	
	3038			NOTED	1+		MANY	
	3043			NOTED	1+		MOD	
	3058			NOTED	1+		MANY	
	3075			NOTED	1+		FEW	
	3076			NOTED	1+		MANY	
	3077			NOTED	1+		MANY	
	2939	M		NOTED	1+		RARE	
	2942			NOTED	1+		RARE	
	2943		PLTS NORM	NOTED	1+		RARE	
	2947			NOTED	1+		MOD	
	2962			NOTED	1+		OCC	
	2968			NOTED	1+		FEW	
	2989			NOTED	1+		MOD	
	2999			NOTED	1+		FEW	
	3003			NOTED	1+		FEW	

Report:CLPXPR55 CLINICAL PATHOLOGY - HEMATOLOGY ALPHA RESULTS Run date:09/12/
Study (Ref) no.:B86-0272 Run time: 14:14
Period: 1 File no.:860007

Grp Id.	Animal Id.	Sex	Plt Decrease	Plt Increase	Plt mkd Decrease	Plt mkd Increase	Plt clumped	Plt giant
0001	3009	F					MANY	
	3012						MANY	
	3021						MANY	
	3045						MANY	
	3048						MANY	
	3050						MANY	
	3061						MANY	
	3071						MANY	
	3072						MANY	
	3074						MANY	
	2934	M					MANY	
	2936						MANY	
	2941						MANY	
	2944						MANY	
	2946						MANY	
	2948						MANY	
	2952						MANY	
	2969						MANY	
	2994						MANY	
	2996						MANY	
0002	3010	F					MANY	
	3026						MANY	
	3027						MANY	
	3041						MANY	
	3044						MOD	
	3051						MOD	
	3053						MOD	
	3060						MOD	
	3063						MOD	
	3066						MANY	
	2935	M					MOD	
	2953						MOD	
	2964						MANY	
	2967						MANY	
	2974						MOD	
	2981						MOD	
	2997						MOD	
	3001						MOD	
0003	3008	F					MANY	
	3022						MANY	
	3030						MANY	
	3032						MANY	
	3035						MANY	
	3056						MANY	
	3059						MANY	
	3065						MANY	
	3067						MANY	
	3073						MANY	
	2949	M					MANY	
	2951						MANY	
	2955						MOD	
	2956						MANY	

Report:CLPXPR55 CLINICAL PATHOLOGY - HEMATOLOGY ALPHA RESULTS Run date:09/12/
Study (Ref) no.:B86-0272 Run time: 14:14
Period: 1 File no.:860007

Grp Id.	Animal Id.	Sex	Plt Decrease	Plt Increase	Plt mkd Decrease	Plt mkd Increase	Plt clumped	Plt giant
0003	2970	M					MANY	
	2980						MANY	
	2983						MANY	
	2986						MANY	
	3000						MANY	
	3004						MANY	
0004	3015	F					MANY	
	3017						MANY	
	3033						MANY	
	3039						MANY	
	3040						MANY	
	3054						MANY	
	3055						MANY	
	3057						MANY	
	3069						MANY	
	3070						MANY	
	2932	M					MANY	
	2950						MOD	
	2959						MANY	
	2961						MANY	
	2965						MANY	
	2971						MANY	
	2978						MANY	
	2982						MOD	
	2995						MANY	
0005	3006	F					MANY	
	3019						MANY	
	3028						MANY	
	3037						MANY	
	3038						MANY	
	3043						MOD	
	3058						MANY	
	3075						MANY	
	3076						MANY	
	3077						MANY	
	2939	M					MOD	
	2942						MOD	
	2947						MANY	
	2962						MANY	
	2968						MANY	
	2989						MOD	
	2999						MANY	
	3003						MANY	

Report:CLPXPR55 CLINICAL PATHOLOGY - HEMATOLOGY ALPHA RESULTS Run date:09/12/
Study (Ref) no.:B86-0272 Run time: 14:16
Period: 1 File no.:860007

Grp Id.	Animal Id.	Sex	Baso Stippling	Hypo Chromic		Micro cytes	Rbc dim orp pop	Rbc inclu sions
0002	3010	F		2+				
	3026			3+				
	3027			3+				
	3041			2+				
	3044			3+				
	3051			2+				
	3053			3+				
	3069			2+				
	3063			2+				
	3066			2+				
	2935	M		2+				
	2953			2+				
	2964			3+				
	2967			3+				
	2974			3+				
	2981			3+				
	2997			3+				
	3001			3+				
0003	2949	M		2+				
	2951			NOTED				
	2955			4+				
	2986			1+				
	3000			1+				
0004	2950	M		NOTED				

DATA LISTING

STUDY B860272 - 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)	NA (MEQ/L)
NORM.RNG.-LO:		53	10	0.5	4.0	2.9			33	58	18	0.0	141
HI:		110	21	0.9	7.1	4.3			221	202	70	0.33	159
GROUP	ANIMAL												
GROUP 1	2934	261.	15.8	0.6	6.4	4.2	2.2	1.91	197.	108	40.	0.1	145.
M	2936	356	18.1	0.6	6.2	4.2	2.0	2.10	268	109.	47.	0.1	145.
	2941	348	20.4	0.8	5.8	4.2	1.6	2.63	248	83.	31.	0.1	145.
	2944	356.	17.0	0.7	6.4	4.2	2.2	1.91	354	90.	55.	0.1	147.
	2946	310	17.2	0.6	6.1	4.3	1.8	2.39	260	111.	64.	0.1	146.
	2948	418	21.6	0.7	6.6	4.5	2.1	2.14	322	126	55.	0.1	147.
	2952	439	17.2	0.6	7.0	4.5	2.5	1.80	311.	97	68.	0.2	144.
	2969	474	15.6	0.6	6.3	4.3	2.0	2.15	300	94.	66.	0.1	144.
	2994	402	16.7	0.7	6.4	4.3	2.1	2.05	329	134.	75.	0.1	144.
	2996	329	8.9	0.6	6.1	4.1	2.0	2.05	197	80	38.	0.1	143
AVERAGE		369.3	16.82	0.65	6.33	4.28	2.05	2.113	278.6	103.2	53.8	0.11	145.0
STD ERR		20.3	1.07	0.02	0.10	0.04	0.08	0.077	17.1	5.6	4.6	0.01	0.4
GROUP 2	2935	202	42.2	0.5	4.9	3.8	1.1	3.45	210	103	36.	0.1	141.
M	2953	186	31.4	0.4	5.1	3.9	1.2	3.25	263	211	113	0.2	132.
	2964	259	35.7	0.4	4.8	3.6	1.2	3.00	232	119	44.	0.2	143
	2967	398	18.7	0.6	4.8	3.8	1.0	3.80	80	106.	41.	0.2	144
	2974	261	23.3	0.6	5.3	4.1	1.2	3.42	133	118.	52.	0.2	142.
	2981	246.	32.0	0.6	5.7	4.3	1.4	3.07	174	119.	54.	0.3	141
	2997	278.	18.8	0.5	4.5	3.5	1.0	3.50	80	139.	54	0.2	137.
	3001	385.	16.3	0.6	5.4	4.1	1.3	3.15	134.	98.	39.	0.3	142.
AVERAGE		276.9	26.82	0.52	5.06	3.89	1.17	3.330	163.2	126.6	54.1	0.21	140.2
STD.ERR.		27.3	3.47	0.03	0.14	0.10	0.05	0.093	24.1	12.9	8.8	0.02	1.4
GROUP 3	2949	187.	19.9	0.6	6.1	4.1	2.0	2.05	217.	120.	50.	0.1	146.
M	2951	173.	23.6	0.6	5.8	4.0	1.8	2.22	220.	150.	61.	0.1	144.
	2955	381.	19.4	0.6	5.7	4.2	1.5	2.80	425	107.	43.	0.2	145.
	2956	341.	20.6	0.7	6.7	4.5	2.2	2.05	339	82.	47.	0.1	145.
	2970	454.	19.5	0.7	6.4	4.4	2.0	2.20	246.	109.	55.	0.2	146.
	2980	295.	20.9	0.7	6.1	4.3	1.8	2.39	285	89.	52.	0.2	148
	2983	463.	17.1	0.7	7.0	4.5	2.5	1.80	220.	115.	68.	0.2	143.
	2986	277.	21.6	0.6	5.9	4.2	1.7	2.47	359.	97.	49.	0.2	146.
	3000	264.	15.2	0.7	6.3	4.3	2.0	2.15	246.	99.	42.	0.2	144
	3004	301.	19.5	0.6	6.3	4.2	2.1	2.00	223	94	53	0.1	143.
AVERAGE		313.6	19.73	0.65	6.23	4.27	1.96	2.213	278.0	106.2	52.0	0.16	145.0
STD ERR.		31.2	0.73	0.02	0.13	0.05	0.09	0.089	23.0	6.1	2.5	0.02	0.5

DATA LISTING

STUDY B860272 - 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)	NA (MEQ/L)
GROUP 4	2932	384.	15.5	0.7	6.4	4.2	2.2	1.91	286	115	45.	0.0	147.
M	2950	269	19.7	0.7	6.0	4.1	1.9	2.16	238	99	44.	0.0	145
	2959	341	18.7	0.6	6.4	4.4	2.0	2.20	224	84	47.	0.1	147.
	2961	278	23.8	0.7	5.7	4.1	1.6	2.56	215	152	48	0.1	145.
	2965	391	17.9	0.6	6.3	4.3	2.0	2.15	314	128	61	0.1	148
	2971	440	14.8	0.7	6.2	4.3	1.9	2.26	219	94	47	0.1	146
	2972	318	15.0	0.7	5.9	4.3	1.6	2.69	285	101.	66.	0.1	142
	2978	431	13.0	0.7	6.3	4.3	2.0	2.15	174	102	53	0.1	144
	2982	238	15.7	0.6	6.1	4.2	1.9	2.21	168	111	64	0.1	140
	2995	355	20.0	0.7	6.3	4.3	2.0	2.15	198	107	55.	0.1	143.
AVERAGE		350.5	17.41	0.67	6.16	4.25	1.91	2.244	232.1	109.3	53.0	0.08	144.7
STD ERR		21.8	1.02	0.02	0.07	0.03	0.06	0.070	15.5	6.1	2.6	0.01	0.8
GROUP 5	2938	216	19.6	0.6	6.3	4.3	2.0	2.15	295	93	53.	0.1	144.
M	2939	236	20.6	0.6	6.0	4.3	1.7	2.53	204	166	75.	0.1	140.
	2942	201	17.0	0.6	5.9	4.1	1.8	2.28	215	101.	46.	0.1	144.
	2943	290	17.9	0.6	6.1	4.2	1.9	2.21	190	88	41.	0.1	144.
	2947	444	17.2	0.6	6.2	4.3	1.9	2.26	202	135.	58.	0.1	144
	2962	360	13.9	0.7	6.2	4.3	1.9	2.26	284	106	51	0.1	144.
	2968	300	15.1	0.7	6.2	4.1	2.1	1.95	164	111	38	0.1	144
	2989	455	20.6	0.7	6.2	4.2	2.0	2.10	167.	81.	41.	0.1	144.
	2999	410.	16.6	0.7	6.7	4.4	2.3	1.91	331	87.	48.	0.1	144
	3003	407.	17.8	0.7	6.2	4.3	1.9	2.26	261	99.	48.	0.2	142.
AVERAGE		327.9	17.63	0.65	6.20	4.25	1.95	2.191	231.3	106.7	49.9	0.11	143.4
STD.ERR.		31.2	0.70	0.02	0.07	0.03	0.05	0.056	18.2	8.2	3.4	0.01	0.4

DATA LISTING

STUDY 8860272 - MALES

PERIOD 1 VALUES

RESPONSE:		K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	TOT FE (MCG/DL)	TIBC (MCG/DL)	ICTERIC	HEMOLYS	LIPEMIA
NORM.RNG -LO:		3.9	10.2	6.8	18	6					
HI:		7.1	12.2	9.0	122	30					
GROUP	ANIMAL										
GROUP 1	2934	6.3	12.3	9.1	73	104	276	566	0	0	0
M	2936	6.8	11.9	8.0	54	138	141	631	0	0	0.
	2941	6.9	10.4	7.6	41	33	136	437	0	0	0
	2944	7.2	12.6	9.5	71	167	193	522	0	0	0.
	2946	6.7	11.8	8.8	80	170	190	495	0	0	0
	2948	9.0	12.4	8.9	74	75	164	569	0	0	0
	2952	8.5	12.6	10.7	63	201	370	599	0	0	0.
	2969	8.3	12.4	9.8	70	105	186	454	0	0	0.
	2994	8.5	11.8	9.7	74	90	214	665	0	0	0
	2996	6.7	11.6	9.4	72	40	211	476	0	0	0.
AVERAGE		7.49	11.98	9.15	67.2	112.3	208.1	541.4	0.0	0.0	0.0
STD ERR		0.31	0.21	0.28	3.7	17.8	22.0	24.3	0.0	0.0	0.0
GROUP 2	2935	5.5	10.9	7.3	55	296	16	806	0	0	0
M	2953	5.8	10.0	6.5	83	694	13	847	4	1	0.
	2964	7.0	11.1	9.4	49	87	33	689	0	0	0
	2967	7.8	11.8	9.5	41	37	17	750	0	0	0.
	2974	6.6	11.1	8.0	53	211	25	834	0	0	0
	2981	6.1	11.2	6.8	56	312	36	680.	1	0	0.
	2997	8.2	10.5	8.8	47	75	31	619	0.	0.	0.
	3001	8.2	12.2	10.0	50	52	17	850	0	0.	0.
AVERAGE		6.90	11.07	8.29	54.3	223.0	23.5	759.4	0.6	0.1	0.0
STD.ERR.		0.38	0.23	0.47	4.4	77.8	3.2	31.2	0.5	0.1	0.0
GROUP 3	2949	6.2	11.5	8.5	70	85	36	750	0	0	0.
M	2951	6.0	10.7	8.7	72	95	33	490	0	0	0
	2955	7.6	11.9	9.6	56	57	49	788.	0	0.	0.
	2956	5.8	12.0	8.7	50	72	50	606	0	0	0
	2970	8.9	12.8	10.2	72	179	36	718	0	0	0.
	2980	7.3	12.8	10.4	52	74	246	592	0	0	0
	2983	8.8	12.6	10.6	47	46	175	468	0	0.	0
	2986	5.9	11.7	9.9	52	57	44	666	0	0.	0
	3000	6.1	11.6	9.6	61	75	52	730.	0.	0.	0
	3004	7.5	12.0	8.7	74	118	83	656	0	0	0
AVERAGE		7.01	11.96	9.49	60.6	85.8	80.4	646.4	0.0	0.0	0.0
STD ERR		0.37	0.21	0.25	3.3	12.2	22.8	34.0	0.0	0.0	0.0

DATA LISTING

STUDY B860272 - MALES

PERIOD 1 VALUES

RESPONSE:		K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	TOT FE (MCG/DL)	TIBC (MCG/DL)	ICTERIC	HEMOLYS.	LIPEMIA
GROUP 4	2932	7 0	12 6	9 1	51	154	354	534	0	1.	0.
M	2950	5 9	10 8	6 7	62	144	322	522	0	0	0
	2959	6 2	12 0	8 7	84	105	177	667	0	0	0.
	2961	6 1	10 5	8 1	70	91	87	500	0	0	0.
	2965	8 1	11 8	9 1	70	65	178	566	0	0.	0.
	2971	8 1	11 8	9 8	74	95	104	545	0	0	0
	2972	6 8	11 9	9 1	69	115	228	506	0	0	0.
	2978	8 6	12 0	9 6	59	71	91	582	0	0	0.
	2982	8 0	11 2	9 5	59	84	92	547	0	0	0.
	2995	7 8	12 4	9 5	63	83	47	569	0	0.	0
AVERAGE		7 26	11 70	8 92	66 1	100 9	168 0	553 8	0 0	0 1	0 0
STD ERR		0 31	0 21	0 29	2 9	9 3	33 2	15 2	0 0	0 1	0 0
GROUP 5	2938	6 5	11 6	7 8	65	126	459	649	0	1	0
M	2939	7 9	10 2	8 4	83	94	116	725	0	6	0
	2942	5 5	10 4	6 8	51	122	106	516.	0	0.	0.
	2943	5 0	10 7	7 4	42	160	91	562	0	0.	0
	2947	8 4	12 3	10 5	59	261	164	571	0	0	0.
	2962	7 8	11 5	10 1	72	87	172	529	0	0	0.
	2968	7 5	11 5	9 2	67	41	102	533	0	0.	0.
	2989	6 5	11 9	8 5	52	150	83	568	0	0	0
	2999	6 8	12 5	9 5	52	96	150	606	0	0	0.
	3003	6 7	11 3	8 7	55	27	89	492	0	0	0.
AVERAGE		6 86	11 39	8 69	59 8	116 4	153 2	575 1	0 0	0 7	0 0
STD ERR		0 34	0 24	0.37	3 8	21 0	35 5	22 0	0 0	0.6	0.0

DATA LISTING

STUDY 8860272 - 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)	NA (MEQ/L)
NORM.RNG.-LO:		53	10	0 5	4 0	2 9			33	58	18	0.0	141
HI:		110	21	0 9	7 1	4 3			221	202	70	0.33	159
GROUP	ANIMAL												
GROUP 1	3009	293	17 8	0 7	5 8	4 4	1 4	3 14	270	88	36	0 1	146
F	3012	367	16 7	0 6	6 0	4 4	1 6	2 75	227	88	42.	0 1	149
	3021	308	17 6	0 6	6 8	4 7	2 1	2 24	150	91.	46	0.1	149
	3045	306	17 4	0 6	5 8	4 2	1 6	2 63	248	84	51.	0.1	145
	3048	364	22 4	0 7	6 3	4 4	1 9	2 32	342	95	35	0 1	142
	3050	388	20 8	0 6	6 5	4 4	2 1	2 10	197	90	43	0 1	145
	3061	324	15 0	0 6	6 6	4 5	2 1	2 14	206.	94	47	0 1	143
	3071	327	15 0	0 6	6 9	4 8	2 1	2 29	168	80	51.	0.1	143
	3072	355	16 4	0 7	6 6	4 5	2 1	2 14	294	89	50	0 2	143
	3074	522	20 0	0 7	6 5	4 4	2 1	2 10	284	76	48	0 1	141
AVERAGE		355 4	17 92	0 64	6 38	4 47	1 91	2 385	238 4	87 5	44 9	0.11	144 6
STD ERR		20 9	0 77	0 02	0 12	0 05	0 09	0 110	19.0	1 9	1 8	0.01	0.9
GROUP 2	3010	330	22 4	0 5	5 7	4 3	1 4	3 07	85	145	57.	0.1	148.
F	3026	268	35 9	0 6	5 6	4 4	1 2	3 67	254	138	61.	0 3	145.
	3027	313	28 4	0 6	5 8	4 3	1 5	2 87	119	107	35.	0 2	141
	3041	214	41 3	0 5	5 1	4 0	1 1	3 64	257	143.	81	0 2	139
	3044	287	32 7	0 6	5 7	4 3	1 4	3 07	117	132	60.	0.2	140
	3051	370	24 9	0 6	5 6	4 3	1 3	3 31	166.	108	38.	0 2	140
	3053	324.	25 4	0 6	6 7	4 8	1 9	2 53	71	84.	33.	0.4	140
	3060	308.	25 1	0 6	5 7	4 3	1.4	3 07	147	114.	36	0.2	143.
	3063	279.	27.6	0 6	5 8	4 3	1 5	2.87	112.	96.	37.	0 2	141
	3066	442,	23.9	0.6	5 4	4 1	1 3	3 15	119	249	88.	0.2	136
AVERAGE		313.5	28.78	0.58	5 71	4.31	1 40	3 125	144 7	131 6	52 6	0.22	141 3
STD.ERR.		19.4	1.91	0.01	0 13	0 07	0 07	0 110	20 3	14.6	6.4	0.02	1 1
GROUP 3	3008	420.	18 3	0.7	6 2	4 4	1 8	2 44	289	123.	67.	0.1	149.
F	3022	273	18.8	0.6	6 3	4 3	2 0	2 15	175	103.	51.	0 1	150
	3030	321.	22.8	0.6	6 0	4 4	1 6	2.75	344	87	48	0.1	145.
	3032	282	17.5	0 6	6 3	4 6	1 7	2 71	214	79	43.	0.1	148.
	3035	303.	21.0	0 6	6 4	4 5	1 9	2 37	214	75	44.	0 1	146
	3056	411.	19 0	0 7	6 9	4 8	2 1	2 29	185	89	58	0 1	144.
	3059	352.	19.4	0 6	6 3	4 5	1 8	2 50	239	88	44.	0.2	146.
	3065	259	15.8	0 6	5 8	4 3	1 5	2 87	247	93	38.	0.1	141
	3067	257.	16 8	0 7	6 2	4 5	1 7	2 65	199	82	44	0.1	145
	3073	296.	18.4	0.6	6 3	4 5	1 8	2 50	188	92.	43	0.2	145
AVERAGE		317 4	18.78	0 63	6 27	4 48	1 79	2 523	229 4	91 1	48 0	0 12	145 9
STD ERR		18 7	0 64	0 02	0 09	0 05	0 06	0 071	16 7	4 3	2 7	0.01	0 8

DATA LISTING

STUDY B860272 - 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)	NA (MEQ/L)
GROUP 4	3015	283	17 4	0.7	6 3	4 5	1 8	2 50	137	82.	43.	0 1	147
F	3017	376	20.1	0 7	6 3	4 5	1 8	2 50	152	92	45	0 2	150
	3033	354	19 4	0 6	6 6	4 6	2 0	2 30	371	81	48	0 2	145.
	3039	297	18 7	0 6	6 2	4 5	1 7	2 65	208	81	38.	0.1	146.
	3040	341	20 4	0 6	6 3	4 3	2 0	2 15	167	73	44	0 1	146
	3054	422	17 0	0 6	6 4	4 5	1 9	2 37	199	101	69.	0 1	145
	3055	360	19 7	0 6	6 6	4 7	1 9	2 47	270	91	61.	0.1	144.
	3057	271	13 0	0 6	6 1	4 4	1 7	2 59	143	97.	49.	0.1	141
	3069	365	20 0	0 8	6 6	4 6	2 0	2 30	172	98	44	0.1	144
	3070	281	15 4	0 6	6 4	4 4	2 0	2 20	165	89	47.	0.2	143.
AVERAGE		333 0	18 11	0 64	6 38	4 50	1 88	2 403	198 4	88 5	48 8	0 13	145 1
STD ERR		16 6	0 76	0 02	0 06	0 04	0 04	0 052	22 8	2 9	2 9	0.02	0 8
GROUP 5	3006	451	14 7	0 7	6 1	4 4	1 7	2 59	236	108	48.	0 1	148.
F	3019	387	31 0	0 7	6 1	4 4	1 7	2 59	270	81.	42.	0.1	146.
	3028	332	22 2	0 7	5 9	4 3	1 6	2 69	139	73	34	0 1	142.
	3037	482	16 6	0 7	6 8	4 6	2 2	2 09	183	75	45.	0.1	144.
	3038	320	14 0	0 6	6 4	4 6	1 8	2 56	207	102	42.	0.1	146.
	3043	268	16 9	0 6	6 3	4 5	1 8	2 50	283	98	60	0.2	146
	3058	331	18 6	0 7	6 3	4 4	1 9	2 32	298	103.	51.	0.1	145.
	3075	332	15 8	0 7	6 3	4 4	1 9	2 32	220	99	57.	0 1	144
	3076	356	14 3	0 7	6 6	4 7	1 9	2 47	197	97.	66.	0.1	145
	3077	331.	12.0	0.6	6 6	4 6	2.0	2 30	238	76.	31.	0.1	145.
AVERAGE		359.0	17.61	0 67	6 34	4 49	1 85	2 443	227 1	91 2	47.6	0.11	145.1
STD.ERR.		20.3	1.73	0 02	0 09	0 04	0 05	0 057	15 4	4.2	3.5	0.01	0 5

DATA LISTING

STUDY B860272 - FEMALES

PERIOD 1 VALUES

RESPONSE:		K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	TOT FE (MCG/DL)	TIBC (MCG/DL)	ICTERIC	HEMOLYS.	LIPEMIA
NORM.RNG.-LO:		3.9	10.2	6.8	18	6					
HI:		7.1	12.2	9.0	122	30					
GROUP	ANIMAL										
GROUP 1	3009	8.4	10.9	7.7	66	100	219	456	0	0	0
F	3012	7.1	11.5	7.7	58	83	185	461	0	0	0.
	3021	6.6	12.1	7.5	78	119	285	480	0	0	0
	3045	6.7	12.1	8.3	53	63	176	498	0	0	0
	3048	7.9	11.8	8.1	58	63	295	541	0	0	0
	3050	7.6	12.5	8.9	109	66	245	535	0	0	0
	3061	6.3	11.9	8.1	57	78	174	579	0	0.	0
	3071	6.0	12.3	8.6	72	56	160	463	0	0	0
	3072	7.0	12.5	8.3	71	105	352	615	0	0	0
	3074	10.5	12.6	10.4	68	56	252	516	0	0	0
	AVERAGE	7.21	12.02	8.36	69.0	78.9	234.3	517.0	0.0	0.0	0.0
	STD ERR	0.41	0.17	0.26	5.1	7.0	19.9	18.4	0.0	0.0	0.0
GROUP 2	3010	7.6	12.1	9.3	69	88	12	840	0	0	0
F	3026	7.1	11.9	8.7	53	165	9	788	0	0	0.
	3027	6.4	12.4	9.4	77	124	11	834	0	0	0
	3041	5.6	11.5	7.2	48	301	4	878	0	0	0
	3044	6.8	11.9	9.0	47	192	20	709	0	0	0.
	3051	8.0	13.1	11.0	60	151	6	900	0	0.	0.
	3053	7.2	13.1	9.3	47	104.	6	1008	0	0.	0.
	3060	5.8	12.0	9.4	69	176.	16	878.	0.	0.	0.
	3063	6.7	12.6	10.0	48	109	27	1511.	0	0.	0.
	3066	8.2	13.2	10.4	69	264	14	571.	0.	0.	0.
	AVERAGE	6.84	12.38	9.37	58.7	167.4	12.5	881.7	0.0	0.0	0.0
	STD.ERR.	0.27	0.19	0.32	3.6	22.0	2.2	78.2	0.0	0.0	0.0
GROUP 3	3008	8.5	12.8	10.3	72	60.	57.	441.	0.	0.	0.
F	3022	6.7	12.1	8.9	57.	56.	99.	582.	0.	0.	0.
	3030	5.8	12.2	8.8	80.	58.	153	491.	0.	0.	0.
	3032	6.1	12.2	9.6	68.	77.	180	599.	0.	0.	0.
	3035	6.8	12.4	8.3	58.	65.	114.	609.	0	0.	0.
	3056	7.9	13.7	10.6	66	74.	305	564.	0	0.	0.
	3059	6.5	12.3	10.5	66	65	114	473.	0.	0.	0.
	3065	4.1	10.3	8.9	42	22	117.	906	0	0.	0
	3067	6.0	12.2	9.1	69.	53	194	471.	0	0.	0.
	3073	6.4	12.6	10.5	80.	55.	125.	492.	0	0.	0.
	AVERAGE	6.48	12.28	9.55	65.8	58.5	145.8	562.8	0.0	0.0	0.0
	STD.ERR	0.38	0.27	0.27	3.6	4.8	21.7	42.6	0.0	0.0	0.0

DATA LISTING

STUDY B860272 - FEMALES

PERIOD 1 VALUES

RESPONSE:		K (MEQ/L)	CA (MG/DL)	PHOS (MG/DL)	CHOL (MG/DL)	TG (MG/DL)	TOT FE (MCG/DL)	TIBC (MCG/DL)	ICTERIC	HEMOLYS.	LIPEMIA
GROUP 4	3015	6 3	11.6	7 9	94	66	424	567	0	0.	0.
F	3017	6 3	12 6	8 3	58	143	137	525	0	0.	0.
	3033	6.7	12 0	8 2	87	89	281	605	0	0	0.
	3039	7 2	12 4	7 8	54	64	130	527	0	0	0.
	3040	6 5	11 8	8 7	79	55	113	630	0	0	0
	3054	7 8	13 0	10 3	68	94	95	536	0	0.	0.
	3055	7 1	12 1	10 0	77	105	222	761	0	0.	0
	3057	6 9	11 4	7 7	79	47	207	483	0	0	0
	3069	7 6	12 1	8 7	92	43	207	780	0	0	0
	3070	5 6	11 5	8 4	73	81	127	482	0	0	0.
AVERAGE		6 81	12 05	8 60	76 1	78 7	194 3	589 6	0 0	0 0	0 0
STD ERR		0 21	0 16	0 28	4 2	9 7	31 6	33 7	0 0	0 0	0 0
GROUP 5	3006	7 7	11 8	8 5	82	80	147	532	0	0	0.
F	3019	7 6	12 2	8 3	63	46	288	391	0	0.	0.
	3028	6 5	10 9	6 3	74	55	351	491	0	0.	0
	3037	8 6	12 5	8 7	80	87	279	586	0	0	0
	3038	7 4	12 3	8 8	74	55	172	589	0	0	0
	3043	7 3	11 8	8 3	88	81	156	602	0	0	0
	3058	7 2	11 7	8 7	71	56	196	518	0	0	0.
	3075	8 8	12 0	7 7	70	106	213	577	0	0	0
	3076	6 5	11 5	7 7	55	58	114	668	0	0.	0.
	3077	6 9	12 0	10 1	71	39	262	432	0.	0.	0
AVERAGE		7.23	11 88	8 31	72 8	66 3	217 8	538.6	0 0	0 0	0.0
STD.ERR.		0 21	0 14	0.31	3 0	6 7	23.7	26.4	0 0	0.0	0 0

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

PROCTER & GAMBLE PATHOLOGY NUMBER B86-0272

THE EFFECT OF SUPPLEMENTAL DIETARY IRON ON OCTOPIROX TOXICITY

GROSS PATHOLOGY SUMMARY

EPL PROJECT NUMBER 101-990

Submitted to:

The Procter & Gamble Company
Cincinnati, Ohio

Submitted by:

Experimental Pathology Laboratories, Inc.
Ross, Ohio

JIM E. PROCTOR, D.V.M., Ph.D.
Veterinary Pathologist

January 9, 1987

SCIENTIFIC MERIT REVIEW
PATHOLOGIST
2/1/87
DATE

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

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GROSS PATHOLOGY SUMMARY

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

PROCTER AND GAMBLE STUDY NUMBER B86-0272

THE EFFECT OF SUPPLEMENTAL DIETARY IRON ON OCTOPIROX TOXICITY

GROSS PATHOLOGY SUMMARY

CONCLUSION

Fifty male and fifty female rats were divided into five groups and treated as follows: Group 1, 0 mg/kg/day of Octopirox and 0 ppm of iron; Group 2, 300 mg/kg/day of Octopirox and 0 ppm of iron; Group 3, 300 mg/kg/day of Octopirox and 50 ppm of iron; Group 4, 300 mg/kg/day of Octopirox and 100 ppm of iron; and Group 5, 300 mg/kg/day of Octopirox and 200 ppm of iron. Macroscopic evidence of anemia (pale eyes and tissues and enlarged heart) was noted in all Group 2 animals necropsied at the terminal sacrifice. Two Group 2 males died during the study. Fifty ppm or more of iron in the diet prevented the macroscopic observations of anemia in Groups 3, 4, and 5 at necropsy.

INTRODUCTION

Macroscopic examinations were conducted at necropsy on tissues from male and female Sprague-Dawley (Charles River) rats. The purpose of this study was to determine if dietary supplemental iron will prevent the anemia in rats dosed with Octopirox. The rats evaluated for this study are presented under Animal Group Assignment on the following page.

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

MATERIALS AND METHODS

Experimental Model

Type of Study:	The Effect of Supplemental Dietary Iron on Octopirox Toxicity
Species:	Rat
Strain (Source):	Sprague-Dawley (Charles River)
Sex:	Males and females
Test Substance:	Octopirox and iron
Vehicle, Control Substance:	Certified Purina Chow
Route of Exposure:	Diet (iron)

Animal Group Assignment

		Treatment	
Group	Males/Females	Octopirox	Fe in Diet
1	10/10	0 mg/kg/day	0 ppm
2	10/10	300 mg/kg/day	0 ppm
3	10/10	300 mg/kg/day	50 ppm
4	10/10	300 mg/kg/day	100 ppm
5	10/10	300 mg/kg/day	200 ppm

At necropsy all thoracic and abdominal organs were examined, and blood was collected from the posterior vena cava for hematology and clinical chemistry. A bone marrow smear was prepared, and the spleen and femur were fixed in 10% neutral buffered formalin.

Gross observations are summarized by sex and treatment group in the Gross Pathology Incidence Summary Tables. A detailed listing of all tissues examined are presented in the Individual Animal Cross Reference Tables.

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RESULTS

Group 1: 0 mg/kg/day of Octopirox and 0 ppm of Iron

No animals in this group died during the study. The only gross lesion observed at necropsy was a slightly enlarged heart in one male.

Group 2: 300 mg/kg/day of Octopirox and 0 ppm of Iron

Two males died during the study. No gross lesions were detected in these two males at necropsy, and tissues were not collected from these animals. At the terminal sacrifice all tissues, including the eyes, were pale, and the heart was enlarged in all eight males and ten females.

Group 3: 300 mg/kg/day of Octopirox and 50 ppm of Iron

No animals died during the study in this group, and gross lesions were not observed in any animals at necropsy.

Group 4: 300 mg/kg/day of Octopirox and 100 ppm of Iron

No animals died during the study, and only an occasional, incidental gross observation was made at necropsy. The slightly enlarged heart in one male was similar to an observation made in a control animal. Multiple pinpoint red foci were present in the lungs of another male. Macroscopic changes were not noted in females at necropsy.

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Group 5: 300 mg/kg/day of Octopirox and 200 ppm of Iron

No animals died during the study. The right kidney was small in one male, and no macroscopic changes were noted in females.

DISCUSSION

The enlarged hearts and pale tissues noted in eight males and ten females in Group 2 at necropsy were clinical and necropsy evidence of anemia. The addition of 50 ppm or more of iron prevented macroscopic evidence of anemia.

Jim E. Proctor

JIM E. PROCTOR, D.V.M., Ph.D.
Veterinary Pathologist

1/9/87
Date

JEP/vln

GROSS PATHOLOGY INCIDENCE SUMMARY TABLE (MALES, TERMINAL SACRIFICE)

Study: 086-0272
Compound: 60539.02
Start Date:

The Effect of Supplemental Dietary Iron on 60539.02 Toxicity

Organ Pathology Incidence Summary

Page: 1
Date: 8 Aug86
Time: 9:01
SP5002 V3.0

Target... First Dose
None

Director.....
D. Nolan

	1	2	3	4	5
	M	M	M	M	M
Animals on Study:	10	10	10	10	10
Animals Logged:	10	8	10	10	10
Spleen	10	8	10	10	10
Not Remarkable	10	8	10	10	10
Bone (Femur)	10	8	10	10	10
Not Remarkable	10	8	10	10	10
Bone Marrow Smear	10	8	10	10	10
Not Remarkable	10	8	10	10	10
Heart	1	8	0	1	0
Not Remarkable	0	0	0	0	0
Slightly enlarged	1	0	0	1	0
Enlarged	0	0	0	0	0
Eyes	0	8	0	0	0
Not Remarkable	0	0	0	0	0
Pale	0	8	0	0	0
All Tissues	0	8	0	0	0
Not Remarkable	0	0	0	0	0
Pale	0	8	0	0	0
Lung	0	0	0	1	0
Not Remarkable	0	0	0	0	0
Multiple pinpoint red foci	0	0	0	1	0
Kidney	0	0	0	0	1
Not Remarkable	0	0	0	0	0
Right, small	0	0	0	0	1

Removal Reasons Included
Terminal Dose
Removal Dates: 1 Aug86 - 1 Aug86 Data Collection Dates: 8 Aug86 - 8 Aug86

ANATOMIC PATHOLOGY
APPENDIX I

Study Comments

Animal #2933 (Group 1, Male): No tissues collected.
Animal #2937 (Group 2, Male): No tissues collected.

GROSS PATHOLOGY INCIDENCE SUMMARY TABLE (MALES, MORIBUND/DEATHS)

Study: 886-0272
Compound: B0539.02
Start Date:

The Effect of Supplemental Dietary Iron on B0539.02 Toxicity

Gross Pathology Incidence Summary

Page: 1
Date: 8 Aug86
Time: 8:57
BPS002 V3.0

Pathst... Final_Name Discussion.....
None B. Nolan

	1	2	3	4	5
	0	0	0	0	0
Animals on Study:	10	10	10	10	10
Animals Logged:	0	2	0	0	0
Gallbladder	0	0	0	0	0
Not Remarkable	0	0	0	0	0
Bone (Femur)	0	0	0	0	0
Not Remarkable	0	0	0	0	0
Bone Marrow Smear	0	0	0	0	0
Not Remarkable	0	0	0	0	0
Heart	0	0	0	0	0
Not Remarkable	0	0	0	0	0
Eyes	0	0	0	0	0
Not Remarkable	0	0	0	0	0
All Tissues	0	0	0	0	0
Not Remarkable	0	0	0	0	0
Lung	0	0	0	0	0
Not Remarkable	0	0	0	0	0
Kidney	0	0	0	0	0
Not Remarkable	0	0	0	0	0

Removal Reasons Included:
Found Dead.
Removal Dates: 1 Aug86 - 1 Aug86 Data Collection Dates: 8 Aug86 - 8 Aug86

Study Comments

Animal 02931 (Group 2, Male):	No tissues collected.
Animal 02937 (Group 2, Male):	No tissues collected.

GROSS PATHOLOGY INCIDENCE SUMMARY TABLE (FEMALES)

Format: Sort: Dose Director: G. Nolan
None

	1 E	2 E	3 E	4 E	5 E
Animals on Study:	10	10	10	10	10
Animals Logged:	10	10	10	10	10
Spleen	10	10	10	10	10
Not Remarkable	10	10	10	10	10
Bone (Femur)	10	10	10	10	10
Not Remarkable	10	10	10	10	10
Bone Marrow Smear	10	10	10	10	10
Not Remarkable	10	10	10	10	10
Heart	0	10	0	0	0
Not Remarkable	0	0	0	0	0
Enlarged	0	10	0	0	0
Eyes	0	10	0	0	0
Not Remarkable	0	0	0	0	0
Pale	0	10	0	0	0
All Tissues	0	10	0	0	0
Not Remarkable	0	0	0	0	0
Pale	0	10	0	0	0
Lung	0	0	0	0	0
Not Remarkable	0	0	0	0	0
Kidney	0	0	0	0	0
Not Remarkable	0	0	0	0	0

ANATOMIC PATHOLOGY
APPENDIX I

INDIVIDUAL ANIMAL CROSS REFERENCE TABLE (MALES, TERMINAL SACRIFICE)

Study: U06-0272 | The Effect of Supplemental Dietary Iron on G0539.02 Toxicity | Page: 1
Compound: G0539.02 | | Date: 8 Aug86
Start Date: | Individual Animal Cross Reference | Time: 9:03
| | SP8006 V1.0

Format__ Exam.Done Director______
None G. Nolen

	2	2	2	2	2	2	2	2	2	2	2	[illegible]	2	2	2	2	2	3	2	2	2	2	2	2	2	2	3	3	2	2	2	2	2	2	2
	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	9	9	9	9	9	9	9	9	0	9	9	9	9	9	9	9	9
	3	3	4	4	4	4	5	6	9	9	3	5	6	6	7	8	9	0	4	5	5	3	7	0	0	[illegible]	0	0	3	3	5	6	6	7	7
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Group:	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4
Animal Sex (M or F):	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Animal Removal Code (0-7,?):	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Spleen	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bone (Femur)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bone Marrow Smear	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Heart	.	.	+	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	+	.	.	.
Slightly enlarged	.	.	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	+	.	.	.
Enlarged	.	.	.	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Eyes	.	.	.	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Pale	.	.	.	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
All Tissues	.	.	.	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Pale	.	.	.	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Lung	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Kidney	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Notes: - = Not recorded.
. = Not remarkable.
? = Animal or tissue missing.
* = Specified tissue note.
+ = Morphology present.
P = probable cause of death.

Tissue Autolysis
A = Autolysis

Morphology Severity
1 = Minimal
2 = Slight
3 = Moderate
4 = Mod./Sev./High
5 = Severe/High

Removal Reason
0 = Terminal Sac.
1 = Serial Sac.
2 = Moribund
3 = Found Dead
4 = Premature Sac.
5 = Accident

ANATOMIC PATHOLOGY
APPENDIX I

Study: 886-0772 The Effect of Supplemental Dietary Iron on BO539.02 Toxicity
Compound: BO539.02
Start Date:

Individual Animal Cross Reference

Pages 2
Date: 8 Aug88
Time: 9:02
DPGOOs V3.0

Target Name: Effect Dose: Diet Slot: 0. Main

Group:																							
Animal Sex (M or F):																							
Animal Removal Code (0-7,7):																							
Spleen																							
Bone (Femur)																							
Bone Marrow Smear																							
Heart																							
Eyes																							
All Tissues																							
Lung																							
Multiple pinpoint red foci																							
Kidney																							
Right, small																							

Notes: . = not recorded.
- = not remarkable.
7 = animal or tissue missing.
* = specified tissue note.
+ = morphology present.
• = probable cause of death.

Tissue Autolysis
1 = Autolysis

Morphology Severity
1 = Minimal
2 = Slight
3 = Moderate
4 = Mod.Sev./High
5 = Severe/High

Removal Reason
0 = Terminal Sac.
1 = Moribund Sac.
2 = Moribund
3 = Found Dead
4 = Premature Sac.
5 = Accident

Study Comments

Animal 82933 (Group 2, Male)	No tissues collected.
Animal 82937 (Group 2, Male)	No tissues collected.

INDIVIDUAL ANIMAL CROSS REFERENCE TABLE (MALES, MORIBUND/DEATHS)

Study: 886-0272 The Effect of Supplemental Dietary Iron on 60539.02 Toxicity
Compound: 60539.02
Start Date:
Individual Animal Cross Reference

Pages: 1
Date: 8 Aug86
Time: 0158
SPB006 V3.0

Format: None Excel_Done Director: G. Nolen

	2	2
	9	9
	3	3
	5	2
Group:	2	2
Animal Sex (M or F):	M	M
Animal Removal Code (0-7,?):	3	3
Spleen	.	.
Bone (Femur)	.	.
Bone Marrow Smear	.	.
Heart	.	.
Eyes	.	.
All Tissues	.	.
Lung	.	.
Kidney	.	.

Notes: . = not recorded.
- = not remarkable
? = animal or tissue missing.
0 = specified tissue intact.
< = morphology present.
b = probable cause of death.

Tissue Autolysis
1 = Autolysis

Morphology Severity
1 = Minimal
2 = Slight
3 = Moderate
4 = Mod.Sev./High
5 = Severe/High

Removal Reason
0 = Terminal Sac.
1 = Moral Sac.
2 = Moribund
3 = Cause Dead
4 = Premature Sac.
5 = Accident

Study Cyanosis

Animal #2933 (Group 2, Male)	No tissues collected.
Animal #2937 (Group 2, Male)	No tissues collected.

INDIVIDUAL ANIMAL CROSS REFERENCE TABLE (FEMALES)

Study: 866-0272
Compound: 60539.42
Start Date:

The Effect of Supplemental Dietary Iron on 60539.42 Toxicity

Individual Animal Cross Reference

Date: 8 Aug86
Time: 8:54
BP5006 V3.0

Except__ Elect_Done Discontd_____
None D. Nolan

Groups	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	4	4	4	4
Animal Sex (M or F)	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
Animal Removal Code (0-7,?)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Spleen	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bone (Femur)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bone Marrow Smear	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Heart	.	.	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.
Enlarged	.	.	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.
Eyes	.	.	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.
Pale	.	.	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.
All Tissues	.	.	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.
Pale	.	.	.	.	.	.	.	.	.	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.
Lung	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Kidney	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Notes: . = not recorded.
- = not applicable.
? = animal in tissue missing.
n = specified tissue none.
+ = morphology present.
# = primarily cause of death.

Tissue Autolysis
1 = Autolysis

Morphology Severity
1 = Minimal
2 = Slight
3 = Moderate
4 = Mod.Sev./High
5 = Severe/High

Removal Reason
0 = Terminal Sac.
1 = Spinal Bal.
2 = Moribund
3 = Found Dead
4 = Premature Sac.
5 = Accident

Study: 886-0272 The Effect of Supplemental Dietary Iron on U0539.02 Toxicity
Compound: U0539.02
Start Date:
Individual Animal Gross Recorded

Page: 2
Date: 8 Aug86
Time: 0:55
GPB006 v1.0

Sponsor: Excel Corp. Director: G. Nelson
Name

						3	3	3	3	3	3	3	3	3
						0	0	0	0	0	0	0	0	0
						5	5	5	6	7	0	1	2	3
						1	3	2	9	0	6	9	8	2
					Groups:	4	4	4	4	4	5	5	5	5
				Animal Sex (M or F):		F	F	F	F	F	F	F	F	F
				Animal Removal Code (0-7,71):		0	0	0	0	0	0	0	0	0
Spleen						-	-	-	-	-	-	-	-	-
Bone (Femur)						-	-	-	-	-	-	-	-	-
Bone Marrow Smear						-	-	-	-	-	-	-	-	-
Heart						.	.	.	.	.	.	.	.	.
Eyes						.	.	.	.	.	.	.	.	.
All Tissues						.	.	.	.	.	.	.	.	.
Lung						.	.	.	.	.	.	.	.	.
Kidney						.	.	.	.	.	.	.	.	.

Key: . = not recorded.
- = not recoverable.
7 = animal or tissue missing.
n = specified tissue note.
* = morphology present.
* = probable cause of death.

Tissue Autolysis
1 = Autolysis

Morphology Severity
1 = Minimal
2 = Slight
3 = Moderate
4 = Mod.Sev./High
5 = Severe/High

Removal Reason
0 = Terminal Sac.
1 = Serial Sac.
2 = Moribund
3 = Found Dead
4 = Premature Sac.
5 = Accident