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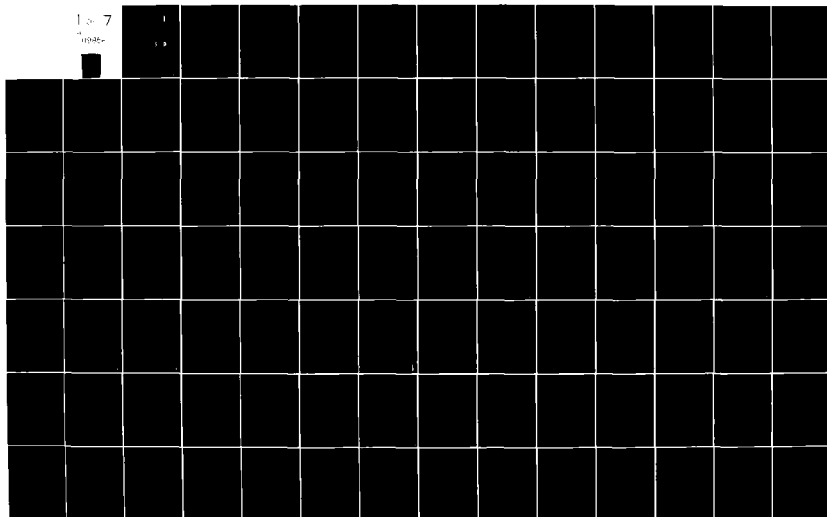
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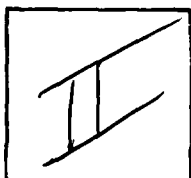
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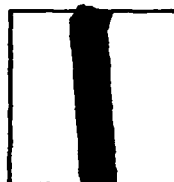
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Toxicity Studies on Antiradiation Agents

DOCUMENT IDENTIFICATION

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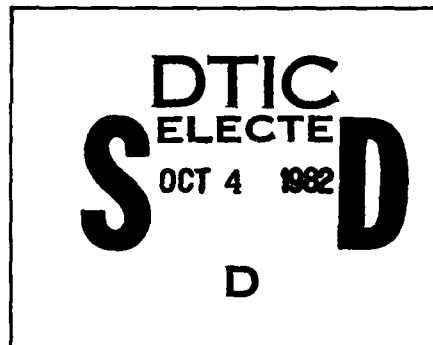
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TOXICITY STUDIES ON ANTIRADIATION AGENTS

AD A119856

Final Report

Frederick E. Reno

March 1979

Supported by:

US Army Medical Research and Development Command
Fort Detrick, Frederick, MD 21701

Contract No. DADA17-69-C-9105

Hazelton Laboratories America, Inc.
Vienna, VA 22180

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FINAL REPORT - Contract No. DADA17-69-C-9105

SUMMARY

This contract was awarded to provide for the conduct of toxicological evaluations on various drugs under study by WRAIR. In general these acute and subacute studies were designed to evaluate and characterize the pharmacotoxic signs of these drugs to support the IND.

Eighteen studies were performed over the period of this contract.

These are listed below:

<u>HLA PROJECT NO.</u>	<u>TEST MATERIAL</u>	<u>STUDY CONDUCTED</u>
193-401	WR 2823	Acute Oral and IV Toxicity in Rats
193-402	WR 2823	Acute Oral and IP Toxicity in Mice
193-403	WR 2823	Acute Oral and IP Toxicity in Guinea Pigs
193-404	WR 2823	14-Day IV Toxicity in Rats
193-405	WR 2823	Acute IV Toxicity in Dogs
193-406	WR 2823	14-Day Subacute IV Toxicity in Dogs
193-407	WR 2721	28-Day Oral Toxicity in Monkeys
193-408	WR 2529	Acute Oral Toxicity in Mice
193-409	WR 2823	Acute Oral Toxicity in Mice (repeat)
193-410	WR 2823	Histopathology on 193-404
193-411	WR 2823	Histopathology on 193-406
193-412	WR 2823	2-Week IV Study in Rats
193-413	WR 149, 024	Acute IV Toxicity in Rats and Mice; Acute IP Toxicity in Guinea Pigs
193-414	WR 149, 024	Acute IV Toxicity in Dogs
193-415	WR 149, 024	Acute IV Toxicity in Monkeys
193-416	WR 149, 024	2-Week IV Toxicity in Dogs
193-417	WR 149, 024	2-Week Toxicity in Monkeys
193-418	WR 2823	Infusion Study in Dogs

Detailed technical reports were submitted for studies identified by Project No. 193-401 through 193-417. For Project No. 193-418 Hazelton Laboratories provided laboratory support and animals for an infusion study under the direction by WRAIR personnel. Data was collected by these WRAIR personnel, and no formal report by HLA was required.

FOREWORD

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: October 17, 1969

Material: WR-2823 (AU 69115)

Subject: REPORT NO. 19
Acute Oral Dose Range - Rats
Acute Oral Administration - Rats
Acute Intravenous Administration - Rats
Project No. 193-401

Date Received July 2, 1969.

Description Fine, white powder with no noticeable odor.

Purity Assumed to be 100% active ingredient.

SUMMARY

WR-2823 (AU 69115) was evaluated for acute oral toxicity by oral intubation to three groups of two male rats each at dosage levels of 100, 1000, and 10,000 mg/kg of body weight (acute oral dose range) in order to more accurately define the toxic range prior to initiating an expanded LD₅₀ study.

WR-2823 (AU 69115) was then further evaluated for acute oral toxicity by oral intubation to eight groups of 10 male rats each at dosage levels of 100 to 2150 mg/kg of body weight. The acute oral LD₅₀ was found to be 2037 mg/kg of body weight (confidence limits, 1281 to 3239 mg/kg of body weight). Signs of toxic effect included depression, labored respiration, hunched appearance, diarrhea or brown stains on body, squinting, ptosis, lacrimation, reddened eyes, yellow stain on fur, urine stains, and slight ataxia.

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In addition, the test material was evaluated for acute intravenous toxicity by intravenous injection into the tail vein of six groups of 10 male rats each at dosage levels of 63.1 to 631 mg/kg of body weight. The acute intravenous LD₅₀ was found to be 543 mg/kg of body weight (confidence limits, 402 to 735 mg/kg of body weight). Toxic signs included labored respiration, depression, ptosis, hunched appearance, reddened eyes, and comatose appearance.

ACUTE ORAL DOSE RANGE - RATS

Procedure Oral intubation to three groups of two male rats each. Initial weight ranged from 200 to 235 grams, and the animals were fasted overnight prior to dosing. Observations for mortality and signs of effect were made immediately after intubation, frequently on the day of intubation, and daily thereafter for 28 days. Necropsies were performed on all animals which died during the study and on those animals sacrificed at termination (chloroform overdose). The solvent was distilled water.

Results**Mortality Data:**

Dose mg/kg	Concentration %	Cumulative Mortality				
		Immediate	Hours		Days	
			1	4-24	2	3-28
100	10	0/2	0/2	0/2	0/2	0/2
1,000	10	0/2	0/2	1/2	2/2	
10,000	50	0/2	2/2			

Principal Toxic Effects: Toxic signs noted at all levels included depression and labored respiration. In addition to these signs, squinting, excessive urination, diarrhea, hunched appearance, and bloody crust on nose were noted at the 1000 mg/kg level; and lacrimation, salivation, and convulsions were noted at the 10,000 mg/kg level.

Major Necropsy Findings:

At Death -

(1000 mg/kg Level) Stomach and intestines distended with fluid resembling compound, pyloric portion of stomach blanched, intestinal tract thin and smooth in appearance, liver dark reddish brown in color, and renal medulla dark red in color.

(10,000 mg/kg Level) Pyloric portion of stomach smooth and blanched with dark pink areas, intestines distended with brown fluid, dark red areas on intestinal walls with blood vessels dilated in appearance, liver mottled, and dark zone at corticomedullary junction.

At Sacrifice - No observable gross pathology.

ACUTE ORAL ADMINISTRATION - RATS

Procedure The compound was administered by oral intubation to eight groups of 10 male rats (Charles River, Sprague-Dawley Caesarean-derived) each. The solvent was distilled water. One group of 10 male rats, which received

distilled water at a dosage level of 1000 mg/kg of body weight, served as a control and was subjected to the same experimental conditions as the test groups. Initial body weight ranged from 135 to 242 grams, and the animals were fasted overnight prior to dosing. Observations for mortality and signs of effects were made immediately after dosing; at one, four, and 24 hours; and once daily thereafter for a total of 14 days. Gross necropsy was performed on all animals which died during the study and on those sacrificed (chloroform overdose) at termination. Mortality data was analyzed statistically by the method of Finney, D. J., Probit Analysis, Cambridge University Press, 1952.

Results

Mortality Data: Values below represent the number of animals dead per number of animals tested, cumulative.

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Dose mg/kg	Concentration of Solution %	Immediate	Time of Death			
			Hours			Days
			1	4	24	2-14
100	10	0/10	0/10	0/10	0/10	0/10
159	10	0/10	0/10	0/10	0/10	0/10
251	10	0/10	0/10	0/10	0/10	0/10
398	10	0/10	0/10	0/10	0/10	0/10
631	10	0/10	0/10	0/10	0/10	0/10
1000	10	0/10	0/10	0/10	2/10	2/10
1590	30	0/10	1/10	1/10	4/10	4/10
2150	10	0/10	5/10	10/10		

LD₅₀, mg/kg - 2037

Confidence Limits (95%), mg/kg - 1281 to 3239

Slope - 2.885

Graphical presentation of the dose-response analysis is appended to this report.

Principal Toxic Effects:

Control - No toxic effects were noted.

100 and 159 mg/kg Levels - No toxic effects were noted.

251, 398, and 631 mg/kg Levels - The following toxic signs were noted

one or four hours postintubation: depression, labored respiration (398 and 631 mg/kg levels), hunched appearance, diarrhea or brown stains on body (398 and 631 mg/kg levels), squinting (398 mg/kg level), ptosis (631 mg/kg level), and lacrimation (631 mg/kg level). In addition, eyes of animals at the 631 mg/kg

level appeared red from 48 hours through Day 3. Animals at the 251 and 398 mg/kg levels appeared normal by Day 5 or Day 13, but animals at the 631 mg/kg level exhibited signs through termination of the study.

1000, 1590, and 2150 mg/kg Levels - Toxic signs noted immediately after intubation of the compound included depression, labored respiration, squinting (1000 mg/kg level), and hunched appearance (2150 mg/kg level). Delayed toxic signs included ptosis, diarrhea or brown stains on body, eyes red in appearance (1000 mg/kg level), yellow stain on fur (1000 mg/kg level), alopecia (one animal at the 1000 mg/kg level), lacrimation (1590 mg/kg level), urine stains (1590 mg/kg level), and slight ataxia (2150 mg/kg level).

Major Necropsy Findings:

At Death - Stomach and intestines distended with gas and amber-colored liquid (1000 mg/kg level); stomach and intestinal walls thin (1000, 1590, and 2150 mg/kg levels); clear, yellowish colored fluid in stomach and intestines (1590 mg/kg level); lining of pyloric portion of stomach blanched (2150 mg/kg level); Peyer's patches enlarged (2150 mg/kg level); kidneys dark red in color (1000 mg/kg level); renal medulla dark red in color (2150 mg/kg level); liver dark red or reddish brown in color (1000 and 2150 mg/kg levels); liver mottled (1590 mg/kg level); and cut surface of kidneys striated (398 and 1590 mg/kg levels).

At Sacrifice - Spleen appeared enlarged (100, 398, and 1000 mg/kg levels), renal cortex pale green-brown or pale brown in color (100, 159, 251, and 1000 mg/kg levels), renal pelvis dilated (100 and 1590 mg/kg levels), renal pelvis dilated with fissures extending into cortex (159 mg/kg level), pyloric region of stomach red in color (100 and 631 mg/kg levels), kidneys pale brown or green-brown in color (159, 398, and 631 mg/kg levels), liver pale brown in color (159 and 1000 mg/kg levels), stomach walls thickened (1000 and 1590 mg/kg levels), and renal medulla dark red in color (1590 mg/kg level).

ACUTE INTRAVENOUS ADMINISTRATION - RATS

Procedure

Experimental Animals:

Species - Adult male albino rats of the Charles River (Sprague-Dawley Caesarean-derived).

Body Weight Range - At initiation, 158 to 225 grams.

Diet - Purina Laboratory Chow and water available ad libitum.

Administration: WR-2823 (AU 69115) was administered by intravenous injection into the tail vein to six groups of 10 males each at dosage levels of 63.1, 100, 159, 251, 398, and 631 mg/kg of body weight. One group of 10 rats, which received saline solution at a dosage level of 6.31 mg/kg

of body weight, served as a control and was subjected to the same experimental conditions as the test groups.

Observations and Records:

Mortality and Toxic Effects - Observations were recorded immediately after dosing; at one, four, and 24 hours; and once daily thereafter for a total of 14 days.

Body Weights - Recorded initially and terminally.

Terminal Studies:

Sacrifice - By chloroform overdose.

Gross Necropsy - Performed on all animals which died during the study and on those sacrificed at termination.

Statistical Analysis: Mortality data analyzed by the method of Finney, D. J., Probit Analysis, Cambridge University Press, 1952.

Results

Mortality Data: Values below represent the number of animals dead per number of animals tested, cumulative.

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Dose mg/kg	Concentration of Solution %	Time of Death			
		Immediate	Hours		Days
			1-4	24	2-14
63.1	2.5	0/10	0/10	0/10	0/10
100	10	0/10	0/10	0/10	0/10
159	10	0/10	0/10	0/10	0/10
251	10	0/10	0/10	0/10	0/10
398	30	0/10	2/10	3/10	3/10
631	30	7/10	10/10		

LD₅₀, mg/kg - 543

Confidence Limits (95%), mg/kg - 402 to 735

Slope - 4.02

Graphical presentation of the dose-response analysis is appended to this report.

Principal Toxic Effects:

Control - No toxic effects were observed.

63.1, 100, 159, and 251 mg/kg Levels - Labored respiration, depression, and ptosis (159 and 251 mg/kg levels) were noted immediately or one hour after intubation followed by hunched appearance and reddened eyes (159 and 251 mg/kg levels) at 24 hours. Animals at the three lower levels recovered by 48 hours (63.1 mg/kg level), by Day 4 (100 mg/kg level), or by Day 5 (159 mg/kg level); but signs persisted in animals at the 251 mg/kg level through termination of the study.

398 and 631 mg/kg Levels - Depression, labored respiration, ptosis (398 mg/kg level), ataxia (398 mg/kg level), and comatose

appearance (631 mg/kg level) preceded partial mortality at 24 hours at the 398 mg/kg level and total mortality by one hour at the 631 mg/kg level. Signs persisting in survivors at the 398 mg/kg level through termination of the study included reddened eyes and hunched appearance.

Major Necropsy Findings:

At Death - Liver mottled, cut surface of kidney striated, and dark red zone between renal cortex and medulla (all observed at the 398 and 631 mg/kg levels).

At Sacrifice - Liver pitted, renal cortex gray or grayish green in color, and renal pelvis dilated (all observed at the 159, 251, and 398 mg/kg levels).

Submitted by

MB Powers

MARCELINA B. POWERS, D.V.M., M.S.
Project Manager, Drugs & Industrial
Chemicals
Toxicology-Biosciences Laboratory

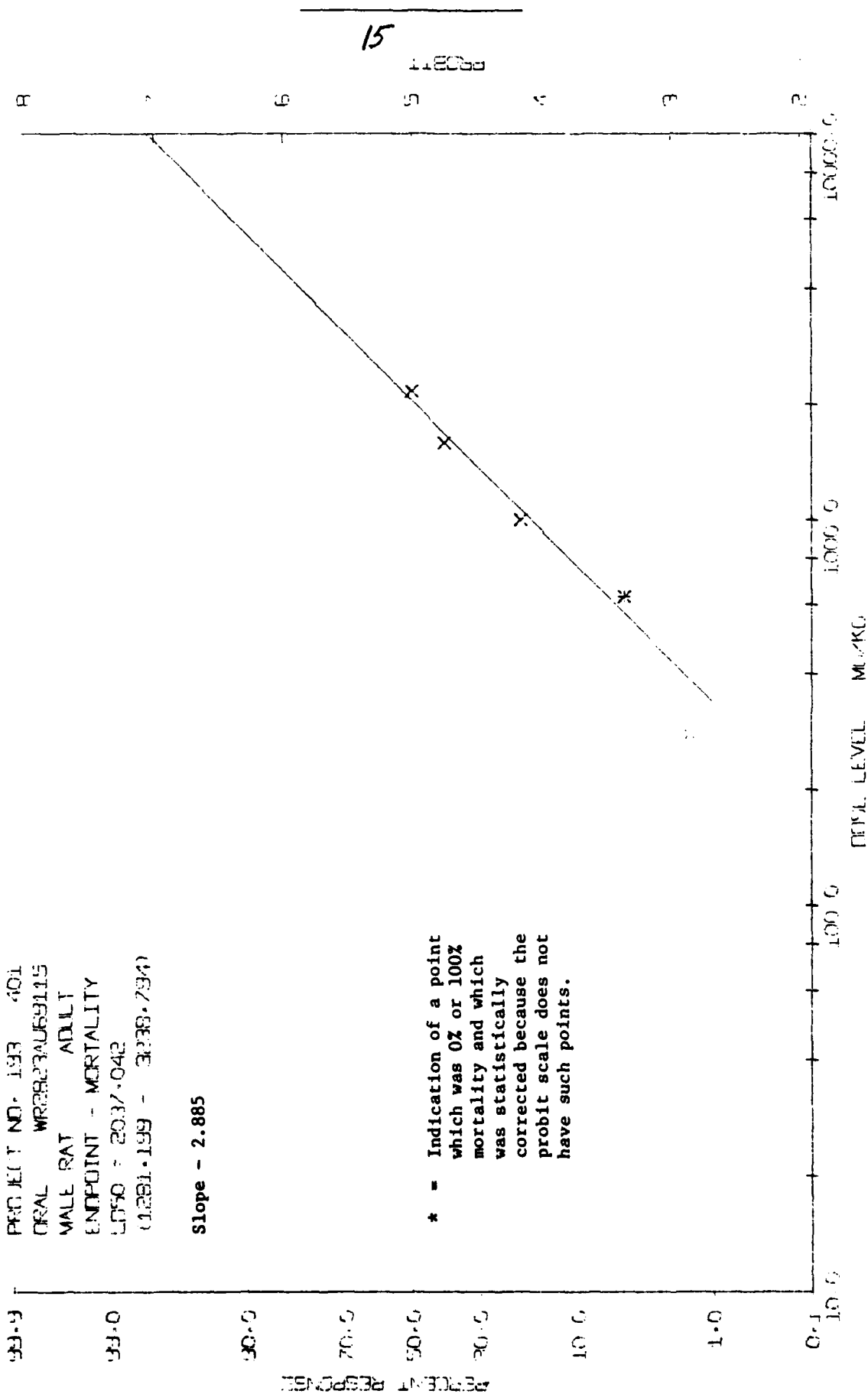
Report Preparation: Lambert
Supervision: Fink

mtg

PROJECT NO. 153 401
 ORAL WREB23AUG8115
 MALE RAT ADULT
 ENDPOINT - MORTALITY
 LYSO = 2037.042
 (1281.199 - 3238.734)

Slope - 2.885

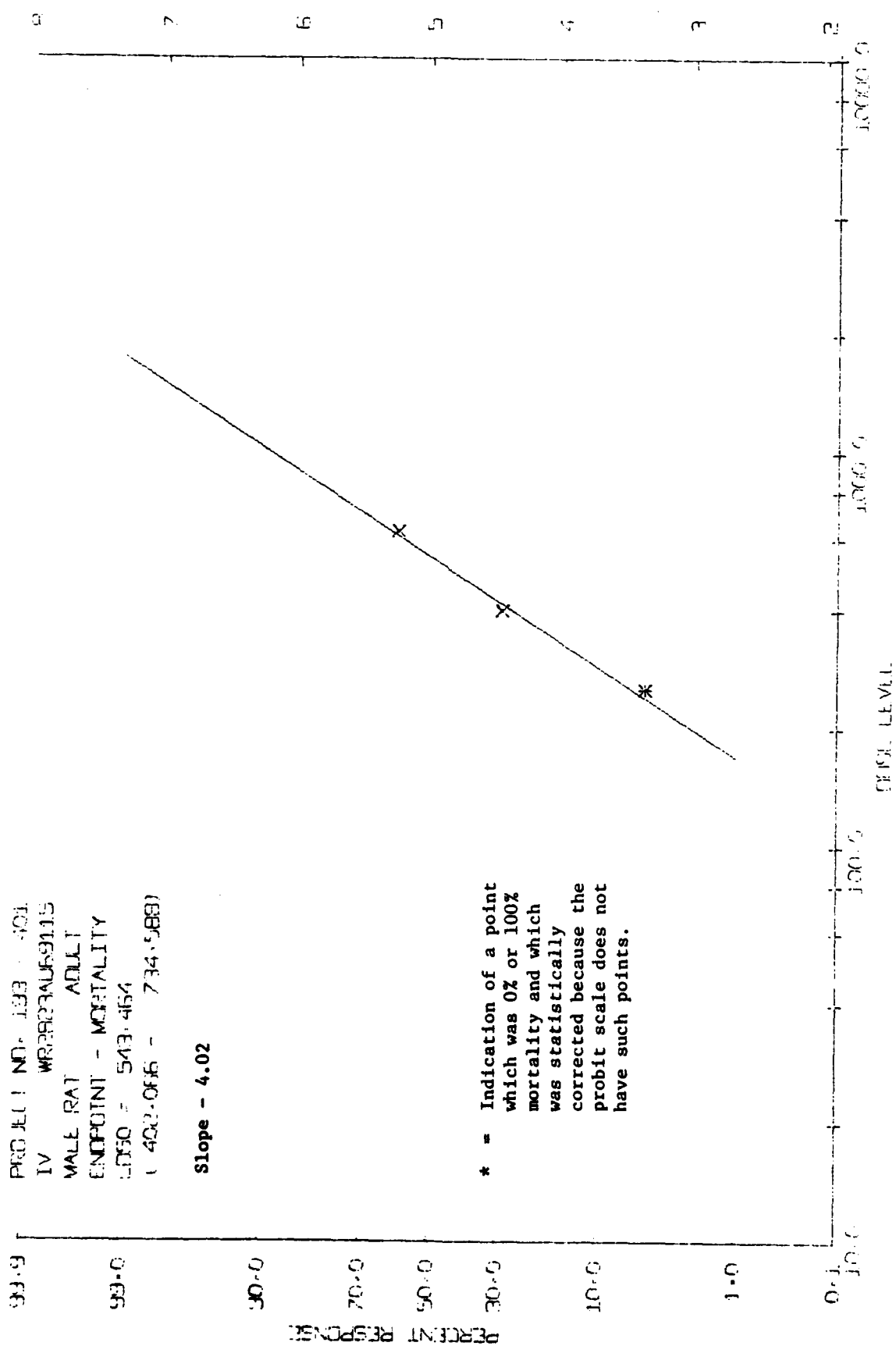
* = Indication of a point
 which was 0% or 100%
 mortality and which
 was statistically
 corrected because the
 probit scale does not
 have such points.



PROB. I NO. 133 - 401
 IV WREBRRAUS9115
 WALE RAT ADULT
 ENDPOINT - MORTALITY
 L050 = 543.454
 (402.066 - 734.588)

Slope - 4.02

* = Indication of a point
 which was 0% or 100%
 mortality and which
 was statistically
 corrected because the
 probit scale does not
 have such points.



HAZLETON LABORATORIES, INC.

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Sponsor: Walter Reed Army Institute of Research

Date: September 11, 1969

Material: WR-2823 (AU 69115)

Subject: FINAL REPORT
Acute Oral and Intraperitoneal Toxicity Studies - Mice
Project No. 193-402

SUMMARY

Acute oral and intraperitoneal toxicity studies were conducted in adult male albino mice using WR-2823 (AU 69115) as the test material. The acute oral LD₅₀ of WR-2823 was 374 mg/kg of body weight (confidence limits, 263 to 531 mg/kg of body weight), and the acute intraperitoneal LD₅₀ was 580 mg/kg of body weight (confidence limits, 449 to 750 mg/kg of body weight).

MATERIAL

Date Received July 2, 1969.

Description White powder with no noticeable odor.

Purity Assumed to be 100% active ingredient.

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PROCEDURES

Animals Seven groups (oral) and seven groups (intraperitoneal), each composed of 10 adult male albino mice of the Carbia strain, weighing from 16 to 29 grams.

Drug Administration The test material was administered by gastric intubation (six groups) or intraperitoneal injection (six groups) as a 0.5%, 1%, or 2% weight-per-volume solution in saline. The control, saline, was administered by gastric intubation to one group at a dosage level of 1000 mg/kg of body weight and by intraperitoneal injection to one group at a dosage level of 631 mg/kg of body weight.

Dosage Levels

Oral: 100, 159, 251, 398, 631, and 1000 mg/kg of body weight.

Intraperitoneal: 63.1, 100, 159, 251, 398, and 631 mg/kg of body weight.

Observations For mortality and pharmacotoxic effects immediately after dosing, frequently on the day of dosing, and daily thereafter for 14 days.

Statistical Analysis Mortality data were analyzed by the method of Litchfield, J. T., and Wilcoxon, F., J. Pharmacol. Exptl. Therap. 96, 99, 1949, or Finney, D. J., Probit Analysis, Cambridge University Press, 1952.

RESULTS

Mortality Data Values below represent the number of animals dead per number of animals tested, cumulative.

Oral:

Dose mg/kg	Concentration of Solution %	Time of Death							
		Immediate	Hours		Days				
			1	4-24	2	3	4-5	6-7	8-14
100	1.0	0/10	0/10	0/10	0/10	1/10	2/10	2/10	3/10
159	1.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
251	1.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10
398	1.0	0/10	0/10	0/10	1/10	2/10	3/10	4/10	5/10
631	2.0	0/10	2/10	4/10	6/10	8/10	8/10	8/10	8/10
1000	2.0	0/10	7/10	9/10	9/10	9/10	9/10	9/10	9/10

LD₅₀, mg/kg - 374

Confidence Limits (95%), mg/kg - 263 to 531

Slope - 2.353

Graphical presentation of the dose-response evaluation is appended to this report.

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Intraperitoneal:

Dose mg/kg	Concentration of Solution %	Time of Death						
		Immediate	Hours		Days			
			1-4	24	2-7	8	9	10-14
63.1	0.5	0/10	0/10	0/10	0/10	0/10	1/10	1/10*
100	0.5	0/10	0/10	0/10	0/10	1/10	1/10	1/10*
159	0.5	0/10	0/10	0/10	0/10	0/10	0/10	0/10
251	1.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10
398	1.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10
631	1.0	0/10	3/10	5/10	6/10	6/10	6/10	6/10

LD₅₀, mg/kg - 580

Confidence Limits (95%), mg/kg - 449 to 750

Slope - 8.960

Graphical presentation of the dose-response evaluation is appended to this report.

* The deaths which occurred at these levels on Day 8 and Day 9 were considered incidental deaths and were not used in LD₅₀ calculations.

Principal Toxic Effects

Following Oral Administration:

Control Group - One animal died on Day 9 with death preceded by labored respiration, prostration, and salivation.

Test Groups -

(100, 159, and 251 mg/kg Levels) Slight depression was noted immediately or at one hour for all animals with piloerection and hunched appearance noted later in the study. Three deaths occurred by Day 10 at the 100 mg/kg level, and one death occurred by Day 11 at

the 251 mg/kg level. Surviving animals appeared normal by Day 6 (100 and 159 mg/kg level) or Day 13 (251 mg/kg level).

(398, 631, and 1000 mg/kg Levels) Animals exhibited depression and labored respiration immediately or one hour after administration of the compound. Signs noted later in the study included ptosis, cold to touch, piloerection, hunched appearance (631 and 1000 mg/kg levels), urine stains (398 mg/kg level), and brown stains on body (398 mg/kg level). One animal at the 631 mg/kg level showed tremors at 48 hours. Five deaths occurred at the 398 mg/kg level by Day 11, eight deaths occurred by Day 3 at the 631 mg/kg level, and nine deaths occurred by four hours at the 1000 mg/kg level. Survivors at these levels appeared normal on Day 14.

Following Intraperitoneal Administration:

Control Group - Slight depression was noted immediately after administration of the compound. One death occurred in this group on Day 9.

Test Groups -

(63.1 and 100 mg/kg Levels) Animals exhibited slight depression immediately or one hour after administration of the compound through four hours. One death occurred on Day 9 at the 63.1 mg/kg level, and one death occurred on Day 8 at the 100 mg/kg level.

(159, 251, 398, and 631 mg/kg Levels) All animals exhibited slight depression immediately after administration of the compound. Toxic

signs noted later in the study included labored respiration, ptosis (three higher levels), piloerection (159 and 631 mg/kg levels), urine stains (three higher levels), squinted eyes (159 and 631 mg/kg levels), slight ataxia (two higher levels), cold to touch (two higher levels), and hunched appearance (631 mg/kg level). Animals at the 159, 251, and 398 mg/kg levels appeared normal by Day 6. Six deaths occurred at the 631 mg/kg level by Day 3 with survivors appearing normal by Day 12.

Major Necropsy Findings

Following Oral Administration:

At Death -

(Control) No necropsy could be performed on the animal which died due to advanced autolysis and cannibalization of the animal.

(Test Groups) Necropsies were not performed on one animal at the 100 mg/kg level and on two animals at the 398 mg/kg level due to cannibalization. One necropsy at the 251 mg/kg level and one at the 398 mg/kg level were not performed due to advanced autolysis.

Gross pathology noted included stomach thin and smooth (100 mg/kg level), stomach distended with yellow fluid or food-like material (100, 398, 631, and 1000 mg/kg levels), intestines filled with yellow fluid (398 mg/kg level), red areas on intestinal walls (398 mg/kg level), liver dark reddish brown in color (100 mg/kg level), liver pale red in color (398 mg/kg level), margins of liver translucent in appearance (631 mg/kg level), kidneys dark

red in color (100 and 1000 mg/kg levels), poor differentiation between cortex and medulla of kidneys (100, 398, 631, and 1000 mg/kg levels), and margins of cut surface of kidneys translucent in appearance (1000 mg/kg level).

At Sacrifice - No observable gross pathology in either control or test groups.
Following Intraperitoneal Administration:

At Death -

(Control) No necropsy was performed on the one animal which died in this group due to cannibalization of the animal.

(Test Groups) Necropsies were not performed on one animal at the 63.1 mg/kg level, on one animal at the 100 mg/kg level, and on one animal at the 631 mg/kg level due to cannibalization of the animals. Gross alterations, all noted at the 631 mg/kg level, included clear fluid in peritoneal cavity, margins of liver translucent in appearance, dark red kidneys, and poor differentiation between cortex and medulla of kidneys.

At Sacrifice - No observable gross pathology in either control or test groups.

Submitted by

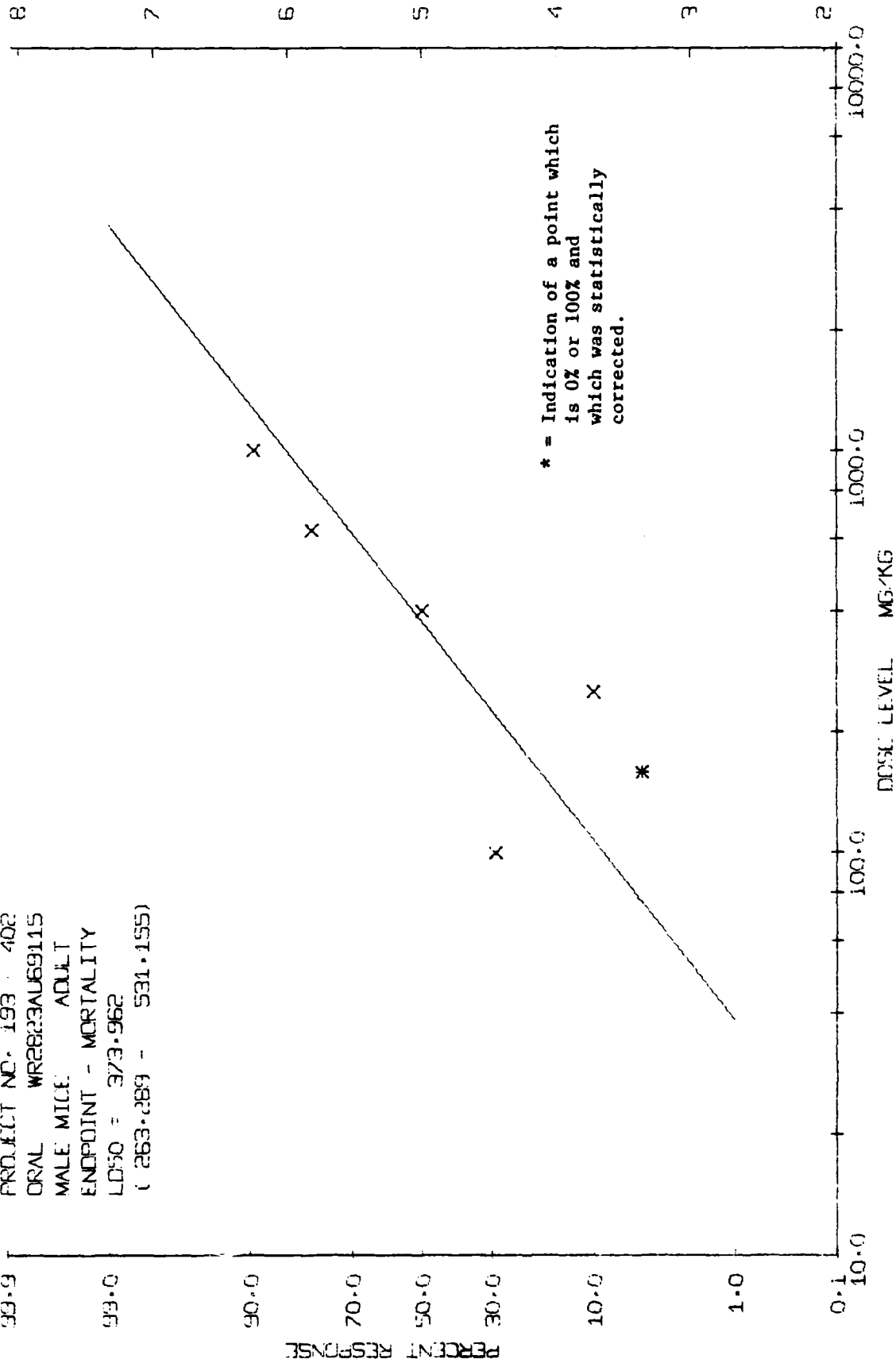
F.E. Powers
Par

MARCELINA B. POWERS, D.V.M., M.S.
Project Manager, Drugs and
Industrial Chemicals
Toxicology-Biosciences Laboratory

Report Preparation: Lambert
Supervision: Minner

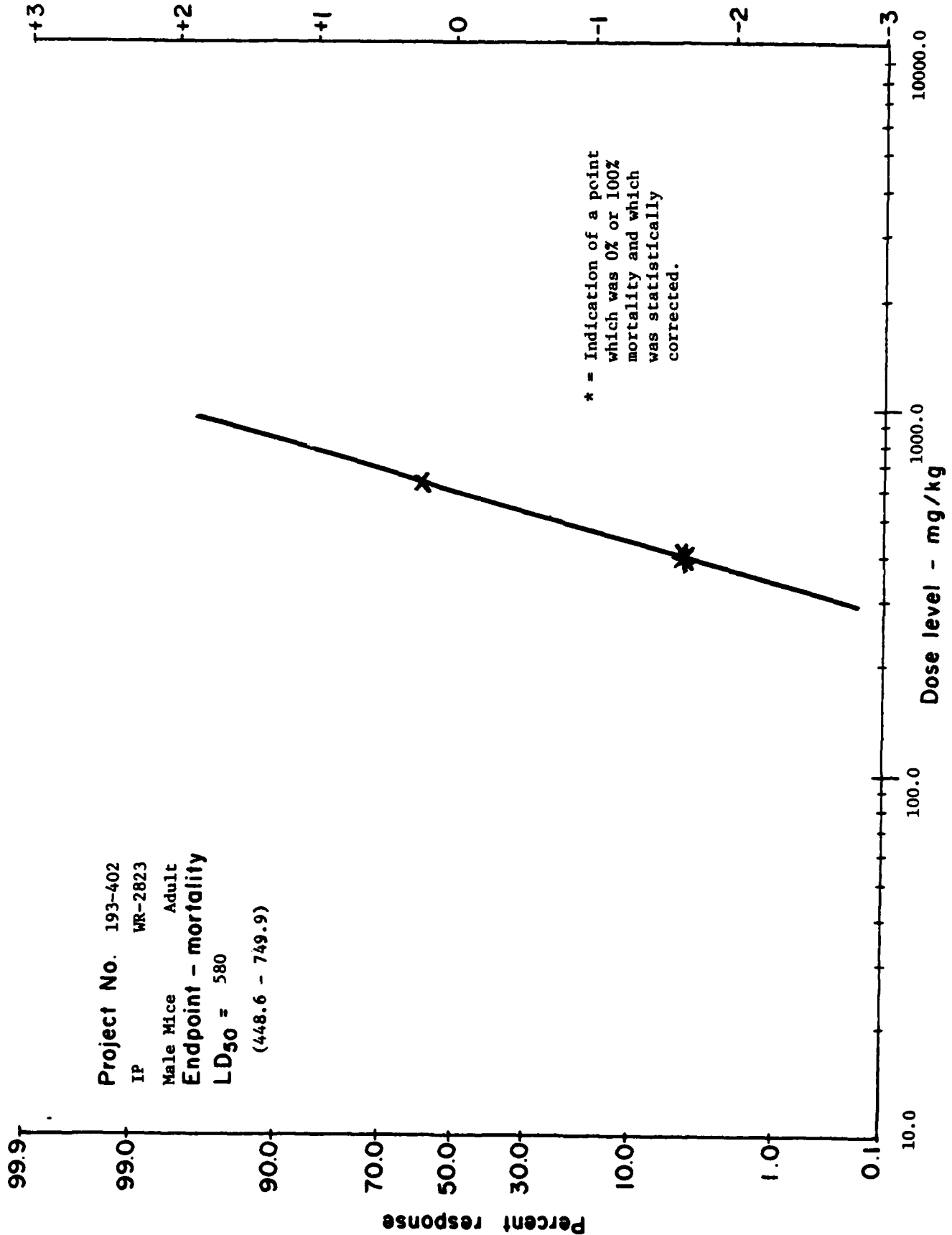
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PROJECT NO. 193 - 402
 ORAL WR2823AU69115
 MALE MICE ADULT
 ENDPOINT - MORTALITY
 LD50 = 373.962
 (263.289 - 531.155)



25

Probit



Project No. 193-402
 IP WR-2823
 Male Mice Adult
 Endpoint - mortality
 LD₅₀ = 580
 (448.6 - 749.9)

HAZLETON LABORATORIES, INC.TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: September 18, 1969

Material: WR-2823 (AU 69115)

Subject: FINAL REPORT
Acute Oral and Intraperitoneal Toxicity Studies - Guinea Pigs
Project No. 193-403

SUMMARY

Acute oral and intraperitoneal toxicity studies were conducted in adult male albino guinea pigs using WR-2823 (AU 69115) as the test material. The acute oral LD₅₀ in guinea pigs obtained for the compound was 800 mg/kg of body weight (confidence limits, 360 to 1778 mg/kg of body weight), and the acute intraperitoneal LD₅₀ was 272 mg/kg of body weight (confidence limits, 185 to 400 mg/kg of body weight).

MATERIAL

Receipt Date July 2, 1969.

Description White powder with no noticeable odor.

Purity Assumed to be 100% active ingredient.

PROCEDURES

Animals Five groups of 10 adult male albino guinea pigs (Camm strain) and two groups of five adult male albino guinea pigs for the oral administration and seven groups of 10 adult male albino guinea pigs for the intraperitoneal administration. The animals weighed from 226 to 412 grams.

Drug Administration The test material was administered by gastric intubation (four groups of 10 animals and two groups of five animals) or intraperitoneal injection (six groups of 10 animals) as a 1% or 10% weight-per-volume solution. The control, saline, was administered by gastric intubation to one group of 10 animals at a dosage level of 1000 mg/kg and by intraperitoneal injection to one group of 10 animals at a dosage level of 631 mg/kg.

Dosage Levels

Oral: 100, 159, 251, 398, 631, and 1000 mg/kg of body weight.

Intraperitoneal: 63.1, 100, 159, 251, 398, and 631 mg/kg of body weight.

Observations For mortality and pharmacotoxic effects immediately after dosing, frequently on the day of administration, and daily thereafter for 14 days.

Statistical Analysis Mortality data was analyzed by the method of Finney, D. J., Probit Analysis, Cambridge University Press, 1952.

RESULTS

Mortality Data Values below represent the number of animals dead per number of animals tested, cumulative.

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Oral:

Dose mg/kg	Concentration of Solution %	Time of Death								
		Immediate	Hours			Days				
			1	4	24	2-3	4	5	6	7-14
100	10	0/10	0/10	0/10	0/10	0/10	0/10	1/10	1/10	1/10
159	10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
251	10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10	1/10
398	10	0/10	0/10	2/10	2/10	2/10	2/10	2/10	2/10	2/10
631	10	0/5	1/5	1/5	2/5	2/5	3/5	3/5	3/5	3/5
1000	10	0/5	1/5	1/5	2/5	2/5	3/5	3/5	3/5	3/5

LD₅₀, mg/kg - 800

Confidence Limits (95%), mg/kg - 360 to 1778

Slope - 1.942

Graphical presentation of the dose-response evaluation is appended to this report.

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Intraperitoneal:

Dose mg/kg	Concentration of Solution %	Time of Death							
		Immediate	Hours			Days			
			1	4	24	2-3	4-11	12	13-14
63.1	1.0	0/10	0/10	0/10	0/10	1/10	1/10	1/10	2/10
100	1.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
159	10.0	0/10	0/10	0/10	0/10	0/10	0/10	1/10	1/10
251	10.0	0/10	2/10	6/10	6/10	6/10	6/10	6/10	6/10
398	10.0	0/10	8/10	8/10	8/10	8/10	8/10	8/10	8/10
631	10.0	0/10	7/10	7/10	7/10	7/10	7/10	7/10	7/10

LD₅₀, mg/kg - 272

Confidence Limits (95%), mg/kg - 185 to 400

Slope - 2.196

Graphical presentation of the dose-response evaluation is appended to this report.

Principal Toxic Effects

Following Oral Administration:

Control Group - Slight depression was noted immediately after administration.

Test Groups -

(100, 159, and 251 mg/kg Levels) All animals exhibited slight depression immediately after administration of the compound through 48 hours. One animal at the 251 mg/kg level exhibited labored respiration immediately after administration of the compound through four hours, and one animal had a swollen right hindleg from Day 5 through termination of the study.

(398, 631, and 1000 mg/kg Levels) Depression and labored respiration were noted in all animals immediately after compound administration. Toxic signs noted later in the study included comatose appearance (two animals at the 398 mg/kg level and one animal at the 631 mg/kg level), squinting (631 and 1000 mg/kg levels), lacrimation (631 and 1000 mg/kg levels), hunched appearance (631 and 1000 mg/kg levels), ptosis (1000 mg/kg level), convulsive jerking (one animal at the 1000 mg/kg level). Two deaths occurred at the 398 mg/kg level by four hours, three deaths occurred at the 631 mg/kg level by Day 4, and three deaths occurred at the 1000 mg/kg level by Day 5. Surviving animals at these levels appeared normal by Day 5 or Day 8.

Following Intraperitoneal Administration:

Control Group - One death occurred on Day 4 preceded by an apparent prolapsed intestine; all other animals appeared normal.

Test Groups -

(63.1 and 100 mg/kg Levels) Depression was noted in all animals immediately after administration of the compound through four hours. One death occurred on Day 3 and one on Day 11 at the 63.1 mg/kg level.

(159 mg/kg Level) Depression and slow, labored respiration were noted one hour after administration of the compound with lacrimation noted later in the study. Animals appeared normal by Day 4 with one death occurring on Day 12 (no toxic signs noted preceding death).

(251, 398, and 631 mg/kg Levels) All animals exhibited depression immediately after administration and labored respiration immediately or one hour after administration. Delayed toxic signs included squinting (251 and 631 mg/kg levels), lacrimation (398 and 631 mg/kg levels), ptosis (398 and 631 mg/kg levels), comatose appearance (one animal at the 251 mg/kg level), and apparent weight loss (one animal at the 631 mg/kg level). Six deaths occurred at the 251 mg/kg level by four hours. Eight deaths at the 398 mg/kg level and seven deaths at the 631 mg/kg level occurred by one hour. Signs subsided in surviving animals at the 251 and 398 mg/kg levels by Day 4 and at the 631 mg/kg level by Day 7.

Major Necropsy Findings

Following Oral Administration:

At Death -

(Test Groups) No necropsy was performed on the animal which died at the 100 mg/kg level due to advanced autolysis and cannibalism of the animal. Gross pathology observed in other animals included: stomach lining dark red (251, 631, and 1000 mg/kg levels), stomach distended with clear fluid

resembling compound (398 mg/kg level), stomach lining blanched (398 mg/kg level), stomach walls thin (631 and 1000 mg/kg levels), renal medulla dark pink (251 mg/kg level), poor differentiation between cortex and medulla of kidneys (398, 631, and 1000 mg/kg levels), kidneys dark red in color (631 and 1000 mg/kg levels), liver surface mottled (398 mg/kg level), and liver dark reddish brown in color (631 and 1000 mg/kg levels).

At Sacrifice -

(Control) No observable gross pathology.

(Test Groups) Blanched areas in stomach (631 mg/kg level) and liver dark reddish brown (631 mg/kg level).

Following Intraperitoneal Administration:

At Death -

(Control) Intestines greatly distended (one animal).

(Test Groups) Lungs distended with yellow abscessed areas (63.1 mg/kg level), lungs distended and dark red in color with lobes adhered to each other (63.1 mg/kg level), thoracic cavity filled with dark red fluid (63.1 mg/kg level), peritoneal cavity filled with clear fluid resembling compound (251, 398, and 631 mg/kg levels), poor differentiation between cortex and medulla of kidneys (251, 398, and 631 mg/kg levels), and liver dark reddish brown in color (251, 398, and 631 mg/kg levels).

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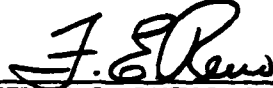
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At Sacrifice -

(Control) No observable gross pathology.

(Test Groups) No observable gross pathology.

Submitted by

for 

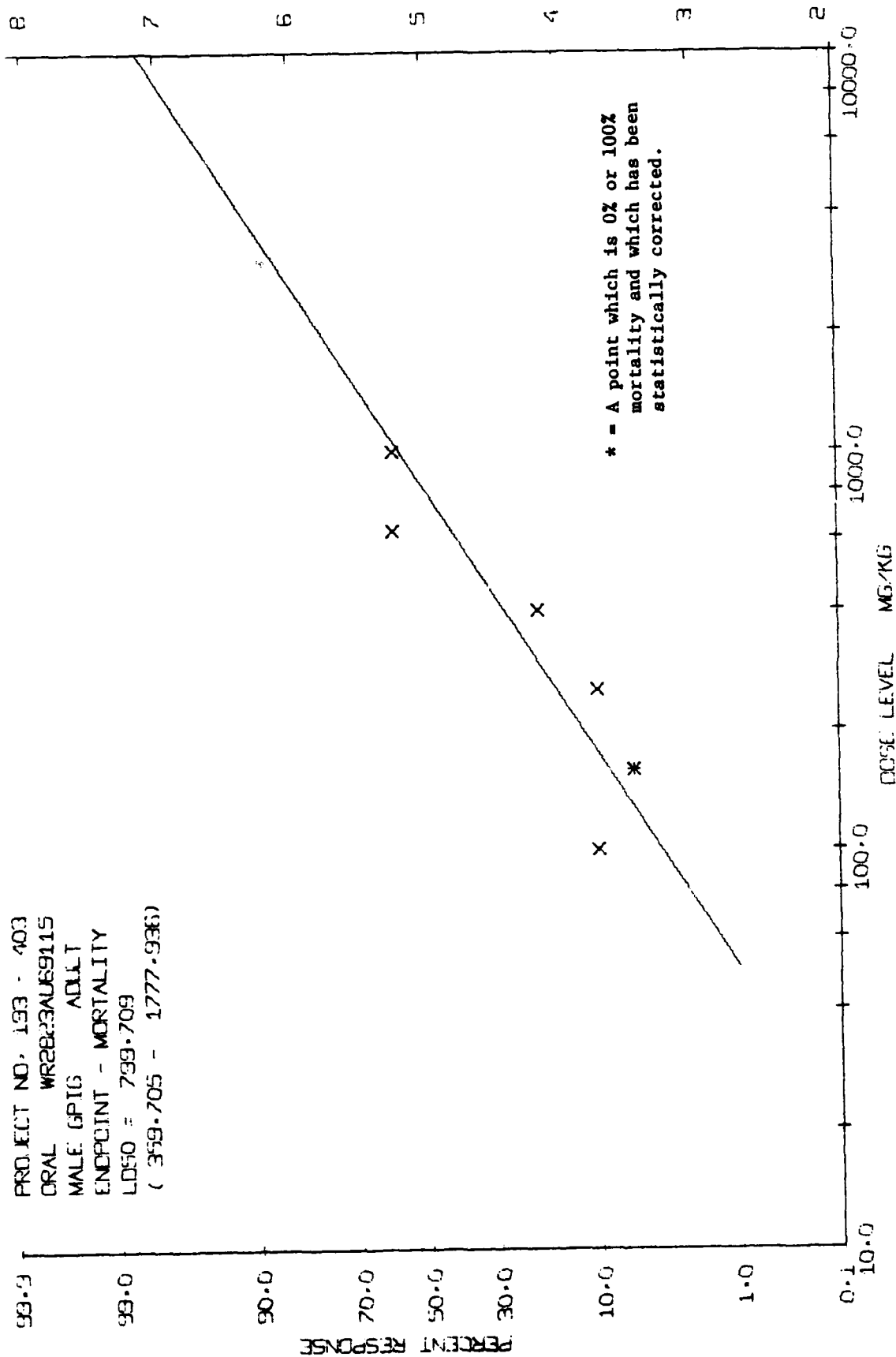
MARCELINA B. POWERS, D.V.M., M.S.
Project Manager, Drugs and
Industrial Chemicals
Toxicology-Biosciences Laboratory

Report Preparation: Lambert

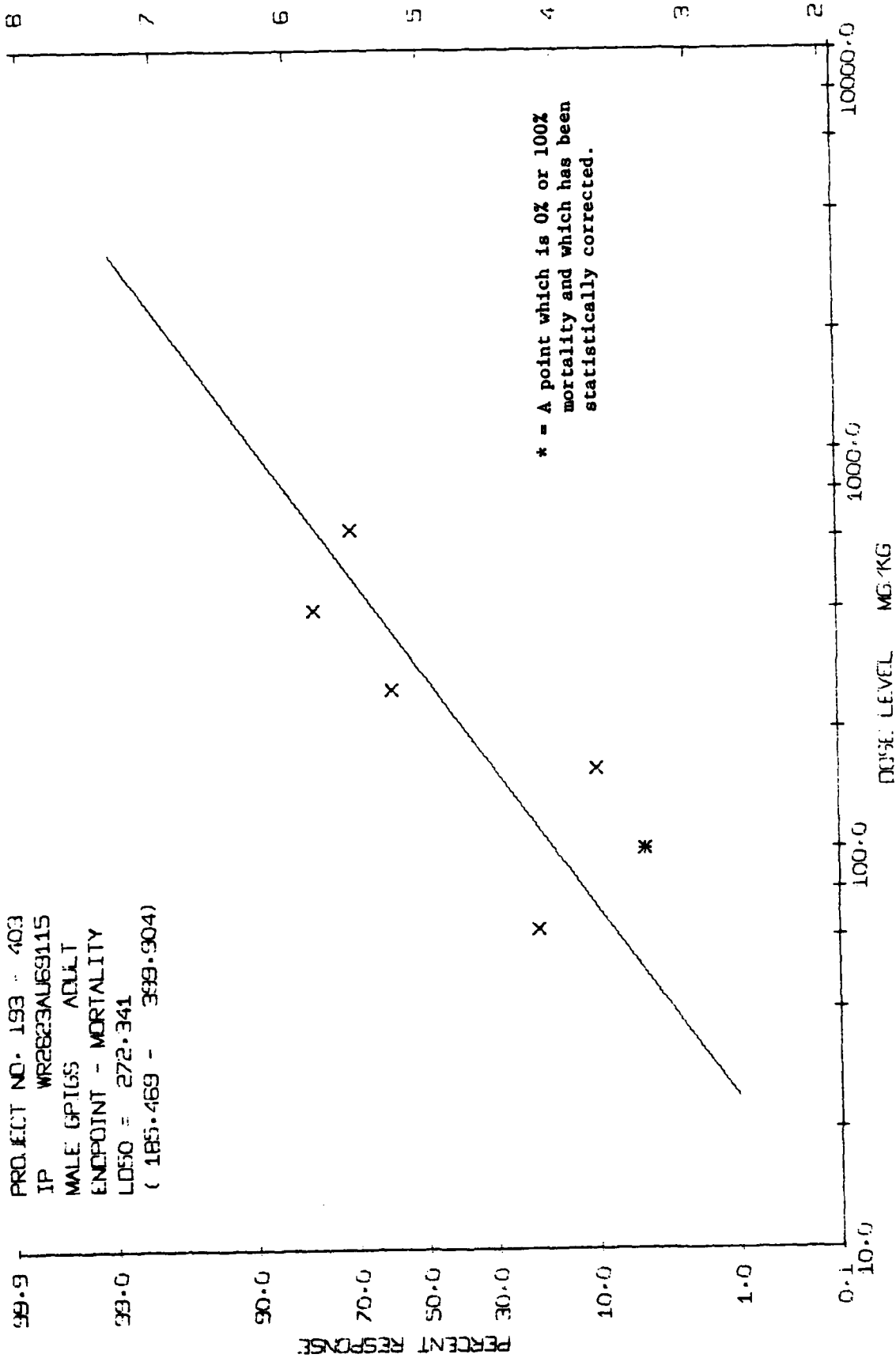
Supervision: Fink

jw

PROJECT NO. 133 - 403
 ORAL WR2823AUG9115
 MALE GP16 ADULT
 ENDPOINT - MORTALITY
 LD50 = 799.709
 (359.705 - 1777.936)



PROJECT NO. 193 - 403
 IP WR2823AUE9115
 MALE PIGS ADULT
 ENDPOINT - MORTALITY
 LD50 = 272.341
 (185.469 - 399.904)



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Sponsor: Walter Reed Army Institute of Research

Date: January 23, 1970

Material: WR-2823 (AU 69115)

Subject: REPORT NO. 31
Two-Week Intravenous Toxicity Study - Rats
Project No. 193-404

SUMMARY OF FINDINGS

This study was conducted to evaluate and characterize the effects of short-term intravenous administration of WR-2823 (AU 69115) in male and female albino rats. The test material was administered daily for 15 days at dosage levels of 30, 60, 120, and 15 mg/kg/day.

Criteria evaluated for compound effect were physical appearance and behavior, body weight gains, food consumption, survival, clinical laboratory results, and gross findings at necropsy.

The following signs were observed in the test rats after the daily dose: marked or slight depression; squinted eyes; lacrimation or watery eyes. The degree and frequency of these signs decreased at each lower dosage level. Salivation after the dose was noted only occasionally, most frequently in the high level test rats.

Growth and food consumption for the test rats were generally comparable with those for the controls. Except for somewhat higher blood sugar values obtained for the male and female test groups at one and two weeks, the results of the clinical values for the test groups were generally comparable with those for the controls.

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At necropsy the following observations were made in test rats only: apparent thickening of the wall of the small intestine (eight test rats); small, yellow foci on the duodenal lining (seven test rats); a thickened-appearing stomach wall (three rats from Groups No. 3 and No. 4); and a rough-appearing lining of the nonglandular portion of the stomach (one rat in Group No. 4).

The preserved tissues were not examined microscopically.

MATERIAL

Identification WR-2823 (AU 69115); S-2-(5 aminopenylamino) ethylphosphorothioic acid monohydrate.

Description A fine, white powder; no odor noted.

Receipt From Walter Reed Army Institute of Research on July 2, 1969.

Purity Considered 100% active ingredient.

METHODS**Experimental Animals**

One hundred young albino rats, 50 males and 50 females, of the Charles River Cesarean-derived strain.

Weight Range at Initiation: For the males from 207 to 247 grams and for the females from 185 to 231 grams.

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Housing: Individually in elevated wire mesh cages.

Diet: Purina Laboratory Chow and water available ad libitum.

Animal Groups and Dosage Levels

Method of Grouping: Stratified randomization.

<u>Group No.</u>	<u>No. of Animals</u>		<u>Dosage Levels</u> mg/kg/day
	male	female	
1 (vehicle control)	10	10	0
2	10	10	30
3	10	10	60
4	10	10	120
5	10	10	15

Preparation of Solutions

Vehicle: 0.9% Sterile Saline.

Concentrations: 30, 60, 120, and 15 mg. of the test compound per milliliter of vehicle for Groups No. 2, No. 3, No. 4, and No. 5, respectively.

The compound jar was kept in the freezer within a second container; the jar was warmed to room temperature before preparation of the daily solutions.

Drug Administration

Each test rat received a daily intravenous injection via the lateral tail vein of the test compound at the required dosage level as a freshly prepared solution at a volume of 0.1 ml. per 100 grams of body weight. Dosages

were adjusted on the basis of individual body weights. Control rats received equivalent volumes of the vehicle.

The first five rats in each group received 16 injections, and the last five in each group received 15 injections. All rats were sacrificed on the day following the last dosage; no dosages were administered on the day of sacrifice.

Observations and Records

Daily Observations: For appearance, behavior, and mortality.

Daily Observations and Records: Individual body weights and dosages; appearance and behavior of each rat prior to dosage and signs of toxic and/or pharmacologic effects after dosage.

Weekly Records: Individual weekly food consumption.

Clinical Laboratory Studies

Intervals: Initially, at one week, and two weeks (terminal).

Method: Performed on five rats from each group; blood samples were obtained from the tail vein (from the abdominal aorta for biochemical studies at sacrifice). Urine samples were collected from rats housed overnight in individual metabolism cages and pooled by groups.

Hematology: Erythrocyte count; total and differential leukocyte counts; microhematocrit, hemoglobin, and prothrombin and coagulation time determinations.

Biochemistry: Fasting blood sugar, blood urea nitrogen, serum glutamic-pyruvic transaminase, and alkaline phosphatase determinations.

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Urine Analyses: Appearance, pH, specific gravity, sugar acetone, protein, bilirubin, occult blood, and microscopic examination of the sediment.

Ophthalmologic Examinations

Conducted on all rats assigned to the study initially and at termination, prior to sacrifice, using "Mydriacyl" (Alcon) and a binocular indirect ophthalmoscope.

Terminal Studies

Terminal Sacrifice: Performed on each rat one day after the last injection (the 15th or 16th dose).

Method - Exsanguination under Diabutal anesthesia.

Gross Observations - Recorded at necropsy for each rat.

Organ Weights (Determined for Each Rat) - Liver, kidney, spleen, heart, testes with epididymis, and ovaries - prior to fixation; thyroid and adrenals - after fixation.

Tissues Preserved From Each Rat -

(In 10% Neutral Buffered Formalin) Brain, pituitary, spinal cord (three levels), thyroid, lung, heart, liver, spleen, kidney, adrenal, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testis, prostate, ovary, uterus, bone, bone marrow, and unusual lesions.

(In Alcoholic Formalin) Eyes.

No tissues were examined microscopically.

All tissues are being held at Hazleton Laboratories, Inc., for possible future reference.

RESULTS

Gross Appearance and Behavior

Transient wheezing and a swollen left eyelid were noted each in one male control rat; staining of the abdominal fur by urine was observed on Days 4 - 16 in another control male. The remaining male control animals and all control females had a normal appearance.

Wheezing, nasal discharge, red eyelid, urine stains on the abdominal fur, or alopecia on the body were noted in a few rats in the various test groups before the daily dose. Seven female test rats, one or two from each test group, developed a yellow discoloration of the furcoat first noted toward the end of the first experimental week and observed daily until sacrifice. Most of the rats, however, appeared normal prior to treatment.

Depression following injection was observed daily in all animals in Groups No. 4 and No. 3 (120 mg/kg and 60 mg/kg, respectively). Slight depression was observed daily in the majority of the test rats in Group No. 2 (30 mg/kg) and less frequently in Group No. 5 test rats (15 mg/kg).

Squinted eyes following treatment were observed daily in almost all rats in Group No. 4, less frequently in the animals in Group No. 3, and only once in one female in Group No. 2.

Lacrimation or watery eyes were noted daily after treatment in numerous high level rats and less frequently at each lower test level.

Salivation after the dose was observed occasionally in several animals in the various test groups, the frequency being highest in the high level group.

Growth, Food Consumption, and Survival

Mean weekly body weight and food consumption data are presented below.

TABLE NO. 1
Mean Weekly Body Weights and Food Consumption

Week	Male									
	Group No. 1		Group No. 2		Group No. 3		Group No. 4		Group No. 5	
	Weight	Food Cons.	Weight	Food Cons.	Weight	Food Cons.	Weight	Food Cons.	Weight	Food Cons.
	g.	g.	g.	g.	g.	g.	g.	g.	g.	g.
0	231	-	226	-	223	-	231	-	229	-
1	277	144	268	150	261	137	256	113	276	148
2	315	151	306	159	296	158	284	152	316	160

Week	Female									
	Group No. 1		Group No. 2		Group No. 3		Group No. 4		Group No. 5	
	Weight	Food Cons.	Weight	Food Cons.	Weight	Food Cons.	Weight	Food Cons.	Weight	Food Cons.
	g.	g.	g.	g.	g.	g.	g.	g.	g.	g.
0	209	-	212	-	205	-	206	-	205	-
1	229	130	230	114	229	109	232	110	222	116
2	248	131	245	122	245	136	255	141	239	124

Weight gains and food consumption for the high level males (Group No. 4 - 120 mg/kg) were slightly lower compared with those for the male control and the remaining male test groups. Body weight gain and food consumption were comparable among the female control and test groups. Survival was 100%.

Results of Ophthalmoscopic Examination

Gross ophthalmoscopic examination performed on all rats in this study at initiation and prior to sacrifice revealed no gross eye abnormalities in any of the animals.

Clinical Laboratory Studies

The hematological values determined at one and two weeks for the male and female test groups showed no significant differences from control values, and no dose-related trends were apparent. At one week, all mean values for the test groups were comparable with those for the respective control groups. At two weeks, the group means for hematocrit and hemoglobin for the high level female group (Group No. 4 - 120 mg/kg/day) were lower than the respective control values due to abnormally decreased values for one high level female (Rat No. 82-766, one of the rats that had showed a yellow discoloration of the fur during the second week of the study). At two weeks, the percent of segmented neutrophils in female Group No. 4 was somewhat elevated. Except for a few decreased or elevated individual values obtained for control and test rats, all remaining values were within normal limits and comparable among the test and control groups.

A slight trend toward higher blood sugar values was evident at one week in the male and female test groups, but all values were within normal range. The two-week blood sugar values showed an overall increase in all groups including the controls and were highest for both sexes at the high test level, but only a few individual values were above the normal range for laboratory rats.

The mean alkaline phosphatase values for the test groups were also somewhat higher than the respective control values, but no dose-related trend

was evident. The other biochemical values and the results of urine analyses were within normal range and comparable among the test and the respective control groups.

Gross Observations at Necropsy

The following gross alterations were observed in several test rats only:

A thickened-appearing wall of the small intestine (mostly the duodenum) in one of 10 males in Group No. 2 - 30 mg/kg; in one male and two females in Group No. 3 - 60 mg/kg; and in one male and three females in Group No. 4 - 120 mg/kg. The lining of the duodenum in the above rats in Groups No. 3 and No. 4 showed small, yellow foci.

A thickened-appearing stomach wall in one male in Group No. 3 and in two females in Group No. 4; in addition, a rough-appearing lining of the nonglandular portion of the stomach in a third female in Group No. 4. Similar findings in stomach or small intestine were not observed in the low level test group (15 mg/kg - Group No. 5).

Slight to moderate enlargement of the spleen was noted in four of 10 male control rats, in two males and two females in Group No. 2, one male in Group No. 3, one female in Group No. 4, and two males and one female in Group No. 5. The weights of the above enlarged-appearing spleens ranged from 1.00 to 1.57 grams. These weights are slightly higher than those usually found in young laboratory rats.

Gross alterations in the lung noted in two control male rats, in three 30 mg/kg rats, seven 60 mg/kg rats, seven 120 mg/kg rats, and four 15 mg/kg rats included small, consolidated or abscessed areas; small, gray, cyst-like areas; distension of the lobes, or dark red areas in the lobes. The dark red areas were apparently caused by aspiration of blood at sacrifice.

Findings in the liver included small, yellow foci in the left lateral lobe (one control male); a small, firm, yellow area in the median lobe of the liver (one 60 mg/kg male), a pale yellow-brown discoloration of the liver and/or thickened liver lobes (in one 60 mg/kg and two 120 mg/kg animals).

A control male had a dilated renal pelvis. Eight test rats at various levels showed one or several of the following kidney alterations: both pelves dilated; a greenish or pale yellow-brown kidney cortex; a dark pink outer medulla; or a speckled surface.

A dark red cyst surrounding the left ovary was found in one control female. The uterine horns of one control and several test rats at various test levels were distended with clear fluid.

Two females (Groups No. 3 and No. 4) had severe alopecia on the body; sections of skin were preserved.

Female Rat No. 82-786 (15 mg/kg - Group No. 4) had a dark pink, rough, thickened bladder wall; the bladder contained numerous calculi from small granules to firm, white stones, measuring approximately 1.0 x 5.0 cm. in diameter. Both renal pelves were dilated and contained small, firm granules.

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Microscopic Analyses

At the request of the project officer, no histopathological examination of the tissues was performed. All preserved tissues are being held at Hazleton Laboratories, Inc., for possible future reference.

Submitted by

for

J.E. Powers
MARCELINA B. POWERS, D.V.M., M.S.
Project Manager, Drugs and
Industrial Chemicals
Toxicology-Biosciences Laboratory

Report Preparation: T. Kundzin
Supervision: Fink

lct

EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

T = trace ($\pm$)

0 = negative

1 = slight (+)

2 = moderate (++)

3 = marked (+++)

4 = severe (++++)

193-404

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS

GROUP NUMBER	ANIMAL NUMBER	SEX	HCT %	HGB G%	RBC MILLS	WBC THS	DIFFERENTIAL						
							NETA %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	PLASMA %
1	82696	M	42.0	11.9	5.82	21.6	0	0	10	88	2	0	0
1	82697	M	46.0	13.7	6.54	13.1	0	0	11	88	1	0	0
1	82698	M	43.0	13.2	7.28	12.3	0	1	21	75	0	3	0
1	82699	M	43.0	13.4	6.45	15.6	0	0	17	79	3	1	0
1	82700	M	41.0	12.2	6.27	17.5	0	0	12	83	3	2	0
GROUP MEAN			43.0	12.9	6.47	16.0							
2	82716	M	46.0	13.2	6.74	15.6	0	0	15	84	1	0	0
2	82717	M	38.0	12.0	5.78	17.9	0	0	10	90	0	0	0
2	82718	M	41.0	12.6	6.04	13.8	0	0	19	81	0	0	0
2	82719	M	45.0	14.0	6.40	17.5	0	0	21	78	0	1	0
2	82720	M	45.0	13.4	6.85	13.3	0	0	08	92	0	0	0
GROUP MEAN			43.0	13.0	6.36	15.6							
3	82736	M	50.0	12.6	6.59	11.3	0	0	26	74	0	0	0
3	82737	M	40.0	12.6	6.31	16.0	0	2	14	84	0	0	0
3	82738	M	48.0	14.0	6.96	15.7	0	0	23	77	0	0	0
3	82739	M	48.0	13.7	6.89	19.2	0	0	17	81	2	0	0
3	82740	M	49.0	14.8	7.70	12.6	0	0	25	75	0	0	0
GROUP MEAN			47.0	13.5	6.89	15.0							
4	82756	M	41.0	12.6	6.35	11.0	0	1	24	75	0	0	0
4	82757	M	44.0	12.7	6.69	18.4	0	1	13	94	0	2	0
4	82758	M	43.0	13.0	6.77	15.4	0	1	26	73	0	0	0
4	82759	M	38.0	12.0	6.09	15.6	0	1	30	68	0	1	0
4	82760	M	42.0	12.6	6.55	18.5	0	0	20	79	0	1	0
GROUP MEAN			41.6	12.6	6.49	15.8							

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193-404

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS

GROUP NUMBER	ANIMAL NUMBER	S E X	HCT %	HGB GZ	RBC MILLS	WBC THS	-----DIFFERENTIAL-----						
							META %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	BASO %
5	82776	M	47.0	13.4	6.58	16.9	0	0	25	73	1	1	0
5	82777	M	42.0	12.0	6.04	14.1	0	1	26	72	0	1	0
5	82778	M	41.0	12.6	6.51	08.7	0	0	14	84	0	2	0
5	82779	M	46.0	13.4	6.63	16.4	0	0	22	76	1	1	0
5	82780	M	44.0	12.7	6.63	18.0	0	0	20	80	0	0	0
GROUP	MEAN		44.0	12.8	6.48	14.8							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	HCT %	HGB G%	RBC MILLS	WBC THS	-----DIFFERENTIAL-----						
							MET	BAND	SEG	LYMPH	MUNO	EOSIN	RASO
							%	%	%	%	%	%	%
1	82696	M	47.0	13.5	6.01	28.6	0	0	4	92	0	4	0
1	82697	M	48.0	14.8	6.26	11.9	0	0	13	86	1	0	0
1	82698	M	43.0	13.7	6.39	12.2	0	0	26	71	2	1	0
1	82699	M	43.0	12.6	6.34	20.6	0	0	11	86	2	1	0
1	82700	M	42.0	13.0	6.17	16.3	0	0	21	74	1	4	0
GROUP	MEAN		44.6	13.5	6.23	17.9			75				
2	82716	M	45.0	12.8	6.09	18.1	0	0	10	90	0	0	0
2	82717	M	42.0	13.0	6.07	18.5	0	0	15	84	0	1	0
2	82718	M	45.0	12.6	6.00	16.6	0	0	9	89	1	1	0
2	82719	M	42.0	13.7	6.39	28.5	0	0	8	91	1	0	0
2	82720	M	45.0	13.0	8.49	18.3	0	0	27	73	0	0	0
GROUP	MEAN		43.8	13.0	6.61	20.0							
3	82736	M	50.0	14.2	6.55	11.5	0	0	21	79	0	0	0
3	82737	M	49.0	13.0	6.35	25.4	0	0	7	93	0	0	0
3	82738	M	48.0	13.7	6.55	21.9	0	0	4	95	0	1	0
3	82739	M	47.0	13.0	6.57	23.4	0	0	5	95	0	0	0
3	82740	M	47.0	14.0	7.24	12.5	0	0	13	86	1	0	0
GROUP	MEAN		48.2	13.6	6.65	18.9							
4	82756	M	44.0	14.0	6.61	9.5	0	0	22	78	0	0	0
4	82757	M	48.0	14.2	6.77	24.2	0	0	10	90	0	0	0
4	82758	M	50.0	14.6	6.85	9.0	0	0	26	72	2	0	0
4	82759	M	44.0	13.2	6.34	15.5	0	0	18	82	0	0	0
4	82760	M	48.0	14.2	7.30	18.6	0	0	14	86	0	0	0
GROUP	MEAN		46.8	14.0	6.77	15.4			90				

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	HCT %	HGB GZ	RUC MILLS	WBC THS	-----DIFFERENTIAL-----						
							HETA	BAND	SEG	LYMPH	MONO	EOSIN	BASO
							%	%	%	%	%	%	%
5	82776	M	44.0	13.7	6.18	18.4	0	0	7	93	0	0	0
5	82777	M	40.0	11.5	6.08	13.8	0	0	15	85	0	0	0
5	82778	M	41.0	13.0	6.28	15.5	0	0	9	90	0	1	0
5	82779	M	48.0	13.0	6.50	17.6	0	0	21	79	0	0	0
5	82780	M	44.0	13.0	6.42	24.5	0	0	12	87	1	0	0
GROUP	MEAN		43.4	12.8	6.29	18.0							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2023 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	HCT %	HGB G	RBC MILLS	WBC THS	META %	BAND %	SEG %	LYMPH %	DIFFERENTIAL		
											MONO %	EOSIN %	BASO %
1	82696	M	45.0	13.2	6.19	29.1	0	0	15	85	0	0	0
1	82697	M	51.0	15.0	6.91	18.0	0	0	16	83	0	1	0
1	82698	M	50.0	14.4	7.48	13.6	0	0	20	79	0	1	0
1	82699	M	45.0	13.0	6.55	15.7	0	0	8	91	1	0	0
1	82700	M	47.0	13.7	7.02	18.1	0	0	25	74	0	1	0
GROUP MEAN			47.6	13.9	6.83	18.9							
2	82716	M	46.0	14.4	7.00	25.8	0	0	8	92	0	0	0
2	82717	M	43.0	13.4	6.17	26.1	0	0	9	90	0	1	0
2	82718	M	44.0	13.7	7.80	13.2	0	0	15	85	0	0	0
2	82719	M	44.0	14.4	6.31	6.2	0	0	9	91	0	0	0
2	82720	M	51.0	15.0	7.32	14.3	0	0	19	81	0	0	0
GROUP MEAN			45.6	14.2	6.92	17.1							
3	82736	M	46.0	13.2	7.24	9.7	0	0	16	84	0	0	0
3	82737	M	44.0	13.5	6.96	23.1	0	0	11	86	1	2	0
3	82738	M	50.0	15.0	7.36	22.7	0	0	11	88	0	1	0
3	82739	M	44.0	13.7	6.26	21.3	0	0	6	94	0	0	0
3	82740	M	44.0	12.7	6.92	11.6	0	0	12	88	0	0	0
GROUP MEAN			45.6	13.6	6.95	17.7							
4	82756	M	44.0	13.0	6.78	19.4	0	0	10	90	0	0	0
4	82757	M	45.0	12.7	6.83	18.3	0	0	11	89	0	0	0
4	82758	M	44.0	13.2	6.76	11.1	0	0	30	70	0	0	0
4	82759	M	44.0	12.6	7.32	12.8	0	0	36	62	0	1	1
4	82760	M	46.0	13.4	6.92	18.2	0	0	23	77	0	0	0
GROUP MEAN			44.6	13.0	6.92	16.0							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E	HCT %	HGB GZ	RBC MILLS	WBC THS	DIFFERENTIAL						
							META %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	HASO %
5	82776	M	46.0	14.6	7.24	16.0	0	0	17	83	0	0	0
5	82777	M	42.0	12.6	6.39	17.1	0	0	20	77	0	3	0
5	82778	M	45.0	12.7	6.58	16.1	0	0	20	80	0	0	0
5	82779	M	45.0	13.5	7.00	14.6	0	0	21	78	0	1	0
5	82780	M	43.0	13.7	7.47	23.6	0	0	10	90	0	0	0
GROUP MEAN			44.2	13.4	6.94	17.5							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS

GROUP NUMBER	ANIMAL NUMBER	SEX	HCT %	HGB G%	RBC MILLS	WBC THS	DIFFERENTIAL							BASO %
							INITIAL	METAB	BAND	SEG	LYMPH	MONO	EOSIN	
							%	%	%	%	%	%	%	%
1	82706	F	48.0	14.0	7.47	19.4	0	0	0	18	82	0	0	0
1	82707	F	51.0	15.0	7.90	13.6	0	0	0	17	82	0	1	0
1	82708	F	48.0	15.0	7.44	16.6	0	0	0	18	82	0	0	0
1	82709	F	51.0	14.8	7.31	21.6	0	1	1	15	84	0	0	0
1	82710	F	44.0	13.4	6.88	19.4	0	0	0	19	79	0	1	1
GROUP MEAN			48.4	14.4	7.40	18.1								
2	82726	F	45.0	12.4	6.79	13.7	0	1	1	15	83	1	0	0
2	82727	F	41.0	13.0	6.58	17.6	0	0	0	11	86	3	0	0
2	82728	F	43.0	16.4	6.79	15.6	0	0	0	18	80	0	2	0
2	82729	F	49.0	16.4	8.31	17.2	0	0	0	28	72	0	0	0
2	82730	F	45.0	13.5	6.92	14.9	0	0	0	21	79	0	0	0
GROUP MEAN			44.6	14.3	7.08	15.8								
3	82746	F	42.0	13.0	6.50	12.3	0	0	0	17	83	0	0	0
3	82747	F	42.0	14.0	7.20	13.1	0	0	0	11	88	0	1	0
3	82748	F	43.0	13.0	6.60	11.9	0	0	0	15	85	0	0	0
3	82749	F	48.0	14.2	7.18	15.1	0	0	0	29	70	0	1	0
3	82750	F	43.0	13.0	6.64	13.9	0	0	0	21	77	1	1	0
GROUP MEAN			43.6	13.4	6.82	13.3								
4	82766	F	48.0	14.4	7.80	16.7	0	0	0	29	70	0	1	0
4	82767	F	42.0	13.4	7.22	12.3	0	0	0	07	90	1	2	0
4	82768	F	46.0	14.6	7.08	11.1	0	0	0	22	77	0	1	0
4	82769	F	44.0	13.4	6.76	10.9	0	0	0	14	85	0	1	0
4	82770	F	44.0	13.4	7.08	18.1	0	0	0	20	80	0	0	0
GROUP MEAN			44.8	13.8	7.19	13.8								

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS

GROUP NUMBER	ANIMAL NUMBER	S E X	HCT %	HGB g	RBC MILLIS	WBC THS	DIFFERENTIAL						BASO %
							MET	BAND	SEG	LYMPH	MONO	EOSIN	
							%	%	%	%	%	%	
5	82786	F	43.0	12.4	7.27	14.0	0	0	19	80	0	01	0
5	82787	F	51.0	14.6	7.26	12.5	0	0	24	73	0	02	1
5	82788	F	46.0	12.7	6.80	13.7	0	0	12	86	1	01	0
5	82789	F	42.0	12.0	6.99	15.4	0	0	28	69	0	03	0
5	82790	F	45.0	13.5	6.87	35.8	0	0	06	93	0	01	0
GROUP MEAN			45.4	13.0	7.04	18.3							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E	HCT %	HGB G	RBC MILLS	WBC THS	-----DIFFERENTIAL-----						
							MET	BAND	SEG	LYMPH	MONO	EOSIN	BASO
							%	%	%	%	%	%	%
1	82706	F	45.0	14.0	6.81	14.2	0	0	9	90	0	1	0
1	82707	F	50.0	14.6	6.79	13.7	0	0	29	70	0	1	0
1	82708	F	44.0	14.2	8.07	17.7	0	0	12	85	0	3	0
1	82709	F	40.0	13.4	6.30	20.9	0	0	13	82	2	3	0
1	82710	F	44.0	14.6	6.64	12.9	0	0	12	87	0	1	0
GROUP MEAN			44.6	14.2	6.92	15.9			75				
2	82726	F	44.0	14.4	6.66	14.3	0	0	18	80	0	2	0
2	82727	F	42.0	13.0	6.25	24.3	0	0	4	94	2	0	0
2	82728	F	44.0	14.6	6.55	14.8	0	0	13	85	0	2	0
2	82729	F	52.0	16.4	8.25	18.1	0	0	10	90	0	0	0
2	82730	F	43.0	13.5	6.68	16.8	0	0	12	88	0	0	0
GROUP MEAN			45.0	14.4	6.88	17.7							
3	82746	F	48.0	14.8	6.04	11.5	0	0	12	87	0	1	0
3	82747	F	44.0	14.2	6.66	13.0	0	0	6	93	1	0	0
3	82748	F	48.0	14.4	6.74	20.7	0	0	7	92	1	0	0
3	82749	F	49.0	15.0	7.36	15.1	0	0	9	91	0	0	0
3	82750	F	45.0	13.5	6.55	14.1	0	0	13	87	0	0	0
GROUP MEAN			46.8	14.4	6.67	14.9							
4	82766	F	52.0	14.8	7.84	17.7	0	0	28	72	0	0	0
4	82767	F	45.0	13.0	6.38	10.8	0	0	16	80	2	2	0
4	82768	F	46.0	13.0	6.67	11.6	0	0	21	78	0	1	0
4	82769	F	42.0	12.2	7.72	14.6	0	0	12	88	0	0	0
4	82770	F	44.0	12.6	6.66	17.7	0	0	20	80	0	0	0
GROUP MEAN			45.8	13.1	7.05	14.5			97				

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	SEX	S	HCT %	HGB GZ	RBC MILLS	WBC THS	-----DIFFERENTIAL-----						
								MET %	HAND %	SEG %	LYMPH %	MONO %	EOSIN %	BASO %
5	82786	F		50.0	13.9	7.58	21.6	0	0	26	74	0	0	0
5	82787	F		39.0	13.5	6.80	11.6	0	0	22	76	1	1	0
5	82788	F		44.0	12.3	6.95	17.6	0	0	7	93	0	0	0
5	82789	F		44.0	13.0	6.72	11.3	0	0	11	85	1	3	0
5	82790	F		45.0	13.7	6.51	53.1	0	0	6	94	0	0	0
GROUP MEAN				44.4	13.3	6.91	23.0							

TABLE NO. 2 - INDIVIDUAL HEHATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	HCT %	HGB GZ	RBC MILLS	WBC THS	META %	HAND %	DIFFERENTIAL					BASO %
									SEG %	LYMPH %	MONO %	EOSIN %		
1	82706	F	45.0	14.2	6.69	11.2	0	0	13	84	2	1	0	
1	82707	F	44.0	14.4	6.31	11.9	0	0	16	82	2	0	0	
1	82708	F	42.0	12.4	6.39	16.0	0	0	13	85	0	2	0	
1	82709	F	45.0	14.6	6.87	16.8	0	0	7	91	2	0	0	
1	82710	F	44.0	14.2	6.50	15.2	0	0	17	80	3	0	0	
GROUP MEAN			44.0	14.0	6.55	14.2			66					
2	82726	F	44.0	14.0	6.54	14.9	0	0	5	92	2	0	1	
2	82727	F	41.0	13.0	6.32	27.3	0	0	6	94	0	0	0	
2	82728	F	43.0	14.0	5.60	15.4	0	0	8	88	2	2	0	
2	82729	F	51.0	15.5	6.66	16.0	0	0	13	84	1	2	0	
2	82730	F	40.0	13.0	6.36	15.6	0	0	9	90	1	0	0	
GROUP MEAN			43.8	13.9	6.30	17.8								
3	82746	F	47.0	14.4	6.63	9.6	0	0	34	64	2	0	0	
3	82747	F	46.0	14.0	6.94	11.3	0	0	11	88	0	1	0	
3	82748	F	44.0	13.0	6.46	23.9	0	0	15	81	3	1	0	
3	82749	F	46.0	14.6	6.98	15.7	0	0	26	72	2	0	0	
3	82750	F	47.0	14.4	6.68	17.1	0	0	28	66	1	5	0	
GROUP MEAN			46.0	14.1	6.74	15.5			114					
4	82766	F	32.0	10.0	5.08	15.4	0	0	56	44	0	0	0	
4	82767	F	41.0	12.3	6.17	24.3	0	0	23	71	4	2	0	
4	82768	F	46.0	14.0	5.70	19.2	0	0	46	53	0	1	0	
4	82769	F	43.0	13.4	6.26	15.0	0	0	28	70	1	1	0	
4	82770	F	47.0	13.5	5.82	21.0	0	0	39	59	0	2	0	
GROUP MEAN			41.8	12.6	5.81	19.0			192					

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS

GROUP NUMBER	ANIMAL NUMBER	S E X	HCT %	HGB GZ	RBC MILLS	WBC THS	-----DIFFERENTIAL-----							BASO %
							MET %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %		
5	82786	F	39.0	12.7	5.23	23.0	0	0	9	86	2	3	0	
5	82787	F	48.0	15.3	7.11	20.2	0	0	24	75	1	0	0	
5	82788	F	44.0	14.0	6.50	17.8	0	0	19	79	0	2	0	
5	82789	F	43.0	13.5	6.79	5.9	0	0	9	90	1	0	0	
5	82790	F	49.0	13.7	7.56	19.2	0	0	6	90	3	1	0	
GROUP	MEAN		44.6	13.8	6.64	17.2								

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING PR-2823 FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS	COAGULATION	
				MIN	SEC
1	82696	M	13.0	1	30
1	82697	M	12.8	1	05
1	82698	M	12.9	1	15
1	82699	M	12.5	1	14
1	82700	M	12.4	1	25
GROUP MEAN			12.7	1	18
2	82716	M	12.6	1	20
2	82717	M	12.3	1	25
2	82718	M	12.3	1	20
2	82719	M	12.5	1	25
2	82720	M	12.3	1	10
GROUP MEAN			12.4	1	20
3	82736	M	13.3	1	23
3	82737	M	12.6	1	20
3	82738	M	12.4	1	12
3	82739	M	11.5	1	10
3	82740	M	12.0	1	10
GROUP MEAN			12.4	1	15
4	82756	M	13.8	1	15
4	82757	M	12.1	1	14
4	82758	M	10.8	1	16
4	82759	M	12.2	1	20
4	82760	M	12.3	1	05
GROUP MEAN			12.2	1	14

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS	COAGULATION MIN	SEC
5	82786	F	11.8	1	2
5	82787	F	13.1	1	5
5	82788	F	13.3	1	15
5	82789	F	13.6	1	15
5	82790	F	12.3	1	17
GROUP MEAN			12.8	1	11

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS	COAGULATION MIN	SEC
1	82696	M	14.9	1	11
1	82697	M	14.6	1	10
1	82698	M	15.7	1	05
1	82699	M	15.1	0	57
1	82700	M	15.7	0	54
GROUP MEAN			15.2	1	03
2	82716	M	11.5	1	08
2	82717	M	12.9	0	54
2	82718	M	15.7	1	03
2	82719	M	11.9	1	06
2	82720	M	12.1	0	52
GROUP MEAN			12.8	1	01
3	82736	M	16.9	0	46
3	82737	M	15.9	0	56
3	82738	M	10.2	0	58
3	82739	M	12.4	1	01
3	82740	M	12.0	0	55
GROUP MEAN			13.5	0	55
4	82756	M	14.4	1	00
4	82757	M	13.4	0	53
4	82758	M	13.8	0	54
4	82759	M	14.5	0	47
4	82760	M	12.2	1	05
GROUP MEAN			13.7	0	56

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	S ANIMAL NUMBER	E X	PRUTHROMBIN SECONDS	COAGULATION MIN	SEC
5	82776	M	13.3	1	10
5	82777	M	11.6	0	56
5	82778	M	13.6	1	01
5	82779	M	11.9	0	52
5	82780	M	15.2	0	57
GROUP	MEAN		13.1	0	59

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING PR-2823 FOR TWO WEEKS

WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS	COAGULATION MIN SEC
1	82696	M	11.5	1 12
1	82697	M	14.1	1 08
1	82698	M	14.1	0 54
1	82699	M	10.3	1 15
1	82700	M	10.7	1 18
GROUP MEAN			12.1	1 09
2	82716	M	11.3	1 21
2	82717	M	12.1	1 08
2	82718	M	13.5	1 16
2	82719	M	11.1	1 15
2	82720	M	13.9	0 53
GROUP MEAN			12.4	1 11
3	82736	M	12.7	0 57
3	82737	M	11.0	1 16
3	82738	M	14.6	1 05
3	82739	M	14.4	1 11
3	82740	M	11.4	1 07
GROUP MEAN			12.8	1 07
4	82756	M	13.4	0 51
4	82757	M	12.4	1 10
4	82758	M	12.8	1 17
4	82759	M	13.2	1 01
4	82760	M	12.2	0 57
GROUP MEAN			12.8	1 03

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	SEX	PROTHROMBIN SECONDS	COAGULATION	
				MIN	SEC
5	82776	M	12.3	1	04
5	82777	M	12.6	1	19
5	82778	M	15.2	0	58
5	82779	M	12.8	1	01
5	82780	M	11.1	1	12
GROUP MEAN			12.8	1	07

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS	COAGULATION MIN	SEC
1	82706	F	11.2	1	9
1	82707	F	12.8	1	0
1	82708	F	10.9	1	5
1	82709	F	11.2	1	6
1	82710	F	13.4	1	0
GROUP MEAN					
			11.9	1	4
2	82726	F	10.2	1	7
2	82727	F	11.0	1	14
2	82728	F	12.6	1	6
2	82729	F	12.5	1	0
2	82730	F	11.9	1	14
GROUP MEAN					
			11.6	1	8
3	82746	F	10.5	1	5
3	82747	F	10.6	1	13
3	82748	F	12.9	1	12
3	82749	F	14.2	1	8
3	82750	F	12.5	1	15
GROUP MEAN					
			12.1	1	11
4	82766	F	11.4	1	17
4	82767	F	10.6	1	15
4	82768	F	13.5	1	14
4	82769	F	12.1	1	18
4	82770	F	11.5	1	22
GROUP MEAN					
			11.8	1	17

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
INITIAL

GROUP NUMBER	S ANIMAL NUMBER	E X	PROTHROMBIN SECONDS	COAGULATION MIN	SEC
5	82776	M	14.0	1	10
5	82777	M	13.8	1	05
5	82778	M	12.6	1	16
5	82779	M	12.0	1	11
5	82780	M	13.6	1	09
GROUP MEAN			13.2	1	10

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS	COAGULATION MIN	SEC
1	82706	F	12.5	1	02
1	82707	F	12.0	1	00
1	82708	F	11.8	1	05
1	82709	F	10.9	1	09
1	82710	F	11.9	1	01
GROUP MEAN			11.8	1	03
2	82726	F	11.4	0	59
2	82727	F	13.8	1	08
2	82728	F	11.5	0	57
2	82729	F	12.5	1	14
2	82730	F	12.1	0	59
GROUP MEAN			12.3	1	03
3	82746	F	13.4	1	05
3	82747	F	9.8	1	09
3	82748	F	9.9	1	02
3	82749	F	13.9	0	53
3	82750	F	15.1	1	06
GROUP MEAN			12.4	1	03
4	82766	F	12.3	1	10
4	82767	F	12.8	1	08
4	82768	F	12.0	1	05
4	82769	F	12.5	0	59
4	82770	F	12.9	0	57
GROUP MEAN			12.5	1	04

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING NR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS	COAGULATION MIN SEC
5	82786	F	11.7	0 56
5	82787	F	12.0	0 55
5	82788	F	14.3	1 02
5	82789	F	10.8	1 05
5	82790	F	12.9	0 51
GROUP MEAN			12.3	0 58

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E	PROTHROMBIN SECONDS	COAGULATION MIN	SEC
1	82706	F	11.3	1	15
1	82707	F	13.1	1	09
1	82708	F	11.0	1	10
1	82709	F	12.0	1	07
1	82710	F	14.0	1	01
GROUP MEAN			12.3	1	08
2	82726	F	14.9	0	56
2	82727	F	9.9	1	06
2	82728	F	12.7	1	12
2	82729	F	16.3	1	04
2	82730	F	11.1	1	07
GROUP MEAN			13.0	1	05
3	82746	F	21.2	1	10
3	82747	F	17.4	1	13
3	82748	F	18.9	1	05
3	82749	F	15.4	1	19
3	82750	F	14.2	1	01
GROUP MEAN			17.4	1	10
4	82766	F	12.2	1	23
4	82767	F	11.7	1	17
4	82768	F	12.9	1	15
4	82769	F	12.2	1	10
4	82770	F	20.1	0	53
GROUP MEAN			13.8	1	12

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS	COAGULATION MIN	SEC
5	82786	F	14.7	1	04
5	82787	F	17.4	1	00
5	82788	F	13.4	1	15
5	82789	F	14.7	1	07
5	82790	F	12.8	0	59
GROUP MEAN			14.6	1	05

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING MR-2823 FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK.PHOS K-A. UNITS
1	82701	M	50.0	16.0	37.5	64.0
1	82702	M	40.0	12.0	36.0	42.8
1	82703	M	39.0	16.0	39.0	46.0
1	82704	M	68.0	17.0	29.0	46.8
1	82705	M	51.0	17.0	36.0	76.6
GROUP MEAN			49.6	15.6	35.5	55.2
2	82721	M	73.0	20.0	41.0	80.8
2	82722	M	45.0	16.0	42.5	66.0
2	82723	M	44.0	15.0	41.0	130.4*
2	82724	M	60.0	14.0	36.0	50.8
2	82725	M	68.0	16.0	37.5	59.6
GROUP MEAN			58.0	16.2	39.6	64.3
3	82741	M	66.0	15.0	34.0	54.0
3	82742	M	73.0	17.0	42.5	43.8
3	82743	M	81.0	16.0	34.0	36.0
3	82744	M	77.0	15.0	37.5	73.6
3	82745	M	66.0	14.0	29.0	47.4
GROUP MEAN			72.6	15.4	35.4	51.0
4	82761	M	78.0	16.0	26.0	79.2
4	82762	M	91.0	16.0	37.5	59.0
4	82763	M	81.0	14.0	32.5	45.4
4	82764	M	82.0	14.0	37.5	41.4
4	82765	M	73.0	13.0	23.0	30.0
GROUP MEAN			81.0	14.6	31.3	51.0

* = VALUE NOT INCLUDED IN MEAN

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS

GROUP NUMBER	ANIMAL NUMBER	SEX	S		GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS
			E	X				
5	82781	M			80.0	15.0	31.0	41.4
5	82782	M			68.0	14.0	34.0	44.8
5	82783	M			94.0	16.0	28.0	71.0
5	82784	M			80.0	14.0	34.0	53.4
5	82785	M			88.0	17.0	36.0	53.4
GROUP MEAN					82.0	15.2	32.6	52.8

TARLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	E X	GLUCOSE		HUN MG%	SGPT R-F.	ALK. PHOS	
			MG%	MG%			K-A. UNITS	
1	82701	M	63.0	14.0	34.0		70.4	
	82702	M	64.0	13.0	29.0		51.2	
	82703	M	69.0	14.0	28.0		48.8	
	82704	M	59.0	13.0	26.0		60.4	
	82705	M	64.0	15.0	36.0		61.2	
GROUP MEAN			63.8	13.8	30.6		58.4	
2	82721	M	66.0	14.0	31.0		65.6	
	82722	M	74.0	14.0	34.0		88.8	
	82723	M	69.0	16.0	32.5		79.2	
	82724	M	55.0	12.0	31.0		53.2	
	82725	M	89.0	15.0	32.5		93.6	
GROUP MEAN			70.6	14.2	32.2		76.1	
3	82741	M	84.0	14.0	29.0		103.6	
	82742	M	103.0	13.0	29.0		61.2	
	82743	M	86.0	14.0	29.0		78.4	
	82744	M	94.0	16.0	39.0		109.2	
	82745	M	75.0	14.0	34.0		87.6	
GROUP MEAN			88.4	14.2	32.0		88.0	
4	82761	M	100.0	21.0	29.0		134.4	
	82762	M	108.0	18.0	37.5		112.0	
	82763	M	100.0	15.0	29.0		82.8	
	82764	M	103.0	14.0	34.0		54.8	
	82765	M	87.0	14.0	26.0		34.4	
GROUP MEAN			99.6	16.4	31.1		83.7	

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	HUN MG%	SGPT R-F.	ALK.PHOS K-A. UNITS
5	82781	M	78.0	17.0	28.0	40.8
5	82782	M	71.0	14.0	41.0	40.0
5	82783	M	83.0	16.0	29.0	87.6
5	82784	M	76.0	15.0	34.0	62.0
5	82785	M	72.0	14.0	32.5	50.4
GROUP	MEAN		76.0	15.2	32.9	56.2

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING NR-2823 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	HUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS
1	82701	M	92.0	16.0	29.0	36.8
1	82702	M	100.0	14.0	25.0	27.6
1	82703	M	104.0	16.0	34.0	36.0
1	82704	M	101.0	19.0	29.0	44.0
1	82705	M	90.0	17.0	39.0	38.8
GROUP MEAN			97.4	16.4	31.2	36.6
2	82721	M	90.0	16.0	25.0	49.6
2	82722	M	122.0	16.0	34.0	46.0
2	82723	M	130.0	19.0	28.0	45.6
2	82724	M	92.0	15.0	29.0	30.0
2	82725	M	118.0	14.0	25.0	35.2
GROUP MEAN			110.4	16.0	28.2	41.3
3	82741	M	134.0	14.0	28.0	50.4
3	82742	M	119.0	14.0	28.0	27.2
3	82743	M	89.0	15.0	26.0	30.8
3	82744	M	136.0	18.0	29.0	64.8
3	82745	M	93.0	18.0	36.0	39.6
GROUP MEAN			114.2	15.8	29.4	42.6
4	82761	M	136.0	20.0	36.0	94.8
4	82762	M	109.0	17.0	32.5	70.4
4	82763	M	175.0	13.0	31.0	56.0
4	82764	M	128.0	15.0	34.0	37.6
4	82765	M	157.0	13.0	37.5	36.0
GROUP MEAN			141.0	15.6	34.2	59.0

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS
5	82781	M	103.0	18.0	29.0	33.2
5	82782	M	99.0	17.0	26.0	28.8
5	82783	M	98.0	15.0	34.0	48.8
5	82784	M	76.0	16.0	31.0	36.4
5	82785	M	82.0	16.0	32.5	30.0
GROUP	MEAN		91.6	16.4	30.5	35.4

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK.PHOS K-A. UNITS
1	82711	F	64.0	18.0	28.0	26.0
1	82712	F	69.0	16.0	26.0	30.2
1	82713	F	61.0	18.0	32.5	22.0
1	82714	F	60.0	16.0	34.0	24.8
1	82715	F	72.0	18.0	31.0	32.8
GROUP MEAN			65.2	17.2	30.3	27.2
2	82731	F	61.0	17.0	39.0	50.0
2	82732	F	72.0	16.0	36.0	64.0
2	82733	F	74.0	19.0	36.0	28.0
2	82734	F	81.0	21.0	39.0	66.0
2	82735	F	96.0	18.0	36.0	46.0
GROUP MEAN			76.8	18.2	37.2	50.8
3	82751	F	46.0	19.0	34.0	26.0
3	82752	F	68.0	21.0	39.0	23.8
3	82753	F	55.0	19.0	37.5	33.2
3	82754	F	51.0	20.0	31.0	38.2
3	82755	F	62.0	19.0	31.0	31.0
GROUP MEAN			56.4	19.6	34.5	30.4
4	82771	F	52.0	15.0	34.0	46.8
4	82772	F	60.0	22.0	31.0	23.0
4	82773	F	72.0	23.0	37.5	38.6
4	82774	F	71.0	18.0	25.0	22.4
4	82775	F	75.0	18.0	28.0	31.6
GROUP MEAN			66.0	19.2	31.1	32.5

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	RUN MG%	SGPT R-F.	ALK.PHOS K-A. UNITS
5	82791	F	80.0	18.0	34.0	33.2
5	82792	F	79.0	23.0	34.0	51.8
5	82793	F	84.0	18.0	23.0	27.4
5	82794	F	76.0	19.0	26.0	57.2
5	82795	F	80.0	19.0	34.0	30.6
GROUP	MEAN		79.8	19.4	30.2	40.0

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING NR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK.PHOS K-A. UNITS
1	82711	F	69.0	14.0	26.0	29.6
1	82712	F	67.0	13.0	22.0	30.8
1	82713	F	80.0	17.0	28.0	28.4
1	82714	F	80.0	19.0	34.0	31.6
1	82715	F	75.0	18.0	31.0	44.8
GROUP MEAN			74.2	16.2	28.2	33.0
2	82731	F	105.0	18.0	25.0	106.8
2	82732	F	90.0	19.0	36.0	83.6
2	82733	F	74.0	18.0	26.0	50.4
2	82734	F	91.0	17.0	29.0	45.6
2	82735	F	89.0	18.0	31.0	52.0
GROUP MEAN			89.8	18.0	29.4	67.7
3	82751	F	121.0	15.0	34.0	50.4
3	82752	F	89.0	15.0	39.0	62.0
3	82753	F	105.0	15.0	31.0	54.0
3	82754	F	95.0	14.0	39.0	70.4
3	82755	F	78.0	16.0	37.5	69.2
GROUP MEAN			97.6	15.0	36.1	61.2
4	82771	F	93.0	20.0	34.0	109.2
4	82772	F	112.0	17.0	31.0	61.2
4	82773	F	157.0	21.0	34.0	94.8
4	82774	F	131.0	15.0	37.5	63.2
4	82775	F	102.0	20.0	34.0	103.6
GROUP MEAN			119.0	18.6	34.1	86.4

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	HUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS
5	82791	F	78.0	16.0	29.0	55.6
5	82792	F	97.0	18.0	26.0	36.8
5	82793	F	80.0	15.0	26.0	55.6
5	82794	F	86.0	19.0	28.0	30.8
5	82795	F	96.0	17.0	32.5	31.6
GROUP MEAN			87.4	17.0	28.3	42.1

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	HUN MG%	SGPT K-F.	ALK. PHOS K-A. UNITS
1	82711	F	76.0	16.0	23.0	19.6
1	82712	F	94.0	17.0	23.0	20.0
1	82713	F	70.0	16.0	25.0	14.4
1	82714	F	102.0	16.0	26.0	16.8
1	82715	F	74.0	19.0	25.0	30.0
GROUP MEAN			83.2	16.8	24.4	20.2
2	82731	F	161.0	20.0	26.0	43.2
2	82732	F	82.0	14.0	26.0	30.8
2	82733	F	92.0	19.0	26.0	27.6
2	82734	F	112.0	15.0	23.0	21.6
2	82735	F	160.0	18.0	28.0	30.8
GROUP MEAN			121.4	17.2	25.8	30.8
3	82751	F	118.0	17.0	28.0	23.6
3	82752	F	92.0	15.0	28.0	26.8
3	82753	F	124.0	18.0	22.0	24.0
3	82754	F	130.0	16.0	31.0	26.8
3	82755	F	106.0	23.0	28.0	28.4
GROUP MEAN			114.0	17.8	27.4	25.9
4	82771	F	138.0	16.0	28.0	34.4
4	82772	F	166.0	17.0	37.5	29.6
4	82773	F	138.0	15.0	32.5	56.0
4	82774	F	202.0	14.0	31.0	49.6
4	82775	F	116.0	16.0	36.0	48.4
GROUP MEAN			152.0	15.6	33.0	43.6

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS
5	82791	F	90.0	16.0	25.0	31.2
5	82792	F	114.0	16.0	23.0	19.6
5	82793	F	110.0	16.0	23.0	36.0
5	82794	F	100.0	20.0	20.0	12.8
5	82795	F	159.0	16.0	22.0	23.6
GROUP MEAN			114.6	16.8	22.6	24.6

TABLE NO. 4 - URINE ANALYSIS
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
INITIAL

GROUP NUMBER	NUMBER S OF AN-E IMALS X	APPEAR.	P H	SP. GR.	SU- GAR	PRO- TEIN	BILI- RUBIN	OCC BLD	RBC	WBC	EPITH	AMORPH	CRYS	BACT	SPERM
1	5* M	T YEL	7	1.015	0	0	0	0	0-1					FEW	MANY
2	5* M	C YEL	7	1.015	0	0	0	0	0-2						MANY
3	5* M	C YEL	7	1.009	0	0	0	0						FEW	MANY
4	5* M	C YEL	7	1.021	0	0	0	0				LITTLE			MANY
5	5* M	C YEL	7	1.011	0	0	0	0	1-3						MANY

* = POOLED SAMPLES

193-404

TABLE NO. 4 - URINE ANALYSIS
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	NUMBER S OF AN- E IMALS X	P H	SP. GR.	SU- GAR	PRO- TEIN	BILI- RUBIN	OCC BLD	-----MICROSCOPIC FINDINGS-----						
								RBC	WBC	EPITH	AMORPH	CRYS	BACT	SERM
1	5* M	T YEL	7	1.012	0	0	0		1-2	1-3	LITTLE	FEW	MANY	
2	5* M	T YEL	7	1.013	0	0	0		0-1	0-1	LITTLE	MANY	MANY	FEW
3	5* M	T YEL	7	1.012	0	0	0	0-1	1-3		MUCH	MANY	MANY	FEW
4	5* M	T YEL	7	1.005	0	0	0		1-3	2-4	MUCH	MANY	MANY	FEW
5	5* M	T YEL	7	1.012	0	0	0	0-1	1-2	1-3	LITTLE	FEW	MANY	

* = POOLED SAMPLES

TABLE NO. 4 - URINE ANALYSIS
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	NUMBER S OF AN- E INIALS X	APPEAR.	P H	SU- SP. GR.	PRO- GAR	HILI- TEIN	RUBIN BLD	OCC	MICROSCOPIC FINDINGS			
									RBC	WBC	EPITH	AMORPH CRYSTALS
1	5*	M T YEL	6	1.026	0	T	0	0	1-2	0-1	LITTLE	MANY MANY MANY
2	5*	M T YEL	7	1.024	0	T	0	0	0-1	0-1	MUCH	MANY MANY FEW
3	5*	M T YEL	7	1.017	0	T	0	0	1-3	8-10	MUCH	MANY MANY
4	5*	M T YEL	6	1.022	0	T	0	0	1-3	0-1	2-4	MUCH MANY MANY
5	5*	M T YEL	7	1.018	0	0	0	T	2-4	1-3	MUCH	MANY MANY

* = POOLED SAMPLES

TABLE NO. 4 - URINE ANALYSIS
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS

GROUP NUMBER	NUMBER OF AN- THALS X	APPEAR.	P H	SP.GR.	SU- GAR	PRO- TEIN	BILI- RUBIN	OCC BLD	RBC	WBC	EPITH	AMORPH	CRYSTALS	SPERM
1	5*	F T YEL	7	1.023	0	0	0	0			MUCH	MANY	MANY	
2	5*	F C YEL	7	1.020	0	0	0	0	2-3					MANY
3	5*	F T YEL	7	1.016	0	0	0	0		1-2		FEW	MANY	
4	5*	F C YEL	7	1.021	0	0	0	0		4-5		FEW	MANY	
5	5*	F C YEL	7	1.010	0	0	0	0		2-3		MANY	MANY	

* = POOLED SAMPLES

TABLE NO. 4 - URINE ANALYSIS
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER	NUMBER S OF AN- IMALS X	E APPEAR.	P H	SP.GR.	SU- GAR	PRO- TEIN	BILI- RUBIN	OCC BLD	-----MICROSCOPIC FINDINGS-----			
									RBC	WBC	EPITH	AMORPH CRYSTALS
1	5* F	T YEL	7	1.022	0	0	0	0	1-3	1-2	MUCH	MANY MANY
2	5* F	T YEL	7	1.018	0	0	0	0		1-3	MUCH	MANY MANY
3	5* F	T YEL	7	1.013	0	0	0	0	1-3	2-4	MUCH	MANY MANY
4	5* F	T YEL	7	1.010	0	0	0	0		1-2	MUCH	MANY MANY
5	5* F	T YEL	7	1.008	0	0	0	0			LITTLE	FEW MANY

* = PUULED SAMPLES

TABLE NO. 4 - URINE ANALYSIS
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

GROUP NUMBER	NUMBER S OF AN- E IMALS X	P H SP. GR.	SU- GAR	PRO- TEIN	BILI- RUBIN	OCC BLD	-----MICROSCOPIC FINDINGS-----			
							RHC	WRC	EPITH	AMORPH CRYSTALS
1	5* F	T YEL	7	1.013	0	0	0-1	1-3	MUCH	MANY
2	5* F	T YEL	7	1.020	0	0	1-3	0-1	LITTLE	FEW
3	5* F	T YEL	6	1.020	0	0		2-4	LITTLE	MANY
4	5* F	T YEL	6	1.017	0	0		1-3	2-4	MUCH
5	5* F	T YEL	6	1.018	0	0	0-1	0-1	1-3	MUCH

* = POOLED SAMPLES

HAZLETON LABORATORIES, INC.
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Sponsor: Walter Reed Army Institute of Research

Date: February 24, 1970

Material: WR-2823 (AU 69115)

Subject: REPORT NO. 30
Intravenous Toxicity Study - Dogs
Project No. 193-405

SUMMARY

WR-2823 (AU 69115) was administered intravenously at dosage levels of 50, 100, 200, and 400 mg/kg of body weight to four groups of two or four male dogs each for a total of one, four, or five doses.

Depression was noted in dogs receiving 50 and 100 mg/kg following the initial injection, and slight eye and nasal discharge was noted in the 50 mg/kg dogs during Week 1. One 100 mg/kg dog also exhibited loss of motor control, lethargy, and nasal discharge following the fourth injection. Signs noted in two 200 mg/kg dogs prior to death after the fourth or fifth injection included emesis, slightly elevated body temperature, dilated pupils, retching without emesis, depression, eye and nasal discharge (one dog), comatose appearance (one dog), and lack of motor control (one dog). The two additional 200 mg/kg dogs which received only one injection exhibited emesis of food mass, drooping eyelids, and listlessness or lack of energy with complete recovery within several hours after injection.

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Emesis (one dog), inability to stand, dilated pupils, lack of pain reflex, and irregular respiration (one dog) preceded death in the 400 mg/kg dogs on the day of the initial injection. Body weight loss was noted in one Group No. 1 dog, in two Group No. 2 dogs, and in three Group No. 3 dogs.

The one compound-related alteration noted at necropsy was marked reddening of the renal cortex and/or medulla at the two higher levels.

MATERIAL

Identification WR-2823 (AU 69115).

Description Fine, white powder with no noticeable odor.

Receipt Date July 2, 1969.

Purity Assumed to be 100% active ingredient.

METHODS**Experimental Animals**

Breed: Young adult purebred beagles.

Number: Ten males.

Body Weight (At Initiation): 7.2 to 12.8 kg.

Housing: Individually in metal cages.

Diet: Ground Wayne Dog Meal and water ad libitum.

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Groups and Dosage Levels

<u>Group No.</u>	<u>No. of Animals</u>	<u>Dosage Level</u> each day	<u>No. of Days Dose</u> <u>was Received</u>
1	2	50 mg/kg	4
2	2	100 mg/kg	4
3	2	200 mg/kg	5
	2	200 mg/kg	1
4	2	400 mg/kg	1

Compound Administration

The test material was administered by intravenous injection as a 50% solution in distilled water according to the regimen outlined in the above table. Rate of administration was approximately 1 ml. per 10 seconds.

Observations and Records

Daily: Appearance, behavior, and signs of compound effect.

Initially and Terminally: Body weights.

Terminal Studies

Terminal Sacrifice: By exsanguination under anesthesia (Surital) generally nine days following the last intravenous injection.

Gross Necropsies: On all dogs which died during the study and on all dogs sacrificed at termination.

RESULTS

Appearance, Behavior, Body Weight Changes, and Signs of Compound Effect

Group No. 1 (50 mg/kg): Slight depression following the second injection and slight clear-colored eye and nasal discharge during Week 1 were noted in both dogs. One dog showed a weight loss of 1.4 kg. (13%).

Group No. 2 (100 mg/kg): Both animals appeared slightly depressed following the second injection of compound and both animals exhibited terminal body weight loss (0.7 kg. or 8% and 0.8 kg. or 7%). In addition to these signs, loss of motor control, depression, lethargy, and nasal discharge were noted in one animal following the final injection.

Group No. 3 (200 mg/kg):

Four or Five Injections - Following the initial injection, animals showed emesis of food mass or white, mucoid material; slightly elevated body temperature; dilated pupils; lethargy; and retching without emesis. Depression was noted after the third injection. One animal died following the fourth injection, and one animal exhibited weakness and inability to stand.

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1. *Chlorophyll a* (Chl *a*)

Following the fifth injection, one animal showed eye and nasal discharge, comatose appearance, and lack of motor control with death occurring on the day after the fifth injection. Weight losses of 0.5 kg. (4%) and 0.3 kg. (3%) were noted.

One Injection - Emesis of food mass (one dog), drooping eyelids, and listlessness or lack of energy were noted following injection with signs subsiding within several hours following injection.

One animal exhibited a terminal body weight loss of 0.1 kg. (1%).

Group No. 4 (400 mg/kg): Emesis of food mass (one dog), inability to stand, dilated pupils, lack of pain reflex, and irregular respiration (one dog) were noted after injection with death occurring in both dogs on the day of injection.

Gross Pathology

At Death: Large amount of blood on cut surface of spleen and liver (two 200 mg/kg level dogs and two 400 mg/kg level dogs); bile in gallbladder dark and thickened (one 200 mg/kg level dog); kidneys reddened and/or enlarged (one 200 mg/kg level dog and in one 400 mg/kg level dog); cortex and/or medulla of kidneys markedly reddened (one 200 mg/kg level dog and two 400 mg/kg level dogs); mucosal surface of urinary bladder reddened and contained calculi closely adhered to surface (one 400 mg/kg level dog); and skin around injection site purplish in color (one 200 mg/kg level dog).

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At Sacrifice: Spleen approximately twice normal size in one 100 mg/kg
level dog.

Submitted by

MB Powers

MARCELINA B. POWERS, D.V.M., M.S.
Project Manager, Drugs and
Industrial Chemicals
Toxicology-Biosciences Laboratory

Report Preparation: Lambert
Supervision: Pate

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HAZLETON LABORATORIES, INC.
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Sponsor: Walter Reed Army Institute of Research

Date: January 14, 1970

Material: WR-2823 (AU 69115)

Subject: REPORT NO. 29
14-Day Subacute Intravenous Toxicity - Dogs
Project No. 193-406

SUMMARY

WR-2823 (AU 69115) was administered by intravenous injection as a 22.4% or 44.8% weight-per-volume solution in saline to four groups of two male and two female beagles each once daily for a total of 14 days at dosage levels of 20, 40, 80, and 160 mg/kg of body weight. One group of two male and two female beagles served as a control and received only saline.

All control animals were normal in appearance and behavior throughout the study, but all exhibited 8% to 12% body weight losses. Toxic signs noted in all test animals included slow or no pupillary response to light and/or relaxed nictitating membranes following early injections and within 10 to 30 minutes following each subsequent injection. Terminal body weight losses were noted in all test groups and ranged from 11% to 16% in Group No. 2 animals, from 10% to 25% in Group No. 3 animals, from 16% to 35% in Group No. 4 animals, and from 8% to 12% in Group No. 5 animals. Additional toxic signs noted in Group No. 4 animals included droopy eyes (two dogs) and excessive thirst (one dog) following the initial injection; sporadic episodes of emesis throughout the study; decreased activity during Week 2; mucoid

discharge from both eyes during Week 2 (Dog No. 14494); and slight nasal discharge and slight salivation during Week 2 (one dog). Additional toxic signs noted in Group No. 5 animals prior to total mortality by the latter part of Week 1 included emesis (one dog); inability to stand (one dog); listlessness and inactivity or decreased activity (two dogs); slight response to touch and no response to sound (one dog).

Clinical laboratory studies indicated a decrease in leukocyte count of Group No. 4 (80 mg/kg/day) animals at one and two weeks, a slight increase in the erythrocyte count in one or two animals at 80 mg/kg/day at two weeks, a slight increase in blood urea nitrogen values in treated males and females at one and two weeks, and an increase in blood sugar values in females at two weeks. Most of the values generally remained within the normal limits of variation; however, with some individual treated animals showing marked deviations from normal values. Urine analyses revealed no compound effects.

Gross necropsy findings revealed a compound-related enlargement of the spleen in all Group No. 5 animals. One Group No. 5 male and both Group No. 5 females showed high spleen weights and spleen/body weight ratios at termination.

Terminal ophthalmologic examination showed severe bilateral conjunctivitis with mucopurulent discharge and scleral injection in one Group No. 4 male (Dog No. 14494) and one Group No. 4 female (Dog No. 14458). Dog No. 14458 also exhibited relaxed nictitating membranes. The cornea of these eyes were grossly normal, and eye transparency was not affected. These conditions were symptoms of compound-related systemic disease. No microscopic examination of the preserved tissues was performed.

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MATERIAL

Identification WR-2823 (AU 69115).Description Fine, white powder with no noticeable odor.Receipt Date July 2, 1969.Purity Assumed to be 100% active ingredient.

METHODS

Experimental AnimalsBreed: Young adult purebred beagles.Number: Ten males and 10 females.Body Weight: At initiation, 6.4 to 13.8 kg.Housing: Individually in metal cages.Diet: Ground Wayne Dog Meal and water ad libitum.Animal Groups and Dosage Levels

<u>Group No.</u>	<u>No. of Animals</u>		<u>Dose Levels</u>
	<u>male</u>	<u>female</u>	
1	2	2	control
2	2	2	20 mg/kg
3	2	2	40 mg/kg
4	2	2	80 mg/kg
5	2	2	160 mg/kg

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Compound Preparation and Administration

The test material was administered by intravenous injection as a 22.4% weight-per-volume solution in saline to Groups No. 2 and No. 3 and as a 44.8% weight-per-volume solution in saline to Groups No. 4 and No. 5. Group No. 1, control, received intravenous injections of physiological saline at the rate of 0.4 ml/kg of body weight. Doses were administered once daily for a total of 14 days.

Observations and Records

Mortality and Pharmacotoxic Effects: Daily.

Body Weight: Initially, Day 5, Day 7, Day 8, Day 12, and terminally.

Ophthalmologic Examination: Initially and terminally.

Clinical Laboratory Studies

Performed: Initially, at seven days, and terminally (14 days).

Hematological Studies: Hematocrit and hemoglobin determinations, erythrocyte count, total and differential leukocyte count, prothrombin time, and clotting time.

Blood Chemistry Studies: Determinations of blood urea nitrogen, fasting blood sugar, serum glutamic-pyruvic transaminase, and alkaline phosphatase.

Urine Analyses: Volume, pH, specific gravity, protein, glucose, bilirubin, occult blood, and microscopic examination of sediment.

Ophthalmologic Examination Performed initially and terminally.

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Terminal Studies

Terminal Sacrifice: By exsanguination under anesthesia (Surital) after 14 days of intravenous administration of the compound.

Gross Necropsies: Performed on all animals which died during the study or were sacrificed at termination.

Organ Weights: Weights for thyroid, heart, liver, spleen, kidneys, adrenals, and testes or ovaries were recorded for all animals at necropsy.

Tissues Preserved: Brain, pituitary, thoracic spinal cord, thyroid, lung, heart, liver, gallbladder, spleen, kidney, adrenal, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testes, ovaries, prostate, uterus, rib junction, bone marrow, and nerve with muscle were preserved in 10% neutral buffered formalin. Eyes were preserved in alcoholic formalin.

RESULTS**Appearance, Behavior, Body Weight Changes, and Signs of Compound Effect**

Individual body weights and compound administration are presented in Table No. 1.

Group No. 1 (Control - 0.4 ml. Saline Per Kilogram of Body Weight): All animals in this group were normal in appearance and behavior throughout the study. Body weight losses of 1.5 kg. (12%), 1.3 kg. (10%), 1.2 kg. (10%), and 0.6 kg. (8%) were noted.

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Group No. 2 (20 mg. WR-2823 Per Kilogram of Body Weight): Slow pupillary reflex or relaxed nictitating membrane were noted following the fourth or fifth injection and within 10 to 30 minutes following each injection thereafter. Body weight losses of 1.3 kg. (13%), 1.2 kg. (11%), 1.4 kg. (16%), and 1.3 kg. (15%) were noted.

Group No. 3 (40 mg. WR-2823 Per Kilogram of Body Weight): Slow pupillary response to light or no pupillary response to light (one dog) and/or relaxed nictitating membranes were noted following the third injection of compound and within 10 to 30 minutes following each subsequent injection. Body weight losses of 1.0 kg. (10%), 2.5 kg. (19%), 1.4 kg. (15%), and 1.6 kg. (25%) were noted.

Group No. 4 (80 mg. WR-2823 Per Kilogram of Body Weight): Emesis of white mucoid material in two dogs and droopy eyes in two dogs were noted after the first injection. One animal also appeared to be very thirsty. Slow pupillary response to light and/or relaxed nictitating membranes were noted in all animals following the second injection and generally within five to 30 minutes following each subsequent injection. Decreased activity was noted in all animals during the second week of the study, and all animals exhibited sporadic episodes of emesis throughout the study. One animal showed mucoid discharge from both eyes during the early part of Week 2, and slight nasal discharge and slight salivation were noted in one animal during the early part of Week 2. Weight losses of 4.2 kg. (35%), 2.3 kg. (16%), 2.4 kg. (29%), and 2.2 kg. (21%) were noted.

Group No. 5 (160 mg. WR-2823 Per Kilogram of Body Weight): All animals exhibited emesis following the initial injection. One dog exhibited relaxed nictitating membranes and/or no pupillary response to light following the second and third injections. Following the fourth injection, this animal stood with head hanging and exhibited emesis twice with death occurring on the day after this injection. One dog exhibited relaxed nictitating membranes and no pupillary response to light following the second and third injections with death occurring within 45 minutes after the third injection. Another dog showed no pupillary response to light, inability to stand, listlessness and inactivity, slight response to touch, and no response to light following the second injection with death occurring one hour after the third injection. The fourth animal exhibited no pupillary response to light following the second injection. Decreased activity, relaxed nictitating membranes, and no pupillary response to light were noted 10 minutes following the third injection with death 30 minutes postdose. Dogs showed terminal weight losses of 0.9 kg. (8%), 1.1 kg. (12%), and 1.2 kg. (12%). One terminal weight was inadvertently omitted.

Clinical Laboratory Studies

Results of clinical laboratory studies are presented in Tables No. 2 (hematology), No. 3 (blood chemistry), and No. 4 (urine analyses).

All hematological values were generally within normal limits of variation. However, the leukocyte counts among the Group No. 4 animals tended to be somewhat lower at one and two weeks when compared both with control animals and with pretreatment values for those animals. In addition, slightly elevated erythrocyte counts were recorded for one male and one female dog in Group No. 4 at one week and in one Group No. 4 male at two weeks.

A review of blood chemistry data revealed two dose-related changes. Blood urea nitrogen values showed a slight dose-related increase in treated males and females at one and two weeks when compared with values for control animals. However, values generally remained within the normal limits of variation with the exception of one Group No. 4 male (Dog No. 14494) at one and two weeks and one Group No. 4 female (Dog No. 14458) at two weeks, both of which had higher than normal values. A dose-related increase in blood sugar values was noted in females at two weeks with one Group No. 3 female (Dog No. 14435) and two Group No. 4 females (Dogs No. 14458 and No. 14468) exhibiting values higher than the normal limits of variation. Group No. 4 males also exhibited high blood sugar values at two weeks.

Results of urine analyses showed no compound-related effects.

Ophthalmologic Examination

Initial and terminal eye examinations were performed using Mydriacyl as a mydriatic, a binocular indirect ophthalmoscope, and for some animals a direct ophthalmoscope. The following ocular changes were observed at the initial examination: slightly injected sclera in the left eye of Dog No. 14125 (Group No. 1 male); entropion of the left eye of Dog No. 14333 (Group No. 1 male); bilateral,

slight, veil-shaped cloudiness in vitreous of Dog No. 14355 (Group No. 2 female); and epiphora of the left eye of Dog No. 14417 (Group No. 3 female). The conditions present in Dogs No. 14333 and No. 14355 at initiation were still present at termination, and Dog No. 14468 (Group No. 4 female) had moderately injected sclera at termination. In addition, compound-related symptoms of systemic illness in the form of severe bilateral conjunctivitis with mucopurulent discharge and scleral injection were noted in female Dog No. 14458 and male Dog No. 14494, both of Group No. 4. Female Dog No. 14458 also showed relaxed nictitating membranes. The cornea of these eyes were grossly normal, and eye transparency was not affected.

Gross Pathology

At Death:

Group No. 5 - Liver pale in appearance in one female (Dog No. 14470); spleen enlarged in all animals; liver and thyroid enlarged in one male (Dog No. 14504).

At Sacrifice: Right thyroid 2 mm. by 3 mm. in size with cyst-like

formation on anterior end in one Group No. 4 male (Dog No. 14494); small cyst at base of pituitary in one Group No. 2 female (Dog No. 14355); gallbladder not observable in one Group No. 2 female (Dog No. 14457); gallbladder distended in one Group No. 3 male (Dog No. 14389), one Group No. 3 female (Dog No. 14435), one Group No. 4 male (Dog No. 14502), and one Group No. 4 female (Dog No. 14458); one hookworm in small intestine of one Group No. 2 male (Dog No. 14251);

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capsular surface of kidneys covered with gray, pitted areas in one Group No. 4 male (Dog No. 14494); capsular surface of kidneys rough with gray discoloration and medulla reddened in one Group No. 4 female (Dog No. 14458); capsular surface of kidneys white and pitted with medulla and hilus reddened in one Group No. 4 male (Dog No. 14502); capsular surface of kidney roughened and medulla reddened in one Group No. 3 male (Dog No. 14389); odd brown tinge to testes in one Group No. 4 male (Dog No. 14502); walls of urinary bladder thickened and/or mucosa reddened or hemorrhagic in appearance in one Group No. 1 female (Dog No. 14333), in one Group No. 2 male (Dog No. 14251), in two Group No. 2 females (Dogs No. 14355 and No. 14457), in one Group No. 3 male (Dog No. 14389), and in two Group No. 2 males (Dogs No. 14494 and No. 14502).

Organ Weights Individual terminal body weights, organ weights, and organ/body weight ratios are presented in Table No. 5.

One Group No. 5 male (Dog No. 14515) and both Group No. 5 females (Dogs No. 14470 and 14471) exhibited high spleen and spleen/body weight ratios. High kidney weights and kidney/body weight ratios were noted in one Group No. 5 male (Dog No. 14515) and one Group No. 5 female (Dog No. 14471). Low liver weights and liver/body weight ratios were noted in one Group No. 2 female (Dog No. 14355), in one Group No. 3 female (Dog No. 14435), and in two Group No. 4 females (Dogs No. 14458 and No. 14468). High liver weights and liver/body weight ratios were observed in one Group No. 1 female (Dog No. 14348) and in two Group No. 5 females (Dogs No. 14470 and No. 14471).

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Histopathological Evaluation No microscopic examination of tissues was performed; however, all preserved tissues are being stored at Hazleton Laboratories, Inc., for possible future reference.

Submitted by

for

J. E. Powers
MARCELINA B. POWERS, D.V.M., M.S.
Project Manager, Drugs and
Industrial Chemicals
Toxicology-Biosciences Laboratory

Report Preparation: Lambert
Supervision: Pate

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EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

T = trace ($\pm$)

0 = negative

1 = slight (+)

2 = moderate (++)

3 = marked (+++)

4 = severe (++++)

TNTC = too numerous to count

Table No. 1 - Individual body weights and compound administered for male and female purebred beagles.

TIME INTERVAL days	GROUP NO. 1 - CONTROL (0.4 ML. SALINE PER KG. BODY WEIGHT)							
	DOG NO. 14121	DOG NO. 14125	DOG NO. 14333	DOG NO. 14348	WT.	WT.	WT.	COMPOUND
	WT. kg.	WT. kg.	WT. kg.	WT. kg.	ml.	ml.	ml.	ml.
Initial	11.9	13.0	11.2	7.0				
1		4.8	5.2	4.5	2.8			
2		4.8	5.2	4.5	2.8			
3		4.8	5.2	4.5	2.8			
4		4.8	5.2	4.5	2.7			
5	11.3	4.5	5.0	4.2	6.7			
6		4.5	5.0	4.2	2.7			
7	11.3	4.5	4.9	4.1	7.1			
8	10.8	4.3	4.7	4.0	6.5			
9		4.3	4.7	4.0	2.6			
10		4.3	4.7	4.0	2.6			
11		4.3	4.7	4.0	2.6			
12	11.0	4.4	4.9	4.2	6.6			
13		4.4	4.2	4.2	2.6			
14	10.5	4.2	4.7	3.9	2.6			
Terminal	10.4	11.7	9.6	6.4				
Wt. Change, kg.	-1.5	-1.3	-1.2	-0.6				

Table No. 1 - Continued

TIME INTERVAL days	GROUP NO. 2 - 20 MG. WR-2823 PER KG. OF BODY WEIGHT					
	DOG NO. 14251		DOG NO. 14253		DOG NO. 14355	
	WT. kg.	COMPOUND mg.	WT. kg.	COMPOUND mg.	WT. kg.	COMPOUND mg.
Initial	9.7		10.5		8.4	
1		0.97		1.1		0.84
2		0.97		1.1		0.84
3		0.97		1.1		0.84
4		0.97		1.1		0.84
5	10.0	1.0	10.4	1.0	7.7	0.77
6		1.0		1.0		0.77
7	9.6	0.96	9.7	0.97	8.0	0.80
8	9.1	0.91	9.3	0.93	7.3	0.73
9		0.91		0.93		0.73
10		0.91		0.93		0.73
11		0.91		0.93		0.73
12	9.0	0.90	9.5	0.95	7.7	0.77
13		0.90		0.95		0.77
14	8.1	0.81	9.2	0.92	7.1	0.71
Terminal	8.4		9.3		7.0	
Wt. Change, kg.	-1.3		-1.2		-1.4	
						-1.3

Table No. 1 - Continued

TIME INTERVAL days	GROUP NO. 3 - 40 MG. WR-2823 PER KG. OF BODY WEIGHT							
	DOG NO. 14366	DOG NO. 14389	DOG NO. 14417	DOG NO. 14435	WT.	WT.	WT.	WT.
	WT. kg.	WT. kg.	WT. kg.	WT. kg.	COMPOUND mg.	COMPOUND mg.	COMPOUND mg.	COMPOUND mg.
Initial	9.4	12.7	9.0	6.4				
1	1.9	2.5	1.8	1.3				
2	1.9	2.5	1.8	1.3				
3	1.9	2.5	1.8	1.3				
4	1.9	2.5	1.8	1.3				
5	1.9	2.4	1.7	1.1				
6	1.9	2.4	1.7	1.1				
7	1.8	2.3	1.7	1.1				
8	8.5	10.8	8.0	5.4				
9	1.7	2.2	1.6	1.1				
10	1.7	2.2	1.6	1.1				
11	1.7	2.2	1.6	1.1				
12	1.8	2.1	1.6	1.1				
13	1.8	2.1	1.6	1.6*				
14	8.3	10.2	7.5	5.0				
Terminal	8.4	10.2	7.6	4.8				
Wt. Change, kg.	-1.0	-2.5	-1.4	-1.6				

* Technical error in weighing; animal received incorrect dose.

Table No. 1 - Continued

TIME INTERVAL days	GROUP NO. 4 - 80 MG. WR-2823 PER KG. OF BODY WEIGHT							
	DOG NO. 14494		DOG NO. 14502		DOG NO. 14458		DOG NO. 14468	
	WT. kg.	COMPOUND mg.	WT. kg.	COMPOUND mg.	WT. kg.	COMPOUND mg.	WT. kg.	COMPOUND mg.
Initial	11.8		13.8		8.1		10.2	
1		2.4		2.8				2.0
2		2.4		2.8				2.0
3		2.4		2.8				2.0
4		2.4		2.8				2.0
5	9.7	1.9	12.6	2.5	7.4		9.3	1.9
6		1.9		2.5				1.9
7	9.2	1.8	12.7	2.5	6.7		8.8	1.8
8	8.9	1.8	11.8	2.4	6.4		8.4	1.7
9		1.8		2.4				1.7
10		1.8		2.4				1.7
11		1.8		2.4				1.7
12	8.2	1.6	12.5	2.5	6.2		8.6	1.7
13		1.6		1.5				1.7
14	7.7	1.5	11.2	2.2	5.6		7.7	1.5
Terminal	7.6		11.5		5.7		8.0	
Wt. Change, kg.	-4.2		-2.3		-2.4		-2.2	

///

Table No. 1 - Continued

TIME INTERVAL days	GROUP NO. 5 - 160 MG. MR-2823 PER KG. OF BODY WEIGHT							
	DOG NO. 14504		DOG NO. 14515		DOG NO. 14470		DOG NO. 14471	
	WT. kg.	COMPOUND mg.	WT. kg.	COMPOUND mg.	WT. kg.	COMPOUND mg.	WT. kg.	COMPOUND mg.
Initial	12.1		10.5		9.1		9.7	
1		4.8		4.2		3.6		3.9
2		4.8		4.2		3.6		3.9
3		4.8		4.2		3.6		3.9
4		4.8	9.6	*	8.0	*	8.5	*
5	**	*						
Wt. Change, kg.			-0.9		-1.1		-1.2	

* Animal died.

** No terminal weight taken.

GROUP NUMBER	ANIMAL NUMBER	SEX	S	HCT %	HGB G%	RBC MILLS	WBC THS	DIFFERENTIAL						BASO %
								MET %	HAND %	SEG %	LYMPH %	MONO %	EOSIN %	
1	14121	M		51.0	17.7	6.72	12.7	0	0	64	28	1	7	0
1	14125	M		49.0	17.0	6.47	9.6	0	0	65	25	3	7	0
GROUP	MEAN			50.0	17.4	6.60	11.2							
2	14251	M		49.0	16.4	6.39	13.9	0	0	45	44	0	11	0
2	14253	M		47.0	16.4	6.67	9.2	0	1	59	35	1	4	0
GROUP	MEAN			48.0	16.4	6.53	11.6							
3	14366	M		48.0	16.6	6.35	12.5	0	0	60	33	2	5	0
3	14389	M		52.0	17.5	6.94	16.5	0	0	56	37	3	4	0
GROUP	MEAN			50.0	17.1	6.65	14.5							
4	14494	M		47.0	15.0	7.95	10.6	0	0	50	44	4	2	0
4	14502	M		49.0	16.2	6.64	19.7	0	0	67	27	4	2	0
GROUP	MEAN			48.0	15.6	7.30	15.2							
5	14507	M		54.0	18.0	7.62	13.8	0	0	56	38	4	2	0
5	14515	M		53.0	17.7	6.89	11.1	0	1	60	31	1	7	0
GROUP	MEAN			53.5	17.9	7.26	12.5							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED REAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	HCT %	HGB GZ	RBC MILLS	WBC THS	META %	DIFFERENTIAL					EOSIN %	BASO %
								BAND %	SEG %	LYMPH %	MONO %			
1	14121	M	47.0	16.0	6.07	12.7	0	0	58	27	2	13	0	
	14125	M	49.0	16.8	5.87	9.9	0	0	62	28	2	8	0	
GROUP MEAN			48.0	16.4	5.97	11.3								
2	14251	M	47.0	16.2	6.03	13.2	0	0	56	33	3	8	0	
	14253	M	49.0	17.0	6.02	11.1	0	0	46	53	1	0	0	
GROUP MEAN			48.0	16.6	6.03	12.2								
3	14366	M	48.0	16.6	5.97	10.5	0	0	45	54	0	1	0	
	14389	M	54.0	18.5	5.82	10.5	0	0	57	40	2	1	0	
GROUP MEAN			51.0	17.6	5.90	10.5								
4	14494	M	51.0	16.2	6.55	9.2	0	3	60	35	1	1	0	
	14502	M	48.0	16.4	7.84	8.2	0	0	54	40	0	6	0	
GROUP MEAN			49.5	16.3	7.20	8.7								

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 2

GROUP NUMER	ANIMAL NUMRFR	S E X	DIFFERENTIAL										
			HCT %	HGB GZ	RBC MILLS	WBC THS	MET %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	BASEO %
1	14121	M	46.0	16.2	6.07	12.5	0	0	53	44	0	3	0
1	14125	M	44.0	15.3	5.69	11.5	0	0	64	32	0	4	0
GROUP	MEAN		45.0	15.8	5.88	12.0							
2	14251	M	44.0	14.8	6.02	10.7	0	1	64	28	0	7	0
2	14253	M	42.0	14.8	5.95	8.6	0	0	32	62	2	4	0
GROUP	MEAN		43.0	14.8	5.99	9.7							
3	14366	M	42.0	14.6	5.48	11.5	0	0	58	35	3	4	0
3	14389	M	51.0	17.0	6.65	8.9	0	0	56	42	2	0	0
GROUP	MEAN		46.5	15.8	6.07	10.2							
4	14494	M	51.0	16.8	8.52	8.8	0	3	53	39	5	0	0
4	14502	M	47.0	16.6	6.66	7.2	0	0	53	38	3	6	0
GROUP	MEAN		49.0	16.7	7.59	8.0							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	SEX	S	PROTHROMBIN SECONDS	COAGULATION	
					MIN	SEC
1	14121	M		7.4	3	50
1	14125	M		8.6	4	51
GROUP MEAN				8.0	4	21
2	14251	M		7.9	3	32
2	14253	M		7.5	4	02
GROUP MEAN				7.7	3	47
3	14366	M		7.8	1	37
3	14389	M		7.6	4	16
GROUP MEAN				7.7	2	57
4	14494	M		8.2	2	09
4	14502	M		7.4	2	40
GROUP MEAN				7.8	2	25
5	14507	M		7.4		ND
5	14515	M		7.5	2	42
GROUP MEAN				7.5	2	42

ND - NO DETERMINATION

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS
1	14121	M	7.8
1	14125	M	7.5
GROUP MEAN			7.7
2	14251	M	7.6
2	14253	M	7.5
GROUP MEAN			7.6
3	14366	M	7.4
3	14389	M	7.2
GROUP MEAN			7.3
4	14494	M	7.3
4	14502	M	7.3
GROUP MEAN			7.3

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS	COAGULATION MIN	SEC
1	14121	M	6.6	4	36
1	14125	M	7.1	6	45
GROUP MEAN			6.9	5	41
2	14251	M	6.5	5	53
2	14253	M	6.7	5	18
GROUP MEAN			6.6	5	36
3	14366	M	7.1	8	20
3	14389	M	6.6	7	45
GROUP MEAN			6.9	8	03
4	14494	M	6.4	4	30
4	14502	M	6.5	6	43
GROUP MEAN			6.5	5	37

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED REAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS

GROUP NUMBER	ANIMAL NUMBER	SEX	INITIAL										DIFFERENTIAL					BASO	
			HCT %	HGB G%	RBC MILLS	WBC THS	MET %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	BASO %						
1	14333	F	52.0	18.0	6.96	11.9	0	0	53	41	3	3	0	0					
1	14348	F	54.0	18.2	7.72	15.6	0	0	39	61	0	0	0	0					
GROUP	MEAN		53.0	18.1	7.34	13.8													
2	14355	F	45.0	15.8	6.25	12.1	0	0	57	43	0	0	0	0					
2	14457	F	50.0	16.4	6.22	13.8	0	1	53	39	2	5	0	0					
GROUP	MEAN		47.5	16.1	6.24	13.0													
3	14417	F	56.0	19.6	7.76	11.4	0	0	51	46	0	3	0	0					
3	14435	F	49.0	17.0	6.41	9.2	0	0	63	31	0	6	0	0					
GROUP	MEAN		52.5	18.3	7.09	10.3													
4	14458	F	47.0	15.0	6.38	12.5	0	3	50	41	3	3	0	0					
4	14468	F	51.0	16.4	6.39	10.8	0	1	64	32	2	1	0	0					
GROUP	MEAN		49.0	15.7	6.39	11.7													
5	14470	F	51.0	16.8	6.72	12.2	0	1	40	53	2	4	0	0					
5	14471	F	50.0	16.8	6.78	12.5	0	0	63	36	0	1	0	0					
GROUP	MEAN		50.5	16.8	6.75	12.4													

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PURERRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	SEX	HCT %	HGB G%	RBC MILLS	WBC THS	DIFFERENTIAL						
							META %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	BASEO %
1	14333	F	54.0	18.5	6.35	12.3	0	0	49	42	2	7	0
1	14348	F	50.0	16.8	6.59	14.9	0	0	42	53	1	4	0
GROUP	MEAN		52.0	17.7	6.47	13.6							
2	14355	F	48.0	16.4	6.44	12.7	0	1	56	42	1	0	0
2	14457	F	48.0	16.2	6.12	13.0	0	0	41	51	3	5	0
GROUP	MEAN		48.0	16.3	6.28	12.9							
3	14417	F	55.0	19.2	6.44	11.1	0	2	65	29	2	2	0
3	14435	F	54.0	18.9	6.71	8.8	0	0	64	31	2	3	0
GROUP	MEAN		54.5	19.1	6.58	10.0							
4	14458	F	51.0	17.2	9.06	7.7	0	5	63	30	2	0	0
4	14468	F	58.0	20.0	6.87	10.7	0	1	63	32	3	1	0
GROUP	MEAN		54.5	18.6	7.97	9.2							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PURERRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	SEX	HCT %	HGB GZ	RBC MILLS	WBC THS	DIFFERENTIAL						
							MET	BAND	SEG	LYMPH	MONO	EOSIN	BASO
							%	%	%	%	%	%	%
1	14333	F	52.0	18.2	6.71	11.7	0	0	59	36	1	4	0
1	14348	F	46.0	16.4	6.55	11.6	0	0	41	53	0	6	0
GROUP	MEAN		49.0	17.3	6.63	11.7							
2	14355	F	41.0	14.2	5.54	10.3	0	1	56	39	2	2	0
2	14457	F	44.0	14.6	5.53	9.7	0	0	48	48	1	3	0
GROUP	MEAN		42.5	14.4	5.54	10.0							
3	14417	F	53.0	17.5	7.27	12.4	0	1	73	24	0	2	0
3	14435	F	50.0	17.7	6.54	9.1	0	0	65	29	2	4	0
GROUP	MEAN		51.5	17.6	6.91	10.8							
4	14458	F	50.0	17.2	6.71	10.7	0	0	67	30	1	2	0
4	14468	F	53.0	18.2	7.00	9.7	0	0	69	30	0	1	0
GROUP	MEAN		51.5	17.7	6.86	10.2							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	S F	PROTHROMBIN SECONDS	COAGULATION MIN	SEC
1	14333	F	8.0	1	44
1	14348	F	7.8	3	52
GROUP MEAN			7.9	2	48
2	14355	F	7.8	2	04
2	14457	F	7.6	2	16
GROUP MEAN			7.7	2	10
3	14417	F	7.6	3	34
3	14435	F	7.8	2	27
GROUP MEAN			7.7	3	01
4	14458	F	7.5	4	25
4	14468	F	7.7	3	15
GROUP MEAN			7.6	3	50
5	14470	F	7.4	3	58
5	14471	F	7.6	3	20
GROUP MEAN			7.5	3	39

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED REAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS
1	14333	F	7.7
1	14348	F	7.5
GROUP MEAN			7.6
2	14355	F	7.3
2	14457	F	7.2
GROUP MEAN			7.3
3	14417	F	7.3
3	14435	F	7.3
GROUP MEAN			7.3
4	14458	F	6.9
4	14468	F	7.1
GROUP MEAN			7.0

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	PROTHROMBIN SECONDS	COAGULATION MIN	SEC
1	14333	F	7.3	6	07
1	14348	F	6.8	4	30
GROUP	MEAN		7.1	5	19
2	14355	F	7.1	6	25
2	14457	F	6.5	7	04
GROUP	MEAN		6.8	6	45
3	14417	F	7.0	7	14
3	14435	F	6.9	4	46
GROUP	MEAN		7.0	6	00
4	14458	F	6.0	5	12
4	14468	F	6.7	7	00
GROUP	MEAN		6.4	6	06

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PURENRED REAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK.PHOS K-A. UNITS
1	14121	M	100.0	14.0	37.5	7.0
1	14125	M	104.0	11.0	28.0	8.0
GROUP	MEAN		102.0	12.5	32.8	7.5
2	14251	M	95.0	10.0	28.0	8.1
2	14253	M	101.0	10.0	23.0	11.0
GROUP	MEAN		98.0	10.0	25.5	9.6
3	14366	M	103.0	10.0	28.0	8.0
3	14389	M	90.0	10.0	29.0	9.8
GROUP	MEAN		96.5	10.0	28.5	8.9
4	14494	M	106.0	11.0	23.0	11.9
4	14502	M	110.0	11.5	23.0	10.4
GROUP	MEAN		108.0	11.3	23.0	11.2
5	14507	M	104.0	9.0	25.0	10.0
5	14515	M	108.0	13.0	26.0	11.5
GROUP	MEAN		106.0	11.0	25.5	10.8

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK.PHOS K-A. UNITS
1	14121	M	101.0	13.0	39.0	9.4
1	14125	M	103.0	8.5	32.5	7.8
GROUP	MEAN		102.0	10.8	35.8	8.6
2	14251	M	98.0	12.0	31.0	7.9
2	14253	M	98.0	11.5	28.0	9.0
GROUP	MEAN		98.0	11.8	29.5	8.5
3	14366	M	130.0	13.0	39.0	8.2
3	14387	M	121.0	21.0	37.5	9.7
GROUP	MEAN		125.5	17.0	38.3	9.0
4	14494	M	122.0	57.0	26.0	13.6
4	14502	M	115.0	19.5	25.0	12.3
GROUP	MEAN		118.5	38.3	25.5	13.0

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED REAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	HUN MG%	SGPT R-F.	ALK.PHOS K-A. UNITS
1	14121	M	108.0	12.5	39.0	5.2
1	14125	M	120.0	11.0	34.0	6.8
GROUP	MEAN		114.0	11.8	36.5	6.0
2	14251	M	100.0	14.0	46.0	6.0
2	14253	M	118.0	18.0	37.5	8.2
GROUP	MEAN		109.0	16.0	41.8	7.1
3	14366	M	109.0	14.0	31.0	5.5
3	14389	M	95.0	18.0	34.0	6.9
GROUP	MEAN		102.0	16.0	32.5	6.2
4	14494	M	155.0	108.0	28.0	11.4
4	14502	M	142.0	17.0	37.5	9.3
GROUP	MEAN		148.5	62.5	32.8	10.4

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	RUN MG%	SGPT R-F.	ALK.PHOS K-A. UNITS
1	14333	F	106.0	12.0	23.0	10.1
1	14348	F	99.0	14.0	34.0	14.4
GROUP MEAN			102.5	13.0	28.5	12.3
2	14355	F	110.0	17.5	26.0	13.3
2	14457	F	112.0	12.0	37.5	9.1
GROUP MEAN			111.0	14.8	31.8	11.2
3	14417	F	98.0	10.0	31.0	9.4
3	14435	F	105.0	10.0	22.0	9.0
GROUP MEAN			101.5	10.0	26.5	9.2
4	14458	F	107.0	9.0	28.0	14.2
4	14468	F	100.0	10.0	23.0	9.9
GROUP MEAN			103.5	9.5	25.5	12.1
5	14470	F	102.0	9.0	25.0	10.2
5	14471	F	98.0	10.0	25.0	7.8
GROUP MEAN			100.0	9.5	25.0	9.0

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK.PHOS K-A. UNITS
1	14333	F	116.0	8.0	26.0	9.3
1	14348	F	113.0	14.0	37.5	12.4
GROUP MEAN			114.5	11.0	31.8	10.9
2	14355	F	111.0	21.0	25.0	10.0
2	14457	F	115.0	14.0	37.5	9.0
GROUP MEAN			113.0	17.5	31.3	9.5
3	14417	F	94.0	15.0	26.0	7.9
3	14435	F	105.0	21.0	34.0	8.0
GROUP MEAN			99.5	18.0	30.0	8.0
4	14458	F	98.0	29.5	28.0	17.3
4	14468	F	125.0	20.0	36.0	11.2
GROUP MEAN			111.5	24.8	32.0	14.3

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED REAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	SEX	GLUCOSE		HGB MG%	SGPT R-F.	ALK.PHOS K-A. UNITS
			MG%	MG%			
1	14333	F	112.0	11.0	32.5	7.5	
1	14348	F	115.0	14.0	32.5	130.0	
GROUP MEAN			113.5	12.5	32.5	68.8	
2	14355	F	120.0	20.0	31.0	7.9	
2	14457	F	115.0	13.0	37.5	8.2	
GROUP MEAN			117.5	16.5	34.3	8.1	
3	14417	F	115.0	21.0	32.5	7.5	
3	14435	F	130.0	18.0	32.5	5.9	
GROUP MEAN			122.5	19.5	32.5	6.7	
4	14458	F	126.0	30.3	31.0	10.0	
4	14468	F	139.0	21.0	37.5	8.2	
GROUP MEAN			132.5	25.7	34.3	9.1	

TABLE NO. 4 - URINE ANALYSIS
 PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	F X	P H	SP.GR.	SU- GAR	ACE- TUNE	PRO- TEIN	BILI- RUBIN	OCC	-----MICROSCOPIC FINDINGS----- RBC WBC EPITH AMORPH CRYST BACT SPERM
1	14121	M	7	1.050	0	0	1	0	0	135 8-10 1-3 MUCH MANY MANY MANY
1	14125	M	7	1.052	0	0	1	0	0	75 1-3 16-18 6-8 MUCH MANY MANY MANY
2	14251	M	5	1.06+	0	0	1	T	0	65 2-4 6-8 MUCH MANY MANY FEW
2	14253	M	8	1.045	0	0	1	0	0	135 8-10 3-5 MUCH MANY MANY MANY
3	14366	M	7	1.045	0	0	1	0	0	75 12-14 4-6 MUCH MANY MANY
3	14389	M	6	1.060	0	0	1	0	0	85 1-3 3-5 8-10 MUCH MANY MANY
4	14494	M	8	1.050	0	0	1	0	0	155 6-8 2-4 MUCH MANY MANY
4	14502	M	6	1.052	0	0	1	0	0	135 6-8 4-6 MUCH MANY MANY
5	14507	M	6	1.046	0	0	1	T	0	55 4-6 6-8 3-5 MUCH MANY MANY
5	14515	M	7	1.042	0	0	1	0	0	95 1-3 2-4 4-6 MUCH MANY MANY

TABLE NO. 4 - URINE ANALYSIS
 PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S F	P H	SU- GAR	PRO- TEIN	BILI- RUBIN	OCC HLD	VOL.	RBC	-----MICROSCOPIC FINDINGS-----			
										WBC	EPITH	AMORPH	CRYSTALS
1	14121	M	5	1.044	0	1	0	127		8-10	2-4	MUCH	MANY
1	14125	M	6	1.058	0	1	0	59		20-30	5-7	MUCH	MANY
2	14251	M	5	1.037	0	1	0	119	1-2	8-10	1-3	MUCH	MANY
2	14253	M	5	1.030	0	1	0	75		4-6	6-8	MUCH	MANY
3	14366	M	6	1.024	0	1	0	175	8-10	TNTC	4-6	MUCH	MANY
3	14389	M	5	1.025	0	1	0	163		10-12	4-6	MUCH	MANY
4	14494	M	5	1.038	0	1	0	121	8-10	TNTC	8-10	MUCH	FEW
4	14502	M	6	1.012	0	1	0	397		TNTC	8-10	MUCH	MANY

TABLE NO. 4 - URINE ANALYSIS
 PURERRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S F	P H	SP.GR.	SU- GAR	PRO- TEIN	RILI- RUBIN	OCC	VOL.	-----MICROSCOPIC FINDINGS-----				
										RBC	WBC	EPITH	AMORPH	CRYSTALS
1	14121	M	8	1.042	0	T	T	0	130		6-8	2-4	MUCH	MANY MANY FEW
1	14125	M	7	1.050	0	1	T	0	55		18-20	3-5	MUCH	MANY MANY MANY
2	14251	M	7	1.024	0	1	0	0	115	3-5	1-3		MUCH	MANY MANY MANY
2	14253	M	7	1.050	0	1	0	0	195		8-10	2-4	MUCH	MANY MANY MANY
3	14336	M	5	1.032	0	T	0	0	150	1-2	2-4	1-3	MUCH	FEW MANY MANY
3	14389	M	6	1.022	0	T	0	1	110	TNTC		6-8	MUCH	MANY MANY MANY
4	14494	M	8	1.047	0	1	0	0	75	10-12	20-25		MUCH	MANY MANY FEW
4	14502	M	7	1.018	0	1	0	1	225	TNTC		10-15	MUCH	MANY MANY MANY

TABLE NO. 4 - URINE ANALYSIS
 PUREPRED REAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	P H	SP.GR.	SU- GAR	ACE- TUNE	PRO- TEIN	BILI- RUHIN	OCC	VLDL	-----MICROSCOPIC FINDINGS-----			
											RBC	WBC	EPITH	AMORPH CRYSTALS BACT SPERM
1	14333	F	5	1.06+	0	0	1	0	0	115		2-4	4-6	LITTLE MANY MANY
1	14348	F	5	1.06+	0	0	1	0	0	50		10-12	4-6	MUCH MANY MANY
2	14355	F	7	1.000	0	0	1	0	0	65		2-4	2-4	MUCH MANY MANY
2	14457	F	5	1.044	0	0	1	0	0	75		TNTC		MUCH MANY MANY
3	14417	F	7	1.000	0	0	1	0	0	135		12-14	1-3	LITTLE FEW MANY
3	14435	F	9	1.052	0	0	1	0	0	86		2-4	6-8	MUCH MANY MANY
4	14458	F	5	1.050	0	0	1	0	0	75		10-12		MUCH FEW MANY
4	14468	F	5	1.055	0	0	1	0	0	75		12-14	8-10	LITTLE MANY MANY
5	14470	F	7	1.040	0	0	1	0	0	105		2-4	4-6	MUCH MANY MANY
5	14471	F	7	1.042	0	0	1	0	0	115		12-15	2-4	MUCH MANY MANY

TABLE NO. 4 - URINE ANALYSIS
 PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	S ANIMAL NUMBER	P H	SP. GR.	SU- GAR	PRO- TEIN	BILI- RUBIN	OCC.	VOL.	MICROSCOPIC FINDINGS				
									RBC	WBC	EPITH	AMORPH	CRYSTALS
1	14333	F	6	1.038	0	1	0	73		6-8	2-4	MUCH	MANY
1	14348	F	5	1.043	0	1	0	88		TNTC	6-8	MUCH	MANY
2	14355	F	6	1.024	0	1	0	137	2-4	8-10	1-3	MUCH	MANY
2	14457	F	5	1.058	0	1	0	59		10-12	2-4	MUCH	FEW
3	14417	F	6	1.022	0	1	0	199		8-10	2-4	MUCH	FEW
3	14435	F	6	1.018	0	1	0	167		2-4	4-6	MUCH	MANY
4	14458	F	5	1.026	0	1	0	193		8-10	1-3	MUCH	MANY
4	14468	F	5	1.025	0	1	0	135		10-12	6-8	MUCH	FEW

TABLE NO. 4 - URINE ANALYSIS
 PUREBRED HEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	P H	P SP.GR.	SU- GAR	PR0- TEIN	RILI- RUIN	OCC BLD	VUL.	-----MICROSCOPIC FINDINGS-----				
										RBC	WBC	EPITH	AMORPH	CRYS RACT SPERM
1	14333	F	7	1.042	0	1	0	0	102		6-8	4-6	MUCH	MANY
1	14348	F	7	1.043	0	T	0	T	125	4-6		3-5	MUCH	MANY
2	14355	F	5	1.023	0	0	0	T	185		2-4		MUCH	MANY
2	14457	F	5	1.033	0	T	0	T	125		3-5	4-6	MUCH	MANY
3	14417	F	7	1.014	0	1	0	T	335		20-23	10-12	MUCH	MANY
3	14435	F	8	1.021	0	T	0	I	175		TNTC	20-25	MUCH	MANY
4	14458	F	5	1.022	0	1	0	T	110		TNTC	10-12	MUCH	MANY
4	14468	F	7	1.021	0	1	0	T	190		8-10	12-14	MUCH	MANY

TABLE NO. 5 - TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, AND ORGAN/BODY WEIGHT RATIOS

SPECIES AND STRAIN - BEAGLE DOGS
MATERIAL - WR-2823

INTERVAL - TERMINAL
ROUTE OF ADMINISTRATION - INTRAVENOUS

MALES - GROUP 1

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
14121	10.40	0.930	0.0089	94.000	0.9038	251.000	2.4134	35.600	0.3423
14125	11.70	1.020	0.0087	97.300	0.8316	308.000	2.6324	42.000	0.3589
MEAN	11.05	0.975	0.0088	95.650	0.8677	279.500	2.5229	38.800	0.3506

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		TESTES	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
14121	10.40	47.200	0.4538	1.090	0.0104	22.900	0.2201
14125	11.70	57.800	0.4940	1.010	0.0086	28.200	0.2410
MEAN	11.05	52.500	0.4739	1.050	0.0095	25.550	0.2306

TABLE NO. 5 - CONTINUED

MALES - GROUP 2

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
14251	8.40	1.430	0.0170	63.500	0.7559	214.000	2.5476	21.700	0.2583
14253	9.30	0.900	0.0096	64.900	0.6978	292.000	3.1397	26.600	0.2860
MEAN	8.85	1.165	0.0133	64.200	0.7269	253.000	2.8437	24.150	0.2721

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		TESTES	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
14251	8.40	48.700	0.5797	0.810	0.0096	15.700	0.1869
14253	9.30	48.700	0.5236	1.030	0.0110	20.300	0.2182
MEAN	8.85	48.700	0.5517	0.920	0.0103	18.000	0.2025

TABLE NO. 5 - CONTINUED

MALES - GROUP 3

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID WEIGHT G	THYROID RATIO PCT	HEART WEIGHT G	HEART RATIO PCT	LIVER WEIGHT G	LIVER RATIO PCT	SPLEEN WEIGHT G	SPLEEN RATIO PCT
14366	8.40	0.600	0.0071	57.400	0.6833	204.000	2.4285	17.300	0.2059
14389	10.20	0.960	0.0094	72.700	0.7127	214.000	2.0980	19.940	0.1954
MEAN	9.30	0.779	0.0082	65.050	0.6980	209.000	2.2633	18.620	0.2007

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS WEIGHT G	KIDNEYS RATIO PCT	ADRENALS WEIGHT G	ADRENALS RATIO PCT	TESTES WEIGHT G	TESTES RATIO PCT
14366	8.40	42.600	0.5071	0.930	0.0110	21.900	0.2607
14389	10.20	51.900	0.5088	1.230	0.0120	19.000	0.1862
MEAN	9.30	47.250	0.5079	1.080	0.0115	20.450	0.2234

TABLE NO. 5 - CONTINUED

MALES - GROUP 4

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID WEIGHT G	THYROID RATIO PCT	HEART WEIGHT G	HEART RATIO PCT	LIVER WEIGHT G	LIVER RATIO PCT	SPLEEN WEIGHT G	SPLEEN RATIO PCT
14494	7.60	0.690	0.0090	57.500	0.7565	227.000	2.9868	21.600	0.2842
14502	11.50	0.870	0.0075	81.200	0.7060	312.000	2.7130	40.600	0.3530
MEAN	9.55	0.779	0.0083	69.350	0.7313	269.500	2.8499	31.100	0.3186

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS WEIGHT G	KIDNEYS RATIO PCT	ADRENALS WEIGHT G	ADRENALS RATIO PCT	TESTES WEIGHT G	TESTES RATIO PCT
14494	7.60	47.000	0.6184	1.120	0.0147	15.700	0.2065
14502	11.50	59.100	0.5139	1.210	0.0105	29.300	0.2547
MEAN	9.55	53.050	0.5661	1.165	0.0126	22.500	0.2306

TABLE NO. 5 - CONTINUED

MALES - GROUP 5

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
* 14515	9.60	0.850	0.0088	71.300	0.7427	398.000	4.1458	97.500	1.0156
ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		TESTES			
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT		
14515	9.60	87.600	0.9125	1.350	0.0140	13.900	0.1447		

* Weight for Dog No. 14504 was omitted due to technical error.

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TABLE NO. 5 - CONTINUED

FEMALES - GROUP 1

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID WEIGHT G	THYROID RATIO PCT	HEART WEIGHT G	HEART RATIO PCT	LIVER WEIGHT G	LIVER RATIO PCT	SPLEEN WEIGHT G	SPLEEN RATIO PCT
14333	9.60	0.580	0.0060	70.900	0.7385	211.000	2.1979	23.000	0.2395
14348	6.40	0.970	0.0151	61.900	0.9671	250.000	3.9062	23.800	0.3718
MEAN	8.00	0.775	0.0105	66.400	0.8528	230.500	3.0520	23.400	0.3057

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS WEIGHT G	KIDNEYS RATIO PCT	ADRENALS WEIGHT G	ADRENALS RATIO PCT	OVARIES WEIGHT G	OVARIES RATIO PCT
14333	9.60	51.100	0.5322	1.050	0.0109	0.900	0.0093
14348	6.40	36.300	0.5671	0.960	0.0150	0.760	0.0118
MEAN	8.00	43.700	0.5497	1.005	0.0129	0.830	0.0106

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TABLE NO. 5 - CONTINUED

FEMALES - GROUP 2

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID WEIGHT G	THYROID RATIO PCT	HEART WEIGHT G	HEART RATIO PCT	LIVER WEIGHT G	LIVER RATIO PCT	SPLEEN WEIGHT G	SPLEEN RATIO PCT
14355	7.00	0.400	0.0057	56.800	0.8114	164.000	2.3428	16.800	0.2400
14457	7.30	0.090	0.0012	57.100	0.7821	195.000	2.6712	23.200	0.3178
MEAN	7.15	0.245	0.0034	56.950	0.7968	179.500	2.5070	20.000	0.2789

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS WEIGHT G	KIDNEYS RATIO PCT	ADRENALS WEIGHT G	ADRENALS RATIO PCT	OVARIES WEIGHT G	OVARIES RATIO PCT
14355	7.00	30.800	0.4400	0.950	0.0135	0.800	0.0114
14457	7.30	35.800	0.4904	0.860	0.0117	0.700	0.0095
MEAN	7.15	33.300	0.4652	0.904	0.0126	0.750	0.0105

TABLE NO. 5 - CONTINUED

FEMALES - GROUP 3

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
14417	7.60	1.150	0.0151	69.000	0.9078	209.000	2.7500	29.700	0.3907
14435	4.80	0.310	0.0064	49.900	1.0395	103.000	2.1458	12.900	0.2687
MEAN	6.20	0.730	0.0107	59.450	0.9737	156.000	2.4479	21.300	0.3297
ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		OVARIES			
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT		
14417	7.60	36.700	0.4828	0.980	0.0128	0.770	0.0101		
14435	4.80	26.200	0.5458	0.770	0.0160	0.500	0.0104		
MEAN	6.20	31.450	0.5143	0.875	0.0144	0.635	0.0102		

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TABLE NO. 5 - CONTINUED

FEMALES - GROUP 4

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
14458	5.70	0.730	0.0128	54.700	0.9596	137.600	2.4140	18.700	0.3280
14468	8.00	0.740	0.0092	63.200	0.7900	1.920	0.0240	25.700	0.3212
MEAN	6.85	0.735	0.0110	58.950	0.8748	69.759	1.2190	22.200	0.3246
ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		OVARIES			
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT		
		14458	5.70	33.900	0.5947	1.000	0.0175	0.450	0.0078
14468	8.00	46.900	0.5862	1.450	0.0181	0.750	0.0093		
MEAN	6.85	40.400	0.5904	1.225	0.0178	0.600	0.0086		

TABLE NO. 5 - CONTINUED

FEMALES - GROUP 5

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID WEIGHT G	THYROID RATIO PCT	HEART WEIGHT G	HEART RATIO PCT	LIVER WEIGHT G	LIVER RATIO PCT	SPLEEN WEIGHT G	SPLEEN RATIO PCT
14470	8.00	0.920	0.0115	53.300	0.6662	328.000	4.1000	95.800	1.1975
14471	8.50	0.730	0.0085	72.100	0.8482	373.000	4.3882	75.000	0.8823
MEAN	8.25	0.825	0.0100	62.700	0.7572	350.500	4.2441	85.400	1.0399

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS WEIGHT G	KIDNEYS RATIO PCT	ADRENALS WEIGHT G	ADRENALS RATIO PCT	OVARIES WEIGHT G	OVARIES RATIO PCT
14470	8.00	58.400	0.7300	1.070	0.0133	0.700	0.0087
14471	8.50	71.400	0.8400	1.290	0.0151	0.830	0.0097
MEAN	8.25	64.900	0.7850	1.180	0.0142	0.764	0.0092

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Sponsor: Walter Reed Army Institute of Research

Date: December 10, 1969

Material: WR 2721

Subject: REPORT NO. 25
Four-Week Oral Toxicity Study - Monkeys
Project No. 193-407

SUMMARY

WR 2721 was administered orally by gastric intubation daily for four weeks to three groups of four male rhesus monkeys at dosage levels of 8.3, 25.0, and 75.0 mg/kg/day. A fourth group served as a control and received daily doses of the vehicle. Criteria evaluated for compound effect included general appearance and behavior, appetite, elimination, body weight changes, clinical studies, organ weights and organ/body weight ratios, and gross and microscopic pathology.

Body weights in control animals and in animals at the low and intermediate test levels were generally maintained or increased. Animals at the high test level lost from 5% to 14% of their initial weight.

Clinical studies revealed slightly increased prothrombin time values at two weeks for one control monkey, three intermediate level monkeys, and four high level monkeys. The remaining hematological values, the biochemical values, and the results of urine analyses generally were within normal limits and were comparable to values for control animals.

Evaluation of the remaining criteria including microscopic examination of tissues indicated no compound-related effects.

INTRODUCTION

The purpose of this study was to characterize and evaluate the subacute oral toxicity of WR 2721 in rhesus monkeys. The study was initiated on September 15, 1969, and was terminated on October 16, 1969.

MATERIAL

Identification WR 2721.

Description Fine, white powder with a faint odor.

Receipt Date June 7, 1968.

Purity Assumed 100% active.

METHODS

Experimental Animals

Breed: Rhesus monkeys.

Number: Sixteen males.

Body Weight (At Initiation): 2.0 to 2.8 kg.

Housing: Individually in metal cages.

Diet: Purina Monkey Chow, apples five times a week, and water ad libitum.

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Animal Groups and Dosage Levels

<u>Group No.</u>	<u>No. of Monkeys</u>	<u>Material</u>	<u>Dosage Level</u> mg/kg/day
1 (control)	4	distilled water	75.0
2	4	WR 2721	8.3
3	4	WR 2721	25.0
4	4	WR 2721	75.0

Compound Preparation and Administration

The test compound and the vehicle control were prepared weekly using the body weight at the end of a given week for the following week's dose regimen. All control and test monkeys received their dose by oral intubation daily for four weeks. All animals received their appropriate dosages for three days in the fifth week.

Observations and Records

Daily: Appearance, behavior, appetite, elimination, and signs of compound effect.

Weekly: Body weights.

Clinical Studies

Performed: Twice initially and at two and four weeks.

Hematology: Hematocrit and hemoglobin determinations, erythrocyte counts, total and differential leukocyte counts, and prothrombin time.

Biochemistry: Determinations of fasting blood sugar, blood urea nitrogen, total bilirubin, direct bilirubin, serum glutamic-pyruvic transaminase, alkaline phosphatase, total protein, total albumin, albumin/globulin ratio, and

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creatinine. In addition, blood urea nitrogen, total bilirubin, serum glutamic-pyruvic transaminase, and creatinine were performed 24, 48, and 72 hours following the first dose.

Urine Analyses: Specific gravity, pH, protein, sugar, bilirubin, occult blood, volume, and microscopic examination.

Ophthalmologic Examination

Performed: Initially and terminally.

Terminal Studies

Necropsies: Performed on all monkeys sacrificed after four weeks of oral intubation.

Organ Weights: Thyroid, heart, liver, spleen, kidneys, adrenals, testes, and prostate.

Tissues Preserved:

In 10% Neutral Buffered Formalin - Brain, pituitary, thoracic spinal cord, thyroid, lung, heart, liver, gallbladder, spleen, kidney, adrenal, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testes, prostate, rib junction, bone marrow, and nerve with muscle.

In Alcoholic Formalin - Eyes.

Histopathological Examination

From Control and High Level Monkeys: Sections of all tissues listed above.

From Low and Intermediate Level Monkeys: Sections of liver and kidney.

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RESULTS**Appearance, Behavior, and Signs of Compound Effect**

No remarkable pharmacotoxic signs attributable to the test material were observed during the course of the study. Episodes of diarrhea were noted in most of the monkeys in all groups including the controls, but the animals responded within two or three days to the standard laboratory treatment. Other incidental observations included emesis (one control), mucus in feces (one control), piloerection (one control, two low level animals, and one high level animal), and moderate anorexia (one intermediate level animal and one high level animal).

Body Weight Changes

Individual weekly body weights and compound consumption are presented in Table No. 1. Mean body weights by group at initiation and at termination are presented below.

	<u>Mean Body Weights (kg.)</u>			
	<u>Group No.</u>			
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>
Initial	2.5	2.4	2.2	2.1
Terminal	2.5	2.4	2.3	1.9

Animals in Groups No. 1, No. 2, and No. 3 generally maintained their initial weight or gained weight during the study. One animal at the low test level lost 10% of his initial weight. In Group No. 4, a general body weight decrease was noted with two animals losing 14% of their initial weight, one animal losing 10% of his initial weight, and one animal losing 5% of his initial weight.

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Clinical Studies

The results of the clinical studies for individual animals are presented in Tables No. 2 (hematology), No. 3 (biochemistry), and No. 4 (urine analyses).

The hematological data revealed slightly increased prothrombin time values at two weeks for one control monkey, three intermediate level monkeys, and four high level monkeys. The remaining hematological values were generally within normal limits and comparable to the control values.

Alterations in the biochemical data included occasional increases in fasting blood sugar values and serum glutamic-pyruvic transaminase values; but these increases were inconsistent, and no relation to compound administration was evident. A slight, dose-related decrease in alkaline phosphatase values was noted; however, these values remained within the normal range for laboratory monkeys.

The results of urine analyses were not remarkable.

Ophthalmoscopic Examination

Initial and terminal examination of the eyes of all monkeys revealed no compound-related ocular effects.

Gross Pathology

At necropsy there were no gross organ or tissue alterations observed that could be attributed to the administration of the test material. Incidental changes which were noted at sacrifice included adhesions from lungs to pleura (one low level animal), lung mite lesions (one intermediate and one high level animal), enlarged spleen (one intermediate and one high level animal), rough surface of spleen (one intermediate level animal), and granular cut surface of spleen (one control and one intermediate level animal).

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Organ Weights

Individual terminal body weights, organ weights, and organ/body weight ratios are presented in Table No. 5. Mean organ/body weight ratios by group are presented below.

	Organ/Body Weight Ratio - Mean Values (%)			
	Group No.			
	1	2	3	4
Thyroid	0.016	0.015	0.016	0.018
Heart	0.441	0.426	0.415	0.438
Liver	2.739	2.183	2.269	2.472
Spleen	0.113	0.136	0.175	0.136
Kidneys	0.423	0.553	0.385	0.405
Adrenals	0.019	0.018	0.021	0.025
Testes	0.047	0.042	0.054	0.053
Prostate	0.011	0.014	0.013	0.014

With the exception of a high liver weight and ratio in one control monkey, all of the organ weight data were generally comparable among the control and test animals.

Microscopic Pathology

Microscopic examination failed to reveal compound-related changes in the tissues examined. Incidental findings consisted of pituitary cysts in Monkey No. 534J (Group No. 1) and minimal lesions of encephalitis in Monkey No. 534J (Group No. 1) and Monkey No. 566J (Group No. 4). Granular, brown, birefringent pigment suggestive of lung mite infestation was noted in both control and treated animals.

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Occasional foci of hepatocytic necrosis with nonsuppurative pericholangitis, occasional foci of interstitial nephritis, nonsuppurative cystitis, and prostatitis were noted as spontaneous disease lesions.

As an incidental finding, the section of skeletal muscle from Monkey No. 531J (Group No. 4) revealed myositis with mononuclear inflammatory cells, muscle fiber regeneration, and fibroplasia. Sections of skeletal muscle from all other animals were not remarkable in appearance.

Level of activity of the thyroid gland and bone marrow, based on microscopic appearance, was comparable between control and treated animals. Appearance of all other tissues examined was essentially not remarkable and comparable between control and treated animals.

In conclusion, administration of the test compound (WR 2721) at levels of 8.3 mg/kg/day, 25 mg/kg/day, and 75 mg/kg/day for a 28-day period failed to cause microscopically demonstrable, compound-related changes in the tissues examined.

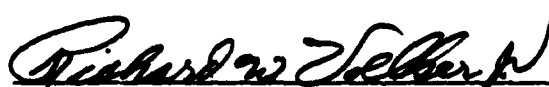
Detailed histologic findings in individual animals and an incidence table of histological alterations are appended to this report.

Submitted by



MARCELINA B. POWERS, D.V.M., M.S.
Project Manager, Drugs and
Industrial Chemicals
Toxicology-Biosciences Laboratory

Pathology by



RICHARD W. VOELKER, Jr., D.V.M., Ph.D.
Staff Pathologist

Report Preparation: Novak
Supervision: Thompson

lct

EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

0 = negative

T = trace ($\pm$)

1 = slight (+)

2 = moderate (++)

3 = marked (+++)

4 = severe (++++)

TNTC = too numerous to count

Table No. 1 - Weekly body weights and compound consumption for male monkeys.
 MR 2721 ORALLY BY INTUBATION DAILY FOR FOUR WEEKS

TIME INTERVAL weeks	CONTROL			
	MALE MONKEY NO. 530J WEIGHT kg.	MALE MONKEY NO. 534J WEIGHT kg.	MALE MONKEY NO. 573J WEIGHT kg.	MALE MONKEY NO. 581J WEIGHT kg.
Initial	2.4	2.7	2.5	2.2
1	2.4	2.6	2.4	2.0
2	2.5	2.8	2.4	2.2
3	2.5	2.7	2.4	2.1
4	2.5	2.8	2.5	1.8
5*	2.6	2.8	2.5	2.1
Wt. Change, kg.	+0.2	+0.1	0	-0.1

* Vehicle was administered for three days in the fifth week.

WR 2721 ORALLY BY INTUBATION DAILY FOR FOUR WEEKS

TIME INTERVAL weeks	8.3 MG/KG/DAY			
	MALE		MALE	
	MONKEY NO. 529J WEIGHT kg.	COMPOUND g/week	MONKEY NO. 561J WEIGHT kg.	COMPOUND g/week
Initial	2.3		2.8	
1	2.3	0.13	2.5	0.16
2	2.4	0.13	2.5	0.15
3	2.3	0.14	2.6	0.15
4	2.5	0.13	2.6	0.15
5*	2.4	0.06	2.5	0.07
Wt. Change, kg.	+0.1		-0.3	
Total Cpd. Adm., g.		0.59		0.68
				0.55
				0.62

* Compound was administered for three days in the fifth week.

Table No. 1 - Continued
 WR 2721 ORALLY BY INTUBATION DAILY FOR FOUR WEEKS

TIME INTERVAL, weeks	25 MG/KG/DAY											
	MALE		MALE		MALE		MALE					
	MONKEY NO. 461J WEIGHT kg.	COMPOUND g/week	MONKEY NO. 462J WEIGHT kg.	COMPOUND g/week	MONKEY NO. 463J WEIGHT kg.	COMPOUND g/week	MONKEY NO. 571J WEIGHT kg.	COMPOUND g/week				
Initial	2.1		2.1		2.2		2.3					
1	2.1	0.37	2.1	0.37	2.1	0.39	2.3	0.40				
2	2.2	0.37	2.1	0.37	2.3	0.37	2.3	0.40				
3	2.1	0.39	2.1	0.37	2.2	0.40	2.3	0.40				
4	2.1	0.37	2.1	0.37	2.4	0.39	2.3	0.40				
5*	2.2	0.16	2.2	0.16	2.3	0.18	2.4	0.17				
Wt. Change, kg.	+0.1		+0.1		+0.1		+0.1					
Total Cpd. Adm., g.	1.66		1.64		1.73		1.77					

* Compound was administered for three days in the fifth week.

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Table No. 1 - Continued
 WR 2721 ORALLY BY INTUBATION DAILY FOR FOUR WEEKS

TIME INTERVAL weeks	MALE		MALE		MALE		MALE	
	MONKEY NO. 531J	WEIGHT	MONKEY NO. 560J	WEIGHT	MONKEY NO. 565J	WEIGHT	MONKEY NO. 566J	WEIGHT
	kg.	g/week	kg.	g/week	kg.	g/week	kg.	g/week
Initial	2.1		2.2		2.0		2.2	
1	1.9	1.12	2.2	1.16	1.7	1.05	2.1	1.16
2	2.0	1.02	2.2	1.16	1.8	0.91	2.1	1.12
3	1.9	1.05	2.0	1.16	1.7	0.95	2.0	1.12
4	1.8	1.02	1.9	1.05	1.7	0.91	2.1	1.05
5*	1.8	0.41	1.9	0.44	1.8	0.39	2.1	0.48
Wt. Change, kg.	-0.3		-0.3		-0.2		-0.1	
Total Cpd. Adm., g.	4.62		4.97		4.21		4.93	

* Compound was administered for three days in the fifth week.

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
1ST INITIAL

GROUP NUMBER	ANIMAL NUMBER	SEX	HCT %	HGB G%	RBC MILLS	WBC THS	DIFFERENTIAL						
							METAS	BANDS	SEG	LYMPH	MONO	EOSIN	BASO
1	530J	M	43.0	15.0	5.65	22.7	0	0	34	64	0	2	0
	534J	M	43.0	14.6	5.56	12.9	0	0	13	82	0	5	0
	573J	M	43.0	15.0	5.69	11.5	0	0	18	78	1	3	0
	581J	M	40.0	14.2	5.89	17.9	0	0	34	66	0	0	0
GROUP MEAN			42.3	14.7	5.70	16.3							
2	529J	M	43.0	14.6	5.80	16.1	0	0	27	71	0	2	0
	561J	M	40.0	13.7	5.65	11.3	0	0	30	68	0	2	0
	572J	M	40.0	14.2	5.88	30.5	0	0	31	69	0	0	0
	575J	M	40.0	14.2	4.98	9.7	0	0	19	78	2	1	0
GROUP MEAN			40.8	14.2	5.58	16.9							
3	462J	M	43.0	14.6	5.49	14.6	0	0	28	68	0	4	0
	463J	M	42.0	15.0	6.10	14.1	0	0	18	77	0	5	0
	461J	M	41.0	14.2	5.50	16.1	0	0	51	49	0	0	0
	571J	M	39.0	13.2	5.53	13.8	0	0	44	56	0	0	0
GROUP MEAN			41.3	14.3	5.66	14.7							
4	531J	M	41.0	14.6	5.42	12.5	0	0	17	82	0	0	1
	560J	M	40.0	14.6	5.44	10.5	0	0	16	81	0	3	0
	565J	M	40.0	13.5	5.61	14.3	0	0	54	44	1	1	0
	566J	M	37.0	12.3	5.18	14.9	0	0	20	80	0	0	0
GROUP MEAN			39.5	13.8	5.42	13.1							

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
2ND INITIAL

GROUP NUMBER	ANIMAL NUMBER	E X	HCT %	HGB G%	RBC MILLS	WBC THS	DIFFERENTIAL						
							MET %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	BASO %
1	530J	M	40.0	13.0	5.72	19.2	0	0	30	68	0	2	0
	534J	M	40.0	13.0	5.75	14.7	0	0	9	90	0	1	0
	573J	M	32.0	10.5	4.60	16.4	0	0	52	48	0	0	0
1	581J	M	40.0	13.0	5.53	19.9	0	0	42	57	0	0	1
GROUP MEAN			38.0	12.4	5.40	17.6							
2	529J	M	41.0	13.2	5.89	17.0	0	0	46	52	1	1	0
	561J	M	35.0	11.0	5.29	13.8	0	0	37	63	0	0	0
	572J	M	34.0	11.0	4.76	19.2	0	0	20	79	0	1	0
2	575J	M	33.0	10.7	4.76	12.8	0	0	25	73	0	2	0
GROUP MEAN			35.8	11.5	5.18	15.7							
3	462J	M	40.0	12.6	5.32	12.5	0	0	10	86	0	4	0
	463J	M	38.0	12.7	5.42	9.4	0	0	20	71	0	9	0
	461J	M	40.0	13.0	5.56	7.6	0	0	12	87	1	0	0
3	571J	M	36.0	11.5	5.24	15.3	0	0	34	66	0	0	0
GROUP MEAN			38.5	12.5	5.39	11.2							
4	531J	M	35.0	11.0	4.91	11.5	0	0	17	82	0	1	0
	560J	M	34.0	11.5	5.07	11.3	0	2	52	45	1	0	0
	565J	M	35.0	11.3	5.35	9.8	0	1	20	77	0	2	0
4	566J	M	36.0	11.7	5.27	16.5	0	0	35	62	0	3	0
GROUP MEAN			35.0	11.4	5.15	12.3							

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
WEEK 2

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GROUP NUMBER	ANIMAL NUMBER	HCT %	HGB G%	RBC MILLS	WBC THS	DIFFERENTIAL						
						MET %	PLT %	SEG %	LYMPH %	MONO %	EOSIN %	BASO %
1	530J M	40.0	13.0	5.34	11.1	0	0	15	79	0	6	0
	534J M	38.0	12.2	5.38	8.2	0	0	16	78	1	5	0
	573J M	40.0	13.2	5.40	5.9	0	0	24	62	3	11	0
1	581J M	42.0	13.5	5.69	13.4	0	0	42	57	0	1	0
GROUP MEAN		40.0	13.0	5.45	9.7							
2	529J M	42.0	14.0	5.60	7.2	0	0	18	81	0	1	0
	561J M	35.0	11.5	5.25	10.5	0	0	21	79	0	0	0
	572J M	40.0	13.0	5.15	11.2	0	0	27	68	3	2	0
2	575J M	40.0	13.0	5.71	7.8	0	0	15	84	0	1	0
GROUP MEAN		39.3	12.9	5.43	9.2							
3	461J M	41.0	13.5	5.47	7.5	0	0	33	66	1	0	0
	462J M	39.0	12.7	5.36	10.7	0	0	19	73	0	7	1
	463J M	40.0	13.5	5.25	6.9	0	0	24	73	0	3	0
3	571J M	37.0	12.0	5.37	9.7	0	0	50	48	2	0	0
GROUP MEAN		39.3	12.9	5.36	8.7							
4	531J M	40.0	12.7	5.27	4.7	0	0	40	55	2	3	0
	560J M	40.0	13.4	5.19	10.4	0	0	49	45	3	2	1
	565J M	39.0	12.3	5.47	5.2	0	0	15	81	2	2	0
4	566J M	33.0	10.7	4.49	7.8	0	0	32	68	0	0	0
GROUP MEAN		38.0	12.3	5.11	7.0							

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TABLE NO. 2 - INDIVIDUAL HEATOLOGICAL VALUES
PHEBUS PORKKEYS RECEIVING VR 272J FOR FOUR WEEKS
WEEK 4

GROUP	ANIMAL NUMBER	HCT %	HGB g	PBC HILLS	WBC THS	DIFFERENTIAL							
						LYMPH	MONO	EOSIN	PLASMA	SEG	LYMPH	MONO	EOSIN
GROUP 1	1	53.0	13.4	5.07	9.3	0	0	0	0	23	74	0	3
	1	53.4	13.0	5.38	8.5	0	0	0	0	14	84	0	2
	1	57.3	13.6	5.15	7.7	0	0	0	0	31	63	0	6
	1	58.1	14.7	5.70	15.0	0	0	0	0	19	77	2	2
GROUP MEAN		41.3	13.7	5.33	10.1								
GROUP 2	2	52.9	13.7	5.63	9.8	0	0	0	0	26	72	2	0
	2	56.1	12.0	5.50	12.4	0	0	0	0	28	70	0	2
	2	57.2	13.1	5.09	9.8	0	0	0	0	30	69	0	1
	2	57.5	12.7	5.53	8.4	0	0	0	0	20	77	2	1
GROUP MEAN		39.0	12.9	5.44	10.1								
GROUP 3	3	46.1	12.4	5.18	10.3	0	0	0	0	44	53	0	3
	3	46.2	14.8	5.94	16.5	0	0	0	0	53	45	0	2
	3	46.3	13.4	5.09	14.4	0	0	0	0	68	30	1	1
	3	57.1	11.8	5.12	15.7	0	0	0	0	56	42	1	1
GROUP MEAN		39.3	13.1	5.33	14.2								
GROUP 4	4	53.1	12.7	4.97	5.1	0	0	0	0	62	38	0	0
	4	56.0	12.3	4.76	10.5	0	0	0	0	37	60	0	2
	4	56.5	12.7	5.40	7.4	0	0	0	0	30	70	0	0
	4	56.6	11.0	4.35	6.2	0	0	0	0	42	54	0	0
GROUP MEAN		36.5	12.2	4.87	7.3								

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
1ST INITIAL

GROUP NUMBER	ANIMAL NUMBER	E X	S PROTHROMBIN SECONDS
1	530J	M	13.6
	534J	M	13.2
	573J	M	13.7
1	581J	M	13.2
GROUP MEAN			13.4
2	529J	M	13.0
	561J	M	12.9
	572J	M	12.0
2	575J	M	13.6
GROUP MEAN			12.9
3	462J	M	11.9
	463J	M	12.2
	461J	M	11.1
3	571J	M	14.3
GROUP MEAN			12.4
4	531J	M	16.5
	560J	M	14.2
	565J	M	12.1
4	566J	M	12.6
GROUP MEAN			13.9

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
2ND INITIAL

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GROUP NUMBER	ANIMAL NUMBER	ES X	PROTHROMBIN SECONDS
1	530J	M	12.4
	534J	M	12.4
	573J	M	13.8
1	581J	M	12.9
GROUP MEAN			12.9
2	529J	M	13.6
	561J	M	14.6
	572J	M	13.9
2	575J	M	13.7
GROUP MEAN			14.0
3	462J	M	12.1
	463J	M	12.8
	461J	M	13.7
3	571J	M	14.4
GROUP MEAN			13.3
4	521J	M	12.1
	560J	M	15.4
	565J	M	13.4
4	566J	M	13.8
GROUP MEAN			13.7

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	5 F X	PROTHROMBIN SECONDS
1	530J	M	14.5
1	534J	M	15.8
1	573J	M	16.4
1	581J	M	17.1
GROUP MEAN			16.0
2	529J	M	16.4
2	561J	M	16.9
2	572J	M	15.8
2	575J	M	15.5
GROUP MEAN			16.2
3	461J	M	17.6
3	462J	M	18.4
3	463J	M	15.9
3	571J	M	18.1
GROUP MEAN			17.5
4	531J	M	18.6
4	560J	M	17.9
4	565J	M	18.2
4	566J	M	18.8
GROUP MEAN			18.4

TABLE NO. 2 - INDIVIDUAL HEPATOLOGICAL VALUES
Rhesus Monkeys Receiving UR 2721 for Four Weeks
Week 4

GROUP NUMBER	ANIMAL NUMBER	S F X	PROTHROMBIN SECONDS
1	530J	M	14.6
	534J	M	12.6
	573J	M	12.8
1	581J	M	13.5
GROUP MEAN			13.4
2	529J	M	14.2
	561J	M	13.1
	572J	M	12.8
2	575J	M	HEM
GROUP MEAN			13.4
3	461J	M	14.8
	462J	M	13.2
	463J	M	14.8
3	571J	M	16.2
GROUP MEAN			14.8
4	531J	M	14.7
	560J	M	14.6
	565J	M	13.8
4	566J	M	12.7
GROUP MEAN			14.0

HEM = SAMPLE HEMOLYZED

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
1ST INITIAL

GROUP NUMBER	ANIMAL NUMBER	SEX	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. K-A. UNITS	PHOS	BILIRUBIN	
								TOTAL MG%	DIRECT MG%
1	1	530J M	105.0	16.0	34.0	63.2		0.20	0.06
	1	534J M	93.0	17.0	37.5	74.4		0.45	0.06
	1	573J M	120.0	8.0	31.0	60.0		0.21	0.06
1	581J M		90.0	21.0	29.0	42.9		0.30	0.02
GROUP MEAN			102.0	15.5	32.9	60.1		0.29	0.05
2	2	529J M	75.0	23.5	64.5	72.0		0.40	0.06
	2	561J M	110.0	19.0	34.0	42.5		0.28	0.13
	2	572J M	104.0	12.0	34.0	43.2		0.20	0.06
2	575J M		120.0	16.0	37.5	46.0		0.20	0.06
GROUP MEAN			102.3	17.6	42.5	50.9		0.27	0.08
3	3	462J M	77.0	26.0	37.5	92.0		0.30	0.04
	3	463J M	105.0	27.0	39.0	85.6		0.49	0.02
	3	461J M	124.0	14.0	39.0	80.8		0.20	0.04
3	571J M		91.0	31.0	32.5	52.0		0.40	0.08
GROUP MEAN			99.3	24.5	27.0	77.6		0.35	0.05
4	4	531J M	105.0	12.0	44.0	37.9		0.20	0.04
	4	560J M	100.0	18.0	37.5	56.0		0.30	0.06
	4	565J M	65.0	23.0	31.0	60.4		0.40	0.04
4	566J M		84.0	15.0	41.0	33.8		0.21	0.06
GROUP MEAN			88.5	17.3	38.4	47.0		0.28	0.05

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
2ND INITIAL

GROUP NUMBER	ANIMAL NUMBER	SEX	GLUCOSE		BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN	
			MG%	MG%				TOTAL MG%	DIRECT MG%
1	530J	M	100.0	15.5	57.0	94.8	0.21	0.04	
	534J	M	110.0	14.0	34.0	98.8	0.29	0.04	
	573J	M	101.0	11.0	31.0	75.2	0.19	0.02	
1	581J	M	81.0	14.5	26.0	78.4	0.30	0.02	
GROUP MEAN			98.0	13.8	37.0	86.8	0.25	0.03	
2	529J	M	110.0	16.0	31.0	72.0	0.20	0.04	
	561J	M	110.0	20.0	34.0	56.8	0.19	0.06	
	572J	M	104.0	15.0	31.0	55.6	0.25	0.02	
2	575J	M	96.0	25.5	34.0	57.6	0.19	0.02	
GROUP MEAN			105.0	19.1	32.5	60.5	0.21	0.04	
3	462J	M	95.0	16.5	29.0	75.2	0.22	0.02	
	463J	M	105.0	16.5	26.0	64.8	0.30	0.04	
	461J	M	95.0	12.0	23.0	77.2	0.30	0.04	
3	571J	M	84.0	24.0	32.5	89.6	0.19	0.04	
GROUP MEAN			94.8	17.3	27.6	76.7	0.25	0.04	
4	531J	M	118.0	16.0	34.0	47.1	0.20	0.02	
	560J	M	70.0	20.5	36.0	74.4	0.41	0.02	
	565J	M	96.0	16.0	31.0	85.6	0.20	0.02	
4	566J	M	95.0	16.0	36.0	42.2	0.21	0.02	
GROUP MEAN			94.8	17.1	34.3	62.3	0.26	0.02	

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
24 HOURS

GROUP NUMBER	ANIMAL NUMBER	S X	BUN MG%	SGPT R-F.	BILIRUBIN	
					TOTAL MG%	
1	530J	M	18.0	41.0	0.22	
	534J	M	23.0	41.0	0.20	
	573J	M	20.0	50.0	0.25	
1	581J	M	20.0	28.0	0.25	
GROUP MEAN			20.3	40.0	0.23	
2	529J	M	19.0	39.0	0.22	
	561J	M	22.0	39.0	0.29	
	572J	M	20.0	37.5	0.16	
2	575J	M	25.0	34.0	0.16	
GROUP MEAN			21.5	37.4	0.21	
3	461J	M	20.0	75.0	0.25	
	462J	M	16.0	39.0	0.25	
	463J	M	18.0	39.0	0.22	
3	571J	M	41.0	34.0	0.27	
GROUP MEAN			23.8	46.8	0.25	
4	531J	M	16.0	42.5	0.22	
	560J	M	23.0	32.5	0.25	
	565J	M	13.0	41.0	0.18	
4	566J	M	16.0	41.0	0.22	
GROUP MEAN			17.0	39.3	0.22	

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
48 HOURS

GROUP	ANIMAL	S	E	RUN	SGPT	BILIRUBIN	
						TOTAL	MG%
NUMBER	NUMBER	X	MG%	R-F.			
1	530J	M	17.0	37.5		0.28	
1	534J	M	14.0	32.5		0.42	
1	573J	M	15.0	29.0		0.34	
1	581J	M	12.0	31.0		0.25	
GROUP MEAN			14.5	32.5		0.32	
2	529J	M	14.0	29.0		0.30	
2	561J	M	14.0	34.0		0.25	
2	572J	M	16.0	34.0		0.28	
2	575J	M	18.0	37.5		0.21	
GROUP MEAN			15.5	33.6		0.26	
3	461J	M	17.0	52.0		0.34	
3	462J	M	16.0	37.5		0.23	
3	463J	M	17.0	36.0		0.25	
3	571J	M	20.0	34.0		0.40	
GROUP MEAN			17.5	39.9		0.31	
4	531J	M	14.0	39.0		0.19	
4	560J	M	14.0	34.0		0.21	
4	565J	M	12.0	39.0		0.17	
4	566J	M	10.5	34.0		0.23	
GROUP MEAN			12.6	36.5		0.20	

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
72 HOURS

GROUP NUMBER	ANIMAL NUMBER	S		SGPT R-F.	BILIRUBIN	
		E	RUN MG%		TOTAL MG%	
1	530J	M	22.0	41.0	0.25	
	534J	M	12.0	37.5	0.20	
	573J	M	12.0	39.0	0.27	
1	581J	M	15.0	36.0	0.36	
GROUP MEAN			15.3	38.4	0.27	
2	529J	M	14.0	39.0	0.27	
	561J	M	16.0	37.5	0.31	
	572J	M	22.0	34.0	0.31	
2	575J	M	21.0	36.0	0.36	
GROUP MEAN			18.3	36.6	0.31	
3	461J	M	20.0	46.0	0.20	
	462J	M	20.0	37.5	0.22	
	463J	M	17.0	36.0	0.29	
3	571J	M	20.0	39.0	0.29	
GROUP MEAN			19.3	39.6	0.25	
4	531J	M	16.0	42.5	0.25	
	560J	M	17.0	36.0	0.22	
	565J	M	14.0	37.5	0.27	
4	566J	M	17.0	34.0	0.25	
GROUP MEAN			16.0	37.5	0.25	

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEBUS MONKEYS RECEIVING MR 2721 FOR FOUR WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	SEX	GLUCOSE		SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN	
			MG%	BUN MG%			TOTAL MG%	RILIRUBIN DIRECT MG%
1	530J	M	95.0	17.5	41.0	73.6	0.51	0.06
	534J	M	85.0	20.5	37.5	74.4	0.26	0.00
	573J	M	60.0	11.5	37.5	45.0	0.22	0.04
1	581J	M	81.0	14.0	34.0	50.0	0.25	0.02
GROUP MEAN			80.3	15.9	37.5	60.8	0.31	0.03
2	529J	M	102.0	17.5	42.5	76.4	0.38	0.06
	561J	M	84.0	19.5	39.0	41.7	0.23	0.02
	572J	M	88.0	16.0	39.0	44.1	0.30	0.04
2	575J	M	82.0	15.0	37.5	39.0	0.25	0.04
GROUP MEAN			89.0	17.0	39.5	50.3	0.29	0.04
3	461J	M	86.0	17.0	41.0	45.0	0.24	0.04
	462J	M	76.0	14.0	48.0	42.6	0.20	0.06
	463J	M	93.0	16.0	39.0	41.0	0.40	0.04
3	571J	M	79.0	35.0	34.0	50.0	0.20	0.02
GROUP MEAN			83.5	20.5	40.5	44.7	0.26	0.04
4	531J	M	78.0	17.0	41.0	30.0	0.30	0.02
	560J	M	89.0	18.0	39.0	57.6	0.29	0.02
	565J	M	85.0	11.5	37.5	48.1	0.28	0.02
4	566J	M	76.0	13.0	37.5	31.5	0.20	0.02
GROUP MEAN			82.0	14.9	38.8	41.8	0.27	0.02

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING MR 2721 FOR FOUR WEEKS

GROUP NUMBER	ANIMAL NUMBER	S X	GLUCOSE		BUN MG%	SGPT P-F.	ALK. PHOS. K-A. UNITS	BILIRUBIN	
			MG%	MG%				TOTAL MG%	DIRECT MG%
1	530J	F	111.0	23.0	34.0	74.4	0.30	0.02	0.06
	534J	M	95.0	11.0	36.0	46.1	0.29	0.06	0.06
	573J	M	90.0	15.0	37.5	37.9	0.20	0.06	0.06
1	581J	F	120.0	18.0	39.0	37.9	0.40	0.06	0.06
GROUP MEAN			104.0	16.8	36.6	49.1	0.30	0.05	0.05
2	529J	F	99.0	18.0	41.0	88.8	0.20	0.04	0.04
	561J	F	95.0	18.0	39.0	33.0	0.20	0.04	0.04
	572J	M	101.0	13.5	34.0	37.0	0.19	0.06	0.06
2	575J	M	125.0	19.0	37.5	36.5	0.21	0.04	0.04
GROUP MEAN			105.0	17.1	37.9	48.8	0.20	0.05	0.05
3	461J	M	191.0	18.5	39.0	35.1	0.20	0.04	0.04
	462J	F	81.0	25.0	39.0	41.1	0.29	0.02	0.02
	463J	F	145.0	16.0	36.0	26.5	0.21	0.06	0.06
3	571J	F	80.0	31.0	28.0	47.8	0.15	0.04	0.04
GROUP MEAN			124.3	22.6	35.5	37.6	0.21	0.04	0.04
4	531J	F	90.0	19.0	42.5	24.0	0.30	0.04	0.04
	560J	M	80.0	15.0	37.5	33.7	0.19	0.04	0.04
	565J	F	81.0	13.0	37.5	45.0	0.19	0.04	0.04
4	566J	M	80.0	13.5	46.0	28.8	0.19	0.04	0.04
GROUP MEAN			82.8	15.1	40.9	32.9	0.22	0.04	0.04

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
1ST INITIAL

GROUP NUMBER	ANIMAL NUMBER	S X	TOTAL PROTEIN G%	TOTAL ALBUMIN G%
1	530J	M	8.30	2.99
	534J	M	8.00	3.50
	573J	M	7.50	3.49
1	581J	M	7.90	3.56
GROUP MEAN			7.93	3.39
2	529J	M	7.10	2.90
	561J	M	7.80	3.10
	572J	M	7.90	3.51
2	575J	M	7.50	3.09
GROUP MEAN			7.58	3.15
3	462J	M	7.80	4.00
	463J	M	8.70	4.15
	461J	M	7.50	3.20
3	571J	M	8.05	3.10
GROUP MEAN			8.01	2.61
4	531J	M	7.70	2.41
	560J	M	8.70	3.11
	565J	M	7.83	3.16
4	566J	M	7.85	3.11
GROUP MEAN			8.02	3.20

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEIUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
2ND INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	TOTAL PROTEIN G%	TOTAL ALBUMIN G%
GROUP MEAN	1	539J M	8.60	3.10
	1	534J M	8.60	3.39
	1	573J M	7.80	2.90
	1	581J M	7.41	2.80
GROUP MEAN				
			8.10	3.05
GROUP MEAN	2	529J M	7.11	2.88
	2	561J M	7.75	2.60
	2	572J M	8.60	3.28
	2	575J M	7.50	2.60
GROUP MEAN				
			7.74	2.84
GROUP MEAN	3	462J M	7.50	3.30
	3	463J M	7.70	3.50
	3	461J M	7.90	3.09
	3	571J M	8.19	3.07
GROUP MEAN				
			7.82	3.24
GROUP MEAN	4	531J M	8.10	3.01
	4	560J M	8.11	2.81
	4	565J M	8.30	3.30
	4	566J M	8.39	2.98
GROUP MEAN				
			8.23	3.03

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEIUS MONKEYS RECEIVING HR 2721 FOR FOUR WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	TOTAL PROTEIN G%	TOTAL ALBUMIN G%
1	530J	M	7.90	3.35
	534J	M	7.34	3.23
	573J	M	7.18	3.20
1	581J	M	7.44	3.27
GROUP MEAN			7.47	3.26
2	529J	M	6.70	2.55
	561J	M	7.00	2.40
	572J	M	8.11	3.46
2	575J	M	7.30	2.78
GROUP MEAN			7.28	2.80
3	461J	M	7.59	2.79
	462J	M	6.75	2.51
	463J	M	7.69	3.19
3	571J	M	7.49	3.10
GROUP MEAN			7.38	2.90
4	531J	M	7.20	3.00
	560J	M	7.71	3.16
	565J	M	7.45	2.90
4	566J	M	7.11	2.28
GROUP MEAN			7.37	2.84

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEBUS MONKEYS RECEIVING WR 272J FOR FOUR WEEKS
WEEK 4

GROUP NUMBER	ANIMAL NUMBER	S F	TOTAL PROTEIN G%	TOTAL ALBUMIN G%
1	530J	M	7.40	3.00
	534J	M	7.89	3.05
	573J	M	7.65	3.40
1	581J	M	7.85	3.20
GROUP MEAN			7.68	3.16
2	529J	M	6.60	2.80
	561J	M	7.15	2.65
	572J	M	7.45	3.15
2	575J	M	6.70	2.60
GROUP MEAN			6.98	2.80
3	461J	M	7.15	2.55
	462J	M	7.75	2.80
	463J	M	7.00	2.55
3	571J	M	7.30	3.00
GROUP MEAN			7.30	2.73
4	531J	M	7.30	3.05
	560J	M	7.30	3.00
	565J	M	7.45	2.95
4	566J	M	7.35	2.55
GROUP MEAN			7.35	2.89

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
1ST INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM CREAT. MG%	A/G RATIO G%
1	530J	M	0.90	0.56
	534J	M	1.20	0.78
	573J	M	1.30	0.87
1	581J	M	1.40	0.82
GROUP MEAN			1.20	0.76
2	529J	M	1.30	0.69
	561J	M	1.20	0.66
	572J	M	0.80	0.80
2	575J	M	1.00	0.70
GROUP MEAN			1.08	0.71
3	462J	M	1.00	1.10
	463J	M	1.30	0.91
	461J	M	1.20	0.74
3	571J	M	1.10	0.63
GROUP MEAN			1.15	0.85
4	531J	M	0.80	0.79
	560J	M	1.20	0.75
	565J	M	1.10	0.68
4	566J	M	0.90	0.66
GROUP MEAN			1.00	0.72

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
2ND INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM CREAT. MG%	A/G RATIO G%
1	530J	M	1.30	0.56
	534J	M	0.80	0.65
	573J	M	1.10	0.49
1	581J	M	1.10	0.50
GROUP MEAN			1.08	0.55
2	529J	M	0.90	0.68
	561J	M	1.00	0.50
	572J	M	0.80	0.62
2	575J	M	1.30	0.53
GROUP MEAN			1.00	0.58
3	462J	M	1.00	0.78
	463J	M	1.20	0.83
	461J	M	1.40	0.64
3	571J	M	1.60	0.59
GROUP MEAN			1.30	0.71
4	531J	M	1.00	0.59
	560J	M	1.40	0.52
	565J	M	1.10	0.66
4	566J	M	1.10	0.68
GROUP MEAN			1.15	0.62

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEIUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS

24 HOURS

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM CREAT. MG%
1	530J	M	1.30
	534J	M	1.10
	573J	M	1.00
1	581J	M	1.10
GROUP MEAN			1.13
2	529J	M	1.20
	561J	M	1.30
	572J	M	1.20
2	575J	M	1.10
GROUP MEAN			1.20
3	461J	M	1.20
	462J	M	1.30
	463J	M	1.30
3	571J	M	1.20
GROUP MEAN			1.25
4	531J	M	1.30
	560J	M	1.20
	565J	M	1.10
4	566J	M	1.30
GROUP MEAN			1.23

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEIUS MONKEYS RECEIVING MR 2721 FOR FOUR WEEKS

48 HOURS

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM CREAT. MG%
1	530J	M	1.10
1	534J	M	1.00
1	573J	M	1.00
1	581J	M	1.00
GROUP MEAN			1.03
2	529J	M	1.20
2	561J	M	1.20
2	572J	M	1.00
2	575J	M	1.00
GROUP MEAN			1.10
3	461J	M	1.10
3	462J	M	1.20
3	463J	M	1.20
3	571J	M	1.20
GROUP MEAN			1.18
4	531J	M	1.20
4	560J	M	1.20
4	565J	M	1.00
4	566J	M	1.30
GROUP MEAN			1.18

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEIUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS

72 HOURS

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM CREAT. MG%
1	530J	M	1.30
	534J	M	1.30
	573J	M	1.20
1	581J	M	1.20
GROUP MEAN			1.25
2	529J	M	1.30
	561J	M	1.30
	572J	M	1.20
2	575J	M	1.30
GROUP MEAN			1.28
3	461J	M	1.20
	462J	M	1.20
	463J	M	1.20
3	571J	M	1.20
GROUP MEAN			1.20
4	531J	M	1.20
	560J	M	1.20
	565J	M	1.10
4	566J	M	1.30
GROUP MEAN			1.20

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEIUS MONKEYS RECEIVING WP 2721 FOR FOUR WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM CREAT. MG%	A/G RATIO G%
1	530J	M	1.10	0.74
	534J	M	1.10	0.79
	573J	M	1.20	0.70
1	581J	M	0.90	0.78
GROUP MEAN			1.08	0.75
2	529J	M	1.00	0.61
	561J	M	1.30	0.52
	572J	M	1.40	0.74
2	575J	M	1.20	0.62
GROUP MEAN			1.23	0.62
3	461J	M	1.00	0.58
	462J	M	1.00	0.59
	463J	M	1.10	0.46
3	571J	M	0.80	0.71
GROUP MEAN			0.98	0.59
4	531J	M	1.20	0.71
	560J	M	1.30	0.69
	565J	M	1.10	0.64
4	566J	M	1.40	0.47
GROUP MEAN			1.25	0.63

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS

GROUP NUMBER	ANTHRA NUMBER	S F X	SERUM CREAT. MG%	A/G RATIO G%	WEEK
1	530J M	1.00	0.68	4	
	534J M	1.00	0.64		
	573J M	1.20	0.80		
1	581J M	1.20	0.69		
GROUP MEAN					1.10
2	529J M	1.00	0.74	4	
	561J M	1.10	0.59		
	572J M	1.30	0.73		
2	575J M	1.20	0.63		
GROUP MEAN					1.15
3	461J M	1.00	0.55	4	
	462J M	1.20	0.57		
	463J M	1.30	0.57		
3	571J M	1.40	0.70		
GROUP MEAN					1.23
4	531J M	1.10	0.72	4	
	560J M	1.00	0.70		
	565J M	1.00	0.66		
4	566J M	1.20	0.53		
GROUP MEAN					1.08
GROUP MEAN					0.65

TABLE NO. 4 - URINE ANALYSIS
RHEBUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
1ST INITIAL

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GROUP NUMBER	ANIMAL NUMBER	SEX	P H	SP. GR.	SU- GAR	PRO- TEIN	BILL- RUBIN	DCC BLD	VOL.	MICROSCOPIC FINDINGS-----				
										RBC	WBC	EPITH	AMORPH	CRYSTALS
1	530J	M	6	1.024	0	T	0	0	35		1-2		LITTLE	FEW
1	534J	M	6	1.017	0	T	1	0	7			0-1	MUCH	FEW
1	573J	M	6	1.031	0	1	0	0	43	1-3	4-6		MUCH	FEW
1	581J	M	6	1.020	0	0	0	0	16		1-3	0-2	MUCH	FEW
2	529J	M	6	1.029	0	T	2	0	13			0-1	MUCH	FEW
2	561J	M	7	1.015	0	0	0	0	48		1-3	0-1	MUCH	FEW
2	572J	M	6	1.012	0	0	0	0	22				LITTLE	FEW
2	575J	M	7	1.032	0	T	0	0	22	1-3	1-3	0-2	MUCH	MANY
3	462J	M	5	1.014	0	0	0	0	29		0-2	3-5	MUCH	FEW
3	463J	M	7	1.023	0	T	0	0	6				MUCH	FEW
3	461J	M	7	1.011	0	0	0	0	35		2-3		LITTLE	FEW
3	571J	M	8	1.008	0	0	0	0	10	4-5	1-3	0-2	MUCH	FEW
4	531J	M	7	1.017	0	T	0	0	8				MUCH	FEW
4	560J	M	6	1.027	0	T	0	0	29	4-5	2-3	3-4	MUCH	FEW
4	565J	M	7	1.025	0	T	0	0	25		2-4		MUCH	FEW
4	566J	M	6	1.010	0	0	0	0	110			0-1	MUCH	FEW

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TABLE NO. 4 - URINE ANALYSIS
RHEBUS MONKEYS RECEIVING NR 2721 FOR FOUR WEEKS
2ND INITIAL

GROUP NUMBER	ANIMAL NUMBER	SEX	AGE	SP. GR.	SU- GAR	PRO- TEIN	BILI- RUBIN	OCC RLD	VOL.	RBC	WBC	MICROSCOPIC FINDINGS-----			
												EPITH	AMORPH	CRYS	BACT SPERM
1	530J	M	7	1.022	0	0	0	0	63						
1	534J	M	8	1.018	0	0	0	0	34						
1	573J	M	7	1.025	0	0	0	0	51			4-6	MUCH	MANY	MANY
1	581J	M	7	1.016	0	0	0	0	21			1-3	MUCH	FEW	MANY
2	529J	M	9	1.015	0	0	0	0	41			2-4	MUCH	FEW	MANY
2	561J	M	7	1.017	0	0	0	0	105				MUCH	MANY	MANY
2	572J	M	8	1.009	0	0	0	0	87				MUCH	MANY	MANY
2	575J	M	7	1.022	0	0	0	0	32			3-5	MUCH	MANY	MANY
3	462J	M	7	1.020	0	0	0	0	60				MUCH	MANY	MANY
3	463J	M	7	1.026	0	0	0	0	40			2-4	MUCH	MANY	MANY
3	461J	M	9	1.020	0	0	0	0	20				MUCH	MANY	MANY
3	571J	M	7	1.026	0	0	0	0	13	0-1		2-4	MUCH	MANY	MANY
4	531J	M	7	1.018	0	0	0	0	81				MUCH	FEW	MANY
4	560J	M	9	1.032	0	0	0	0	12				MUCH	MANY	MANY
4	565J	M	9	1.020	0	0	0	0	24				MUCH	MANY	MANY
4	566J	M	7	1.017	0	0	0	0	216				MUCH	MANY	MANY

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TABLE NO. 4 - URINE ANALYSIS
RHEMUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	SEX	P H	SP. GR.	SU- GAR	PRO- TEIN	BILI- RUBIN	UCC RLD	VOL.	-----MICROSCOPIC FINDINGS-----			
										RBC	WBC	EPITH	AMORPH CRYSTALS
1	530J	M	5	1.021	0	0	0	0	80	1-2		1-3	MUCH FEW MANY
1	534J	M	5	1.030	0	0	0	0	25	0-1		1-3	MUCH MANY MANY
1	573J	M	7	1.020	0	0	0	0	130			2-4	MUCH FEW MANY
1	581J	M	6	1.011	0	0	0	0	80				MUCH FEW MANY
2	529J	M	7	1.020	0	0	0	0	70	0-1		1-3	MUCH MANY MANY
2	561J	M	8	1.015	0	0	0	0	68	1-3	0-1		MUCH FEW MANY
2	572J	M	7	1.014	0	0	0	0	120			1-3	MUCH FEW MANY
2	575J	M	7	1.018	0	0	0	0	60			1-3	MUCH MANY MANY
3	461J	M	7	1.030	0	0	0	0	10				MUCH FEW MANY
3	462J	M	8	1.010	0	0	0	0	60			1-3	MUCH MANY MANY
3	463J	M	7	1.014	0	0	0	0	152				MUCH FEW MANY
3	571J	M	5	1.038	0	T	0	0	14	1-3	2-4		MUCH MANY MANY
4	531J	M	7	1.014	0	T	0	0	105				MUCH MANY MANY
4	560J	M	7	1.050	0	1	0	T	7	6-8	TNTC		MUCH FEW MANY
4	565J	M	7	1.012	0	0	0	0	54			1-3	MUCH MANY MANY
4	566J	M	7	1.013	0	0	0	0	125				MUCH MANY MANY

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TABLE NO. 4 - UPRIME ANALYSIS
RHEIUS MONKEYS RECEIVING MR 2721 FOR FOUR WEEKS
WEEK 4

GROUP NUMBER	ANIMAL NUMBER	SEX	AGE	SP. GR.	SUB-GAR	PRO-TFIN	BLI-RUBIN	OCG	VOL.	RBC	WBC	EPITH	ADIPH	GYPS	RECT	SPERM
1	530J	M	8	1.015	0	0	0	0	97	1-2		1-3	BUCH	MANY	MANY	
1	534J	F	7	1.017	0	0	0	0	70				BUCH	MANY	MANY	
1	573J	F	7	1.012	0	0	0	0	210				BUCH	MANY	MANY	
1	581J	M	7	1.012	0	0	0	0	190				BUCH	MANY	MANY	
2	529J	M	6	1.018	0	0	0	0	125		1-3	2-4	BUCH	MANY	MANY	
2	561J	M	8	1.015	0	0	0	0	93			1-3	BUCH	MANY	MANY	
2	572J	F	7	1.020	0	0	0	0	200		8-10	1-2	BUCH	MANY	MANY	
2	575J	M	7	1.015	0	0	0	0	40			2-4	BUCH	MANY	MANY	
3	461J	M	7	1.012	0	0	0	T	40	2-4			BUCH	MANY	MANY	
3	462J	F	6	1.018	0	0	0	0	95	1-3	4-6		BUCH	MANY	MANY	
3	463J	M	6	1.018	0	0	0	0	44		10-12	4-6	BUCH	MANY	MANY	
3	571J	M	8	1.040	0	0	0	0	21		1-3		BUCH	MANY	MANY	
4	531J	M	8	1.018	0	0	0	0	25	1-2		1-3	BUCH	MANY	MANY	
4	560J	M	6	1.020	0	0	0	0	51		8-10	2-4	BUCH	MANY	MANY	
4	565J	F	6	1.012	0	0	0	0	105				BUCH	MANY	MANY	
4	566J	M	6	1.010	0	0	0	0	205		1-3	2-4	BUCH	FEW	MANY	

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AD-A119 856

HAZELTON LABS AMERICA INC VIENNA VA
TOXICITY STUDIES ON ANTIRADIATION AGENTS. (U)
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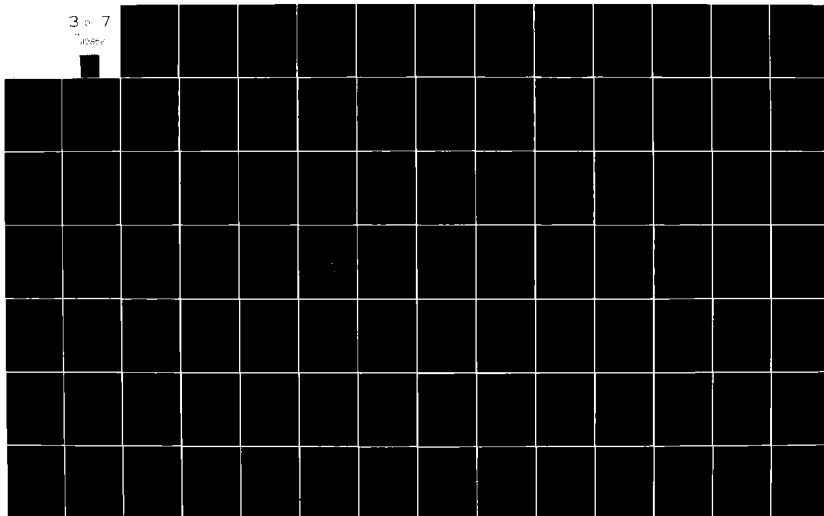


TABLE NO. 5 - TESTICULAR BODY WEIGHTS, ORGAN WEIGHTS, AND ORGAN/BODY WEIGHT RATIOS

SPECIES AND STRAIN - PUSOS COWBYS
MATERIAL - NR 2721 ROUTE OF ADMINISTRATION - INTRAPERITONEAL

VALUES - GROUP 1

ADULT WG.	TESTICULAR WEIGHT KG	TESTICULI		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
0526J	2.60	0.315	0.0121	11.250	0.4326	79.500	3.0576	2.250	0.0865
0536J	2.80	0.380	0.0135	11.250	0.4017	69.250	2.4275	4.000	0.1428
0573J	2.50	0.530	0.0212	10.100	0.4039	66.000	2.6760	2.400	0.0880
0581J	2.10	0.390	0.0185	11.000	0.5238	58.500	2.7257	2.600	0.1258
mean	2.50	0.403	0.0163	10.900	0.4405	68.287	2.7392	2.825	0.1132
ADULT									
WG.	TESTICULAR WEIGHT KG	KIDNEYS		ADRENALS		TESTES		PROSTATE	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
0520J	2.60	10.500	0.4038	0.505	0.0196	1.250	0.0480	0.235	0.0090
0526J	2.80	11.750	0.4196	0.525	0.0191	1.000	0.0357	0.200	0.0730
0573J	2.50	9.500	0.3800	0.420	0.0168	0.850	0.0340	0.255	0.0132
0581J	2.10	10.200	0.4904	0.460	0.0219	1.470	0.0700	0.190	0.0090
mean	2.50	10.512	0.4234	0.479	0.0193	1.142	0.0459	0.267	0.0105

TABLE NO. 5 - CONTINUED

ACTUAL WT.	TESTES WEIGHT KG	TITRATED WEIGHT G	HEART WEIGHT G	LIVER WEIGHT G	SPLEEN WEIGHT G	RATIOS	
						PCT	PCT
0529.1	2.40	0.270	11.500	45.000	3.000	0.0112	0.1250
0561.1	2.50	0.340	8.250	58.500	4.500	0.0136	0.1500
0572.1	2.20	0.310	11.000	54.500	2.250	0.0140	0.1022
0575.1	2.40	0.460	9.500	49.000	3.250	0.0191	0.1356
0560.1	2.37	0.345	10.062	51.750	3.250	0.0145	0.1356
0529.1	2.40	9.000	0.420	0.950	0.240	0.3750	0.0116
0561.1	2.50	8.250	0.490	0.760	0.340	0.3300	0.0152
0572.1	2.20	8.250	0.385	1.250	0.270	0.3750	0.0122
0575.1	2.40	8.000	0.400	1.000	0.605	0.3333	0.0163
0560.1	2.37	8.375	0.423	0.690	0.233	0.3533	0.0160

TABLE NO. 5 - CONTINUED

TABLES - GROUP 3

ANATOMICAL NO.	TENDON WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
06614	2.20	0.230	0.0104	9.500	0.3863	53.750	2.4421	2.500	0.1150
06624	2.20	0.460	0.0209	8.750	0.3877	51.000	2.3191	2.000	0.1362
06634	2.30	0.415	0.0180	11.000	0.4782	53.000	2.3063	4.500	0.1506
06714	2.60	0.355	0.0147	9.500	0.3555	48.250	2.0104	5.000	0.2062
06764	2.27	0.369	0.0160	9.437	0.4145	51.500	2.2690	4.000	0.1742
192									
ANATOMICAL NO.	TENDON WEIGHT KG	KIDNEYS		ADRENALS		TESTES		PROSTATE	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
06614	2.20	8.500	0.3863	0.450	0.0206	1.000	0.0454	0.325	0.0152
06624	2.20	9.000	0.4090	0.530	0.0240	1.500	0.0681	0.260	0.0112
06634	2.30	9.000	0.3913	0.455	0.0197	1.400	0.0608	0.175	0.0076
06714	2.60	8.500	0.3541	0.425	0.0177	1.000	0.0415	0.300	0.0150
06764	2.27	8.750	0.3852	0.465	0.0205	1.225	0.0540	0.288	0.0126

TABLE NO. 5 - CONTINUED

Males - Group 4

ACTUAL WT.	FEEDG. BODY WEIGHT KG.	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G.	RATIO PCT.	WEIGHT G.	RATIO PCT.	WEIGHT G.	RATIO PCT.	WEIGHT G.	RATIO PCT.
0931.4	1.80	0.260	0.0133	6.500	0.3611	40.000	2.2222	1.500	0.0273
0560.4	1.90	0.255	0.0134	9.500	0.5000	47.000	2.4726	1.800	0.0317
0565.4	1.80	0.400	0.0222	7.500	0.4166	46.000	2.6666	4.500	0.2500
0566.4	2.10	0.400	0.0233	10.000	0.4761	53.000	2.5238	2.750	0.1350
1.60	1.89	0.346	0.0180	8.375	0.4384	47.000	2.4715	2.562	0.1302
0521.4	1.40	7.250	0.4027	0.450	0.0250	1.000	0.0555	0.340	0.0112
0560.4	1.90	7.500	0.3947	0.470	0.0247	1.000	0.0526	0.125	0.0067
0565.4	1.80	7.500	0.4166	0.445	0.0247	1.000	0.0555	0.270	0.0150
0566.4	2.10	8.500	0.4047	0.545	0.0259	1.000	0.0476	0.260	0.0125
1.60	1.89	7.687	0.4047	0.477	0.0251	1.000	0.0528	0.263	0.0140

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HISTOPATHOLOGICAL EVALUATION OF MALE RHESUS MONKEYS
SACRIFICED AT TERMINATION

GROUP NO. 1
Male Monkey No. 530J

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Most follicles moderate to large in size and lined by flattened cuboidal epithelium. Activity slight.
Adrenal:	
No alterations observed.	Slight vacuolation of cells in zona fasciculata.
Eye:	
No alterations observed.	Slight artifactual separation of fibers in the substantia propria of the cornea. Artifactual distortion of the lens with formation of small open spaces which contained granular eosinophilic-staining material, representing artifactual distortion at the time of fixation and processing.
Lung:	
No alterations observed.	Numerous small accumulations of phagocytic cells surrounding small blood vessels and air passages. These cells contained brownish black, birefringent crystalline material, suggestive of mite pigment in appearance. Otherwise, not remarkable.
Liver:	
No alterations observed.	Moderate vacuolation of hepatocytes throughout the section. Minimal focal accumulations of mononuclear inflammatory cells in the liver parenchyma.

195

GROUP NO. 1
Male Monkey No. 530J (Continued)

GROSS	MICROSCOPIC
Testis:	
No alterations observed.	Seminiferous tubules small in size; and most contained only Sertoli cells and spermatogonia with occasional primary spermatocytes. Appearance typical of immature testicular tissue.
Prostate:	
No alterations observed.	Most of the acinar structures small in size with the appearance of inactive prostate tissue. Otherwise, not remarkable.
Bone Marrow:	
No alterations observed.	Large numbers of maturing elements of both erythroid and myeloid series. Slight numbers of megakaryocytes.
The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, spleen, kidney, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, nerve/muscle, and rib.	

196

GROUP NO. 1
Male Monkey No. 534J

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Several small vessels in the cerebrum surrounded by accumulations of mononuclear inflammatory cells, constituting perivascular cuffing.

There was no evidence of gliosis or neuronal degeneration.

Pituitary:

No alterations observed.

Small, fluid-filled cyst in the pars anterior.

Thyroid:

No alterations observed.

Most follicles moderate to large in size and lined by slightly flattened cuboidal epithelium. Activity slight.

Adrenal:

No alterations observed.

Slight vacuolation of the zona fasciculata.

Eye:

No alterations observed.

Artifactual separation of the substantia propria of the cornea.

Lung:

No alterations observed.

Slight amount of brownish, granular, birefringent pigment surrounding small blood vessels, suggestive in appearance of lung mite pigment. Otherwise, not remarkable.

197

GROUP NO. 1
Male Monkey No. 534J (Continued)

GROSS	MICROSCOPIC
Spleen:	
Appeared granular, on cut surface.	Lymphoid hyperplasia characterized by increased numbers of small lymphocytes at the periphery of lymphoid follicles and increased cellularity in the parenchyma of the spleen.
Liver:	
No alterations observed.	Moderate vacuolation of hepatocytes throughout the section. Small focal accumulations of mononuclear inflammatory cells.
Kidney:	
No alterations observed.	Minimal incidence of small focal accumulations of mononuclear inflammatory cells in the cortex.
Urinary Bladder:	
No alterations observed.	Small perivascular accumulations of mononuclear inflammatory cells in the submucosal tissue.
Testis:	
No alterations observed.	Appearance typical of immature testicular tissue with Sertoli cells, spermatogonia, and primary spermatocytes in seminiferous tubules; however, spermatids and maturing spermatozoa not evident.
Bone Marrow:	
No alterations observed.	Large numbers of maturing elements of both erythroid and myeloid series. Slight numbers of megakaryocytes.

198

GROUP NO. 1
Male Monkey No. 534J (Continued)

GROSS

MICROSCOPIC

The following organs were not altered grossly or microscopically: spinal cord, heart, gallbladder, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, prostate, nerve/muscle, and rib.

GROUP NO. 1
Male Monkey No. 573J

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Most follicles moderate to large in size and lined by flattened cuboidal epithelium. Activity slight.
Adrenal:	
No alterations observed.	Slight to moderate vacuolation of zona fasciculata
Eye:	
No alterations observed.	Slight artifactual distortion of the cornea. Slight artifactual distortion of the lens.
Heart:	
No alterations observed.	Single small focus of nonsuppurative myocarditis with focal accumulations of mononuclear inflammatory cells.
Lung:	
No alterations observed.	Small amount of brownish, granular, birefringent pigment surrounding small blood vessels, suggestive of mite pigment in appearance. Several small focal areas of lymphoreticular cell proliferation.
Spleen:	
No alterations observed.	Slight lymphoid hyperplasia. Slight increased numbers of lymphocytes in lymphoid follicles and interfollicular tissue.
Liver:	
No alterations observed.	Moderate vacuolation of hepatocytes throughout the section.

200

GROUP NO. 1
Male Monkey No. 573J (Continued)

GROSS

MICROSCOPIC

Urinary Bladder:

No alterations observed.

Minimal focal cystitis with focal accumulations of mononuclear inflammatory cells some of which were in the mucosa.

Testis:

No alterations observed.

Microscopic appearance typical of immature testicular tissue.

Bone Marrow:

No alterations observed.

Moderately large numbers of maturing elements of both erythroid and myeloid series.

Slight numbers of megakaryocytes.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, gallbladder, kidney, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, prostate, nerve/muscle, and rib.

201

GROUP NO. 1
Male Monkey No. 581J

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Most follicles moderate to large in size and lined by flattened cuboidal epithelium.

Activity slight.

Adrenal:

No alterations observed.

Slight to moderate vacuolation of the zona fasciculata.

Small mineralized area at the corticomedullary junction.

Eye:

No alterations observed.

Slight artifactual distortion of the cornea and posterior portion of the lens.

Lung:

No alterations observed.

Slight amount of brownish, granular birefringent pigment surrounding small blood vessels and occasional focal accumulation of foamy macrophages.

Otherwise, not remarkable.

Liver:

No alterations observed.

Slight to moderate vacuolation of hepatocytes throughout the section.

Focal areas of nonsuppurative hepatitis characterized by focal accumulations of mononuclear inflammatory cells and coagulation necrosis of hepatocytes, distribution of these lesions, primarily, in the subcapsular region; although, occasional foci noted throughout the section.

GROUP NO. 1
Male Monkey No. 581J (Continued)

GROSS

MICROSCOPIC

Kidney:

No alterations observed.

Focal interstitial nephritis characterized by accumulations of mononuclear inflammatory cells, necrosis of tubule epithelium, and regeneration of tubule epithelium.

Testis:

No alterations observed.

Histologic picture typical of immature testicular tissue.

Bone Marrow:

No alterations observed.

Large numbers of maturing elements of both erythroid and myeloid series.

Slight numbers of megakaryocytes.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, spleen, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, prostate, nerve/muscle, and rib.

203

GROUP NO. 2
Male Monkey No. 529J

GROSS

MICROSCOPIC

Liver:

No alterations observed.

Slight vacuolation of hepatocytes throughout
the section, most pronounced in centrilobular
region.

Kidney:

No alterations observed.

Minimal interstitial nephritis with focal
accumulations of mononuclear inflammatory cells.

204

GROUP NO. 2
Male Monkey No. 561J

GROSS

MICROSCOPIC

Liver:

No alterations observed.

Slight vacuolation of hepatocytes throughout
the section.

The following organ was not altered grossly or microscopically: kidney.

205

GROUP NO. 2
Male Monkey No. 572J

GROSS

MICROSCOPIC

Liver:

No alterations observed.

Slight to moderate vacuolation of hepatocytes
throughout the section.

Minimal nonsuppurative pericholangitis.

Slight degree of hepatitis characterized by
focal accumulations of neutrophils, primarily,
in the subcapsular region.

Kidney:

No alterations observed.

Minimal interstitial nephritis characterized by
focal accumulations of mononuclear inflammatory
cells in the renal medulla.

206

GROUP NO. 2
Male Monkey No. 575J

GROSS

MICROSCOPIC

Liver:

No alterations observed.

Slight vacuolation of hepatocytes in the
centrilobular regions.

Kidney:

No alterations observed.

Minimal interstitial nephritis with focal
accumulations of mononuclear inflammatory
cells in the renal medulla.

207

GROUP NO. 3
Male Monkey No. 461J

GROSS

MICROSCOPIC

Liver:

No alterations observed.

Moderate vacuolation of hepatocytes throughout the section.

Occasional small focus of nonsuppurative hepatitis characterized by focal accumulations of mononuclear inflammatory cells and necrotic hepatocytes.

Vasculitis affecting the branches of the hepatic arteries in the portal triads with infiltrations of mononuclear inflammatory cells into the vessel walls and in the perivascular tissue.

Slight nonsuppurative pericholangitis.

Kidney:

No alterations observed.

Slight interstitial nephritis characterized by focal accumulations of mononuclear inflammatory cells, regenerative tubule epithelium, and perivascular accumulations of mononuclear cells.

Slight amount of eosinophilic-staining, granular material in Bowman's space of numerous glomeruli representing protein leakage.

In several of the areas of inflammation, eosinophilic-staining intranuclear inclusion bodies noted.

208

GROUP NO. 3
Male Monkey No. 462J

GROSS	MICROSCOPIC
Liver:	
No alterations observed.	Slight to moderate vacuolation of hepatocytes, most pronounced in centrilobular region. Slight nonsuppurative pericholangitis.
Kidney:	
No alterations observed.	Minimal interstitial nephritis characterized by focal accumulations of mononuclear inflammatory cells in the cortex and medulla.
Unusual Lesion:	
Lung - A few lung mite lesions.	Section not examined microscopically.

209

GROUP NO. 3
Male Monkey No. 463J

GROSS

MICROSCOPIC

Liver:

No alterations observed.

Slight vacuolation of hepatocytes, predominantly
in the centrilobular region.

The following organ was not altered grossly or microscopically: kidney.

210

GROUP NO. 3
Male Monkey No. 571J

GROSS

MICROSCOPIC

Liver:

No alterations observed.

Slight nonsuppurative pericholangitis.

Slight vacuolation of hepatocytes throughout the section, predominantly in the centrilobular region.

Kidney:

No alterations observed.

Minimal interstitial nephritis with focal accumulations of mononuclear inflammatory cells.

Unusual Lesion:

Spleen - Slightly enlarged
with rough surface.

Cut surface appeared slightly
granular.

Section not examined microscopically.

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GROUP NO. 4
Male Monkey No. 531J

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Large peripheral follicles lined by flattened epithelium. Follicles in center of gland, moderate in size and lined by slightly flattened cuboidal epithelium. Activity slight to moderate.
Adrenal:	
No alterations observed.	Slight vacuolation of cells in zona fasciculata. A small concentric focus of mineralization at the corticomedullary junction.
Eye:	
No alterations observed.	Slight artifactual distortion of the cornea and lens.
Lung:	
No alterations observed.	Occasional small focal area of lymphoreticular cell proliferation. One of the small muscular arteries in the peribronchial region revealed intimal thickening.
Liver:	
No alterations observed.	Slight vacuolation of hepatocytes throughout the section, especially in the centrilobular region.

2/2

GROUP NO. 4
Male Monkey No. 531J (Continued)

GROSS	MICROSCOPIC
Testis:	
No alterations observed.	Seminiferous tubules composed of Sertoli cells, spermatogonia, occasional primary spermatocytes. Spermatids and maturing spermatozoa were not evident. Appearance typical of immature testicular tissue.
Prostate:	
No alterations observed.	Single small focus of reticuloendothelial cell proliferation, constituting a small focal area of nonsuppurative prostatitis.
Nerve/Muscle:	
No alterations observed.	Nerve tissue essentially normal in appearance; however, a focal area of nonsuppurative myositis characterized by slight numbers of mononuclear inflammatory cells, hemosiderin-laden macrophages, occasional necrotic muscle fibers, and marked proliferation of sarcolemmal nuclei in an attempt at muscle fiber regeneration. Fibroplasia evident.
Bone Marrow:	
No alterations observed.	Large numbers of maturing elements of both erythroid and myeloid series. Slight numbers of megakaryocytes.

GROUP NO. 4
Male Monkey No. 531J (Continued)

GROSS

MICROSCOPIC

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, spleen, kidney, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, and rib.

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GROUP NO. 4
Male Monkey No. 560J

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Most follicles moderate to large in size and lined by flattened cuboidal epithelium. Activity slight.
Adrenal:	
No alterations observed.	Slight to moderate vacuolation of the zona fasciculata. Concentric foci of mineralization at the corticomedullary junction. Small focus of adipose tissue in the medulla.
Eye:	
No alterations observed.	Slight artifactual distortion of the cornea. Severe artifactual distortion of the lens.
Lung:	
No alterations observed.	Slight amount of brownish, granular, birefringent pigment, suggestive of lung mite pigment. Focal area of artifactual collapse of the lung parenchyma.
Liver:	
No alterations observed.	Slight to moderate vacuolation of hepatocytes, most pronounced in the centrilobular region.
Testis:	
No alterations observed.	Appearance typical of immature testicular tissue.
Prostate:	
No alterations observed.	Section not available for examination.

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GROUP NO. 4
Male Monkey No. 560J (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Moderately large numbers of maturing elements
of both erythroid and myeloid series.

Slight numbers of megakaryocytes.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, spleen, kidney, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, nerve/muscle, and rib.

GROUP NO. 4
Male Monkey No. 565J

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Follicles moderate to large in size and lined
by flattened cuboidal epithelium.

Activity slight.

Adrenal:

No alterations observed.

Slight to moderate vacuolation of zona fasciculata

Eye:

No alterations observed.

Slight artifactual distortion of the cornea and
lens.

Lung:

No alterations observed.

Small area of artifactual collapse.
Occasional small focus of lymphoreticular cell
proliferation.
Slight amount of brownish, granular, birefringent
pigment, suggestive of lung mite infestation.

Spleen:

Appeared enlarged.

Proliferation of lymphoreticular elements with
increased prominence of germinal centers and
increased numbers of reticulum cells in the
interfollicular tissue.

Liver:

No alterations observed.

Moderate vacuolation of hepatocytes throughout
the section, most pronounced in centrilobular
region.
Occasional focus of necrotic hepatocytes
surrounded by mononuclear inflammatory cells.
Slight nonsuppurative pericholangitis.

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GROUP NO. 4
Male Monkey No. 565J (Continued)

GROSS	MICROSCOPIC
Kidney:	
No alterations observed.	Minimal interstitial nephritis with focal accumulations of mononuclear inflammatory cells.
Testis:	
No alterations observed.	Appearance typical of immature testicular tissue.
Bone Marrow:	
No alterations observed.	Large numbers of maturing elements of both erythroid and myeloid series.
The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, prostate, nerve/muscle, and rib.	

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GROUP NO. 4
Male Monkey No. 566J

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Small focal accumulations of glial cells with perivascular accumulations of mononuclear inflammatory cells in the cerebral cortex.

Thyroid:

No alterations observed.

Most follicles moderate to large in size and lined by flattened cuboidal epithelium. Activity slight to moderate.

Adrenal:

No alterations observed.

Slight vacuolation of zona fasciculata.

Eye:

No alterations observed.

Artifactual distortion of the cornea and lens.

Lung:

A few lung mite lesions.

Slight amount of brownish, granular, birefringent pigment surrounding small blood vessels, suggestive in appearance of mite pigment. Occasional small focal proliferation of lymphoreticular cells. Small area of artifactual collapse.

Liver:

No alterations observed.

Slight vacuolation of hepatocytes throughout the section. Minimal nonsuppurative pericholangitis characterized by the presence of mononuclear inflammatory cells. Occasional focus of necrotic hepatocytes surrounded by mononuclear inflammatory cells. Slight nonsuppurative pericholangitis.

219

GROUP NO. 4
Male Monkey No. 566J (Continued)

GROSS	MICROSCOPIC
Kidney:	
No alterations observed.	Minimal interstitial nephritis with focal accumulations of mononuclear inflammatory cells.
Large Intestine:	
No alterations observed.	Slight increased numbers of mononuclear inflammatory cells in the submucosa.
Urinary Bladder:	
No alterations observed.	Minimal incidence of focal nonsuppurative cystitis characterized by accumulations of mononuclear inflammatory cells in the mucosa and submucosa.
Testis:	
No alterations observed.	Histological appearance typical of immature testicular tissue.
Prostate:	
No alterations observed.	Focal nonsuppurative prostatitis characterized by focal accumulations of mononuclear inflammatory cells.
Bone Marrow:	
No alterations observed.	Moderately large numbers of maturing elements of both erythroid and myeloid series. Slight numbers of megakaryocytes.
The following organs were not altered grossly or microscopically: spinal cord, pituitary, heart, gallbladder, spleen, stomach, pancreas, small intestine, mesenteric lymph node, nerve/muscle, and rib.	

KEY TO DETAILED HISTOPATHOLOGY INCIDENCE TABLE

N = No Section

X = Not Remarkable

A = Autolysis

P or ✓ = Present or Taken

0 = Absent

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderate to Severe

5 = Severe

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DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS	ANIMAL NUMBER	MALES															
		GROUP NUMBER															
		1				2				3				4			
		530J	534J	573J	581J	529J	561J	572J	575J	461J	462J	463J	571J	531J	560J	565J	566J
BRAIN		X		X	X								X	X	X		
Perivascular Cuffing			P														
Glial Nodules																2	
SPINAL CORD		X	X	X	X								X	X	X	X	
PITUITARY		X		X	X								X	X	X	X	
Cysts			P														
THYROID																	
Level of Activity		2	2	2	2								2-3	2	2	2-3	
ADRENAL																	
Vacuolation of Zona Fasciculata		2	2	2-3	2-3								2	2-3	2-3	2	
EYE																	
Artifactual Distortion		P	P	P	P								P	P	P	P	
HEART		X	X		X								X	X	X	X	
Focal Nonsuppurative Myocarditis																	
					2												
LUNG																	
Artifactual Compression															1	2	
Pigment		2	2	2	2										2	2	
Lymphoreticular Cell Proliferation															2	2	
					2								2		2	2	
GALLBLADDER		X	X	X	X								X	X	X	X	
SPLEEN		X											X	X		X	
Lymphoid Hyperplasia			P	P													
Proliferation of Reticulum Cells																P	
LIVER																	
Hepatitis						2		2		2					2	2	
Necrosis						2				2							
Pericholangitis								1		2	2	2				1	
Vacuolation		3	3	3	2-3	2	2	2-3	2	3	2-3	2	2	2	2-3	3	
Mononuclear Inflammatory Cells		1	2		1					1						1	
Vacuilitis										P							

DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS	ANIMAL NUMBER	MALES											
		GROUP NUMBER											
		1				2				3			
		530J	534J	573J	581J	529J	561J	572J	575J	461J	462J	463J	571J
KIDNEY		X		X			X					X	X
Intranuclear Inclusion										P			
Interstitial Nephritis					2	1		1	1	2	1		1
Regenerative Epithelium					P					P			
Proteinaceous Material in Bowman's Space										2			
Mononuclear Inflammatory Cells			1		1	1		1	1	1	1		1
STOMACH		X	X	X	X								X
PANCREAS		X	X	X	X								X
SMALL INTESTINE		X	X	X	X								X
LARGE INTESTINE		X	X	X	X								X
Mononuclear Cell in Submucosa													
MESENTERIC LYMPH NODE		X	X	X	X								X
URINARY BLADDER		X			X								X
Cystitis				1									X
Mononuclear Inflammatory Cells in Submucosa			2	1									
TESTIS													
Immature		P	P	P	P								P
PROSTATE		X	X	X	X								N
Prostatitis													P
NERVE WITH MUSCLE		X	X	X	X								X
Proliferation of Sarcolemmal Nuclei													X
Fibroplasia													5
Mononuclear Inflammatory Cells													P
RIB		X	X	X	X								2
BONE MARROW													
Hematogenic Activity		5	5	4	5								5

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Sponsor: Walter Reed Army Institute of Research

Date: November 4, 1969

Material: WR 2529 AK (AF 92486) and WR 2529 RCL

Subject: REPORT NO. 21
Acute Oral Dose Range - Mice
Acute Oral Administration - Mice
Project No. 193-408

Date Received September 3, 1969.

Description

WR 2529 AK (AF 92486): Fine, white powder with a disagreeable odor.

WR 2529 RCL: White powder with a disagreeable odor.

SUMMARY

A preliminary study (administration of each test material to three groups of two adult albino mice each at dosage levels of 100, 1000, and 10,000 mg/kg of body weight) served as an indicator of the acute oral toxicity ranges of WR 2529 AK (AF 92486) and WR 2529 RCL.

Following this preliminary study, each test material was more extensively evaluated for acute oral toxicity by oral intubation to groups of 10 adult albino mice each. WR 2529 AK (AF 92486) was administered to three groups of mice at dosage levels of 6810, 10,000, and 14,700 mg/kg of body weight; WR 2529 RCL was administered to six groups of mice at dosage levels of 2150, 3160, 4640, 6810, 10,000, and 14,700 mg/kg of body weight.

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The acute oral LD₅₀ of WR 2529 AK (AF 92486), obtained from this second study, is 8803 mg/kg of body weight (confidence limits - 7625 mg/kg to 10,164 mg/kg of body weight). The acute oral LD₅₀ of WR 2529 RCL is 9664 mg/kg of body weight (confidence limits - 8412 mg/kg to 11,102 mg/kg of body weight).

ACUTE ORAL DOSE RANGE - MICE

Procedure For each compound, oral intubation to three groups of two male rats each at dosage levels of 100, 1000, and 10,000 mg/kg of body weight. Initial weight ranged from 18 to 26 grams, and the animals were fasted overnight prior to dosing. Observations for mortality and signs of effect were made for seven days, the survivors sacrificed (cervical dislocation), and necropsies performed. The diluent for WR 2529 AK (AF 92486) was distilled water; the suspending agent for WR 2529 RCL was a solution of 0.5% carboxymethylcellulose in 0.9% saline.

Results

WR 2529 AK (AF 92486):

Mortality Data - One death occurred 24 hours postdose at the 10,000 mg/kg level with no toxic signs observed prior to death.

Principal Toxic Effects - No toxic signs observed.

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Major Necropsy Findings -

(At Death) Pyloric portion of stomach red; small intestines red
and containing small amount of fluid; kidneys dark red.

(At Sacrifice) No observable gross pathology.

WR 2529 RCL:

Mortality Data - No deaths occurred at any of the levels tested.

Principal Toxic Effects - No toxic signs observed.

Major Necropsy Findings -

(At Sacrifice) No observable gross pathology.

Procedure WR 2529 AK (AF 92486) was administered by oral intubation to three groups of 10 male rats each (Carbia strain) at dosage levels of 6810, 10,000, and 14,700 mg/kg of body weight; WR 2529 RCL was administered to six groups of 10 male mice each (Carbia strain) at dosage levels of 2150, 3160, 4640, 6810, 10,000, and 14,700 mg/kg of body weight each. The diluent for WR 2529 AK (AF 92486) was distilled water; the suspending agent for WR 2529 RCL was a solution of 0.5% carboxymethylcellulose in 0.9% saline. Initial body weight ranged from 16 to 29 grams, and the animals were fasted overnight prior to dosing. Observations for mortality and signs of effects were made immediately after dosing; at one, four, and 24 hours; and once daily thereafter for a total of 14 days. Gross necropsy was performed on all animals which died during the study and on those sacrificed (cervical dislocation) at termination. Mortality data was analyzed statistically by the method of Finney, D. J., Probit Analysis, Cambridge University Press, 1952.

Results

WR 2529 AK (AF 92486):

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Mortality Data - Values below represent the number of animals dead per
number of animals tested, cumulative.

Dose mg/kg	Concentration of Solution %	Immediate	Time of Death			Days 2-14
			1	Hours 4	24	
6,810	30	0/10	0/10	1/10	1/10	1/10
10,000	30	0/10	2/10	2/10	8/10	8/10
14,700	30	0/10	8/10	10/10		

LD₅₀, mg/kg - 8803

Confidence Limits (95%), mg/kg - 7625 to 10,164

Slope - 6.094

Graphical presentation of the dose-response analysis is appended to this report.

Principal Toxic Effects - Depression was noted at the 6810 mg/kg level immediately following intubation through Day 2. Depression, labored respiration, ptosis, diarrhea, and hunched appearance (10,000 mg/kg level only) were followed by partial mortality at the 10,000 mg/kg level by 24 hours and total mortality at the 14,700 mg/kg level by four hours. Survivors at the 10,000 mg/kg level appeared normal by Day 6.

Major Necropsy Findings -

(At Death) Stomach and intestines containing yellow fluid resembling compound; pyloric portion of stomach red in appearance; intestines red in appearance; liver and kidneys dark red in color (all observed at the 10,000 and 14,700 mg/kg levels).

(At Sacrifice) No observable gross pathology.

WR 2529 RCL:

Mortality Data - Values below represent the number of animals dead per
number of animals tested, cumulative.

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Dose mg/kg	Concentration of Solution %	Time of Death Immediate	Hours			Days 2-14
			1	4	24	
2,150	30	0/10	0/10	0/10	0/10	0/10
3,160	30	0/10	0/10	0/10	0/10	0/10
4,640	30	0/10	0/10	0/10	0/10	0/10
6,810	30	0/10	0/10	0/10	0/10	0/10
10,000	30	0/10	0/10	0/10	6/10	6/10
14,700	30	0/10	7/10	8/10	10/10	

LD₅₀, mg/kg - 9664

Confidence Limits (95%), mg/kg - 8412 to 11,102

Slope - 6.208

Graphical presentation of the dose-response analysis is appended to this report.

Principal Toxic Effects - No toxic signs were noted at the 2150 and 3160 mg/kg levels. Toxic signs were evident at the 4640, 6810, and 10,000 mg/kg levels by four or 24 hours postdose and included the following: depression, squinting, hunched appearance (6810 and 10,000 mg/kg levels only), piloerection (6810 and 10,000 mg/kg levels only), diarrhea (10,000 mg/kg level only), and labored respiration (10,000 mg/kg level only). Animals at the 4640 and 6810 mg/kg levels appeared normal by Day 4 and survivors at the 10,000 mg/kg level appeared normal by Day 7. At the 14,700 mg/kg level, depression, diarrhea, labored respiration, and ptosis were noted immediately or one hour following intubation and were followed by total mortality at 24 hours.

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Major Necropsy Findings -

(At Death) Stomach and intestines distended with white fluid resembling compound (10,000 and 14,700 mg/kg levels); stomach lining thin in appearance (10,000 mg/kg level); stomach and intestines blanched and smooth (14,700 mg/kg level); pyloric portion of stomach dark red (14,700 mg/kg level); liver and kidneys dark red (14,700 mg/kg level).

(At Sacrifice) No observable gross pathology.

Submitted by



MARCELINA B. POWERS, D.V.M., M.S.
Project Manager, Drugs and
Industrial Chemicals
Toxicology-Bioscience Laboratory

Report Preparation: Lambert
Supervision: Fink

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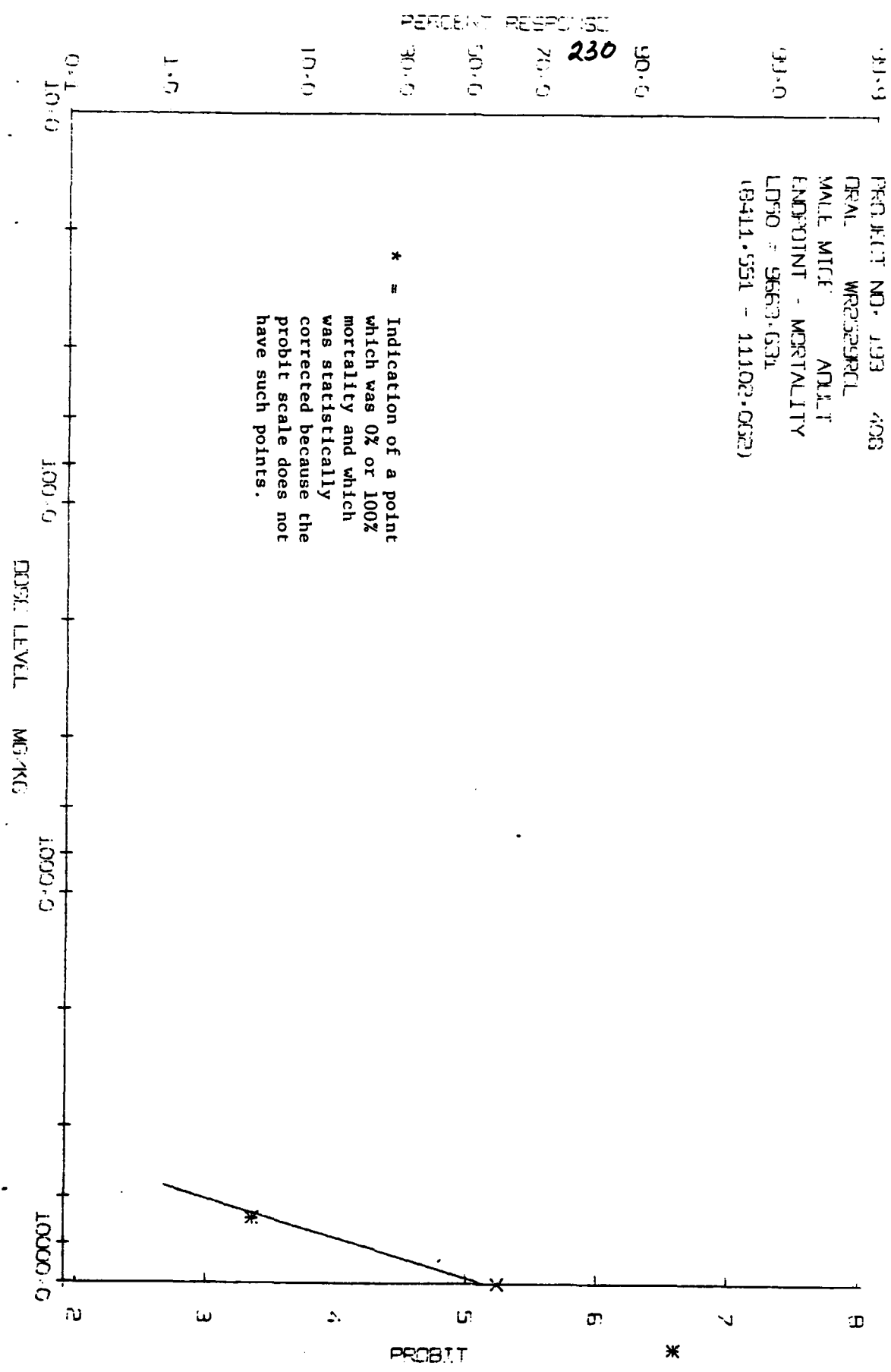
PROJECT NO. 193 408
ORAL WR2529RL
MALE MICE ADULT
ENDPOINT - MORTALITY
LD50 = 9663.631
(8411.551 - 11102.062)

* = Indication of a point which was 0% or 100% mortality and which was statistically corrected because the probit scale does not have such points.

Dose Level (MG/KG)	Percent Response
10.0	0.1
100.0	0.1
1000.0	0.1
10000.0	0.1
10.0	10.0
100.0	10.0
1000.0	10.0
10000.0	10.0
10.0	30.0
100.0	30.0
1000.0	30.0
10000.0	30.0
10.0	50.0
100.0	50.0
1000.0	50.0
10000.0	50.0
10.0	70.0
100.0	70.0
1000.0	70.0
10000.0	70.0
10.0	90.0
100.0	90.0
1000.0	90.0
10000.0	90.0
10.0	99.9
100.0	99.9
1000.0	99.9
10000.0	99.9

* = Indication of a point which was 0% or 100% mortality and which was statistically corrected because the probit scale does not have such points.

PROJECT NO. 103 408
 ORAL WR2229RCL
 MALE MICE ADULT
 ENDPOINT - MORTALITY
 LD50 = 9663.631
 (8411.551 - 11102.062)



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HAZLETON LABORATORIES, INC.
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Sponsor: Walter Reed Army Institute of Research

Date: November 19, 1969

Material: WR 2823 (AU 69115)

Subject: REPORT NO. 23
Acute Oral - Mice
Project No. 193-409

Date Received September 18, 1969.

Description Fine, white powder with no noticeable odor.

Purity Assumed to be 100% active ingredient.

SUMMARY

WR 2823 (AU 69115) was evaluated for acute oral toxicity by gastric intubation to six groups of 10 male albino mice each. The acute oral LD₅₀ of the compound was 940 mg/kg of body weight (confidence limits, 760 to 1163 mg/kg of body weight). Toxic effects produced by WR 2823 (AU 69115) consisted of depression, labored respiration, ptosis, comatose appearance, intermittent tremors, and cold to touch.

PROCEDURE

The compound was administered by oral intubation to six groups of 10 male mice (Carbia strain) each. The solvent was distilled water. Initial body weight ranged from 18 to 27 grams, and the animals were fasted overnight prior to dosing. Observations for mortality and signs of effects were made immediately

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after dosing; at one, four, and 24 hours; and once daily thereafter for a total of 14 days. Gross necropsy was performed on all animals which died during the study and on those sacrificed (cervical dislocation) at termination. Mortality data were analyzed statistically by the method of Litchfield, J. T., and Wilcoxon, F., J. Pharmacol. Exptl. Therap., 96, 99, 1949.

RESULTS

Mortality Data Values below represent the number of animals dead per number of animals tested, cumulative.

<u>Dose</u> mg/kg	<u>Concentration</u> <u>of Solution</u> %	<u>Time of Death</u>		
		<u>Immediate</u>	<u>Hours</u> 1-24	<u>Days</u> 2-14
100	1	0/10	0/10	1/10*
159	1	0/10	0/10	0/10
251	1	0/10	0/10	0/10
398	1	0/10	0/10	1/10*
631	2	0/10	0/10	0/10
1000	2	0/10	5/10	6/10

LD₅₀, mg/kg - 940

Confidence Limits (95%), mg/kg - 760 to 1163

Slope - 6.433

* These deaths were considered incidental and were not used in LD₅₀ calculations.

Graphical presentation of the dose-response analysis is appended to this report.

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Principal Toxic Effects One death on Day 4 at the 100 mg/kg level and one death on Day 9 at the 398 mg/kg level, both preceded by hunched appearance, were considered to be incidental deaths. Animals at the 251 and 398 mg/kg levels exhibited piloerection and depression through four or 48 hours. Depression, labored respiration, ptosis, comatose appearance, intermittent tremors, and cold to touch were signs noted prior to partial mortality by 48 hours at the 1000 mg/kg level. Survivors at this level appeared hunched and thin through Day 9.

Major Necropsy Findings

At Death: Lungs dark red in color (100 mg/kg level); clear, yellowish fluid in stomach (1000 mg/kg level); stomach lining smooth and thin (1000 mg/kg level); blood vessels in stomach and intestinal tract dilated (1000 mg/kg level); renal cortex and medulla dark red with no differentiation between cortex and medulla (1000 mg/kg level).

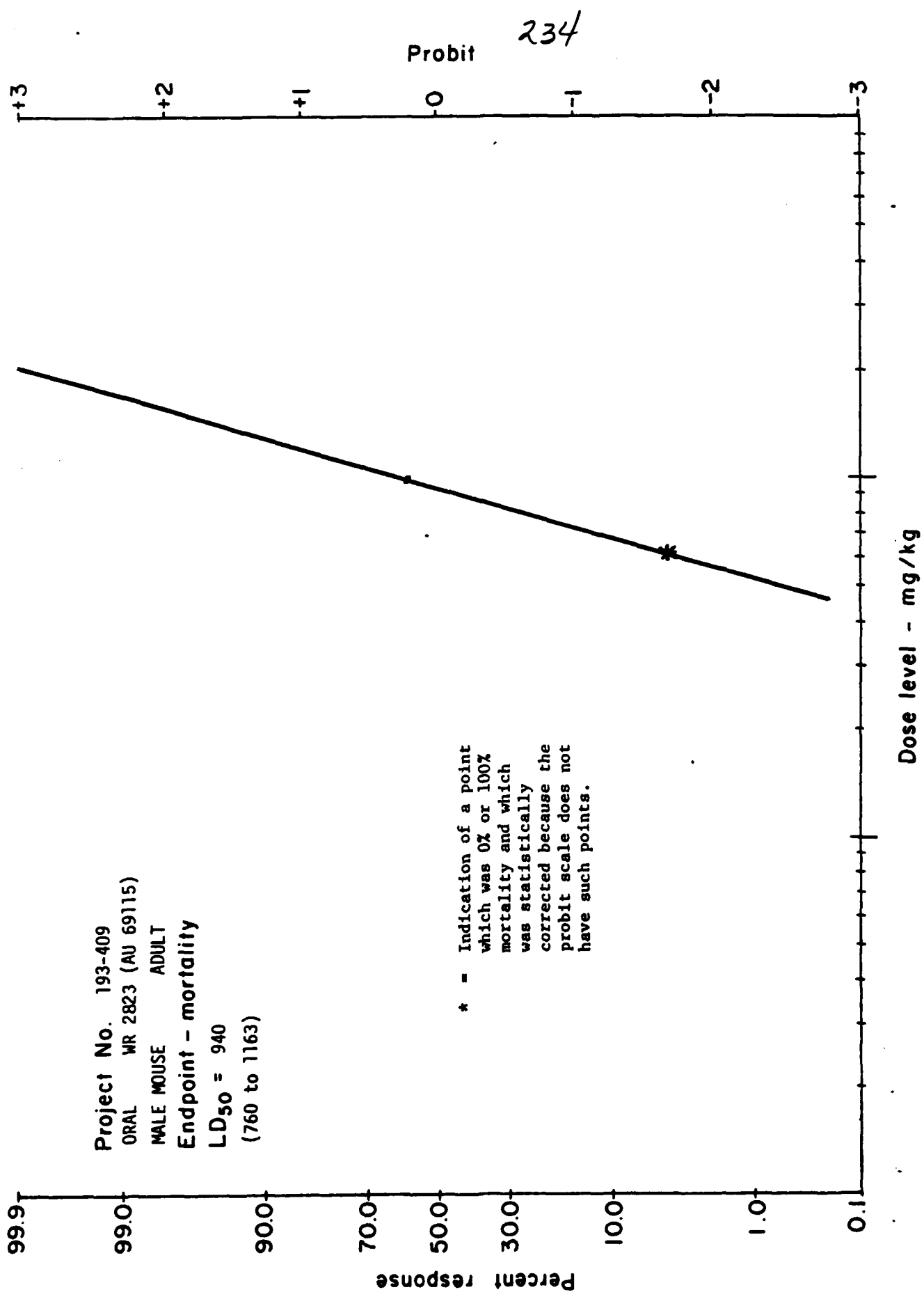
At Sacrifice: No gross pathology noted.

Submitted by

Frederick E. Rens
for MARCELINA B. POWERS, D.V.M., M.S.
Project Manager, Drugs and
Industrial Chemicals
Toxicology-Biosciences Laboratory

Report Preparation: Lambert
Supervision: Fink

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HAZLETON LABORATORIES, INC.
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Sponsor: Walter Reed Army Institute of Research

Date: September 23, 1970

Material: WR-2823 (AU 69115)

Subject: REPORT NO. 36
Pathology Report
Two-Week Intravenous Toxicity Study - Rats
Project No. 193-410

This pathology report is a supplement to Report No. 31 dated, January 23, 1970, entitled "Two-Week Intravenous Toxicity Study - Rats" on compound, WR-2823 (AU 69115). In that report the results were reported without the histopathologic evaluation of tissues.

Submitted by


FREDERICK E. RENO, Ph.D.
Project Manager, Drugs and
Industrial Chemicals Department
Toxicology-Biosciences Laboratory

Pathology by


ROBERT P. KWAPIEN, D.V.M., Ph.D.
Staff Pathologist

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HISTOPATHOLOGICAL EVALUATION OF MALE AND FEMALE ALBINO RATS
SACRIFICED AT TERMINATION

WR-2823 (AU 69115)

GROUP NO. 1

Male Rat No. 82-969

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Slight nonsuppurative meningocephalitis.

Slight focal gliosis.

Spinal Cord:

No alterations observed.

In gray matter of one spinal cord section an
area of focal gliosis.

Pituitary:

No alterations observed.

Only pars distalis included in section.

Otherwise, not remarkable.

Thyroid:

No alterations observed.

Chiefly, medium- and large-sized follicles.

Follicular epithelium chiefly low cuboidal
or cuboidal.

Activity moderate.

Adrenal:

No alterations observed.

Minimal vacuolation of cells in zona
fasciculata.

Eye:

No alterations observed.

Some shatter of the lense and artifactual
displacement of retina.

Section does not included optic nerve.

Otherwise, not remarkable.

GROUP NO. 1
Male Rat No. 82-696 (Continued)

GROSS

MICROSCOPIC

Heart:

No alterations observed.

Minimal interstitial myocarditis.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Minimal peribronchial lymphoid hyperplasia.

Spleen:

No alterations observed.

Slight extramedullary hematopoiesis.

Liver:

No alterations observed.

Minimal chronic pericholangitis.

Occasional foci of nonsuppurative hepatitis
with a component of histiocytic cells.

Kidney:

No alterations observed.

Slight interstitial nephritis.

Occasional foci of regenerating tubular
epithelium.

Pancreas:

No alterations observed.

Slight chronic pancreatitis.

Large Intestine:

No alterations observed.

Nematodiasis.

Mesenteric Lymph Node:

No alterations observed.

Section not available for examination.

Testis:

No alterations observed.

Activity appeared to be within normal limits.

GROUP NO. 1
Male Rat No. 82-696 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Moderate numbers of megakaryocytes.

Moderate numbers of maturing erythroid and
myeloid cells.

Activity appeared to be within normal limits.

Section rather small.

The following organs were not altered grossly or microscopically: stomach,
small intestine, urinary bladder, prostate, and bone.

GROUP NO. 1
Male Rat No. 82-700

GROSS

MICROSCOPIC

Pituitary:

No alterations observed.

Small, dilated space present between pars intermedia and pars distalis which contained small numbers of unidentifiable cells, erythrocytes, and eosinophilic material.

Thyroid:

No alterations observed.

Small- and large-sized follicles present with small follicles predominating.
Epithelium lining follicles chiefly cuboidal or high cuboidal.
Activity judged to be moderately high.

Adrenal:

No alterations observed.

Moderate vacuolation of cells in zona fasciculata.

Eye:

No alterations observed.

Cornea folded.
Segments of iris, ciliary process, and retina missing.
Section does not include optic nerve.
Remaining tissues not remarkable.

Heart:

No alterations observed.

Moderate chronic myocarditis and endocarditis.
One rather large focus of chronic inflammation present in which many histiocytes and mononuclear cells infiltrated the myocardium and endocardium.

GROUP NO. 1
Male Rat No. 82-700 (Continued)

GROSS	MICROSCOPIC
	In affected areas, a few degenerating myocardial fibers persist.
	Mild chronic epicarditis.
Lung:	
Dark red areas on all lobes.	Slight interstitial penumonitis.
	Moderate peribronchiolar lymphoid hyperplasia.
Spleen:	
No alterations observed.	Slight numbers of extramedullary hematopoetic foci.
Liver:	
Left lateral lobe contained small, yellow foci.	Occasional foci of nonsuppurative hepatitis.
	Focal vacuolation of liver cells suggesting lipoidosis.
Large Intestine:	
No alterations observed.	Nematodiasis.
Mesenteric Lymph Node:	
No alterations observed.	Activity appeared to be within normal limits.

241

GROUP NO. 1
Male Rat No. 82-700 (Continued)

GROSS

MICROSCOPIC

Testis:

No alterations observed.

Activity appeared within normal limits.

Bone Marrow:

No alterations observed.

Many megakaryocytes present.

Numerous maturing myeloid and erythroid
cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain,
spinal cord, kidney, stomach, pancreas, small intestine, urinary bladder, prostate,
and bone.

GROUP NO. 1
Male Rat No. 82-702

GROSS	MICROSCOPIC
Brain:	
No alterations observed.	Slight nonsuppurative meningoencephalitis, perivascular cuffing, and focal gliosis.
Spinal Cord:	
No alterations observed.	Focal nonsuppurative meningitis.
Pituitary:	
No alterations observed.	Only pars distalis included in section. Otherwise, not remarkable.
Thyroid:	
No alterations observed.	Small-, medium-, and large-sized follicles present. Epithelium lining follicles chiefly cuboidal. Activity moderate.
Adrenal:	
No alterations observed.	Adrenal medulla not included in section. Moderate vacuolation of cells in zona fasciculata.
Eye:	
No alterations observed.	Optic nerve not included on section. Otherwise, not remarkable.
Heart:	
No alterations observed.	Slight chronic myocarditis, epicarditis, and endocarditis.
Lung:	
No alterations observed.	Moderate interstitial pneumonitis. Mild peribronchiolar lymphoid hyperplasia.

GROUP NO. 1
Male Rat No. 82-702 (Continued)

GROSS

MICROSCOPIC

Spleen:

Appeared enlarged.

Moderate to slight extramedullary hematopoietic activity.

Liver:

No alterations observed.

Slight focal nonsuppurative hepatitis.

Slight chronic pericholangitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis.

Small areas of tubular regeneration in cortex.

Slight chronic pyelitis.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared within normal limits.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: stomach, pancreas, small intestine, large intestine, urinary bladder, testis, prostate, and bone.

244

GROUP NO. 1
Male Rat No. 82-703

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Slight nonsuppurative meningocephalitis.

Slight focal gliosis.

Spinal Cord:

No alterations observed.

One section of spinal cord incomplete.

Otherwise, not remarkable.

Thyroid:

No alterations observed.

Small-, medium, and large-sized follicles with
the small follicles predominating.

Epithelium lining follicles chiefly cuboidal.

Activity moderate.

Adrenal:

No alterations observed.

Slight generalized vacuolation of cells in
zona fasciculata.

Eye:

No alterations observed.

Section of optic nerve not included.

Otherwise, not remarkable.

Heart:

No alterations observed.

Slight myocarditis and epicarditis chronic
in nature.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Slight perivascular lymphoid hyperplasia.

Spleen:

Appeared slightly enlarged.

Slight to moderate extramedullary hematopoietic
activity.

GROUP NO. 1
Male Rat No. 82-703 (Continued)

GROSS

MICROSCOPIC

Liver:

No alterations observed.

Slight chronic pericholangitis.

Slight focal nonsuppurative hepatitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis.

Pancreas:

No alterations observed.

Minimal nonsuppurative pancreatitis.

Urinary Bladder:

No alterations observed.

Minimal nonsuppurative cystitis.

Mesenteric Lymph Node:

No alterations observed.

Moderate erythrophagia seen in medullary
sinusoids.Perivascular chronic inflammation of a few
vessels.

Testis:

No alterations observed.

Activity appeared to be within normal limits.

Prostate:

No alterations observed.

Section not available for examination.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Moderately high numbers of maturing erythroid
and myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: pituitary,
stomach, small intestine, large intestine, and bone.

246

GROUP NO. 1
Male Rat No. 82-704

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Slight focal meningocephalitis with the
absence of focal gliosis.

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.
Epithelium lining follicles flattened or
low cuboidal.
Activity low.

Adrenal:

No alterations observed.

Slight vacuolation of cells in zona fasciculata.
Otherwise, not remarkable.

Eye:

No alterations observed.

Slight nonsuppurative myositis involving
extra ocular muscles in the posterior segment
of the globe.
Section does not include optic nerve.
Otherwise, not remarkable.

Heart:

No alterations observed.

Minimal chronic myocarditis.

Lung:

No alterations observed.

Slight interstitial pneumonitis.
Slight peribronchiolar lymphoid hyperplasia.

Spleen:

Appeared slightly enlarged.

Moderate to moderately high extramedullary
hematopoietic activity.

247

GROUP NO. 1
Male Rat No. 82-704 (Continued)

GROSS

MICROSCOPIC

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Slight chronic pericholangitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis.

Pancreas:

No alterations observed.

Poor histologic section, many wrinkles and folds.

Minimal focal chronic pancreatitis.

Urinary Bladder:

No alterations observed.

Lumen very distended.

Otherwise, not remarkable.

Mesenteric Lymph Node:

No alterations observed.

Section of node missing.

Testis:

No alterations observed.

Slight testicular tubular degeneration.

Slight nonsuppurative orchitis.

Bone Marrow:

No alterations observed.

Section too small to conduct a meaningful
histopathological evaluation.

The following organs were not altered grossly or microscopically: spinal cord,
pituitary, adrenal, stomach, small intestine, large intestine, prostate, and bone.

248

GROUP NO. 2
Male Rat No. 82-716

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Chiefly, medium- and large-sized follicles. Epithelium lining follicles often flattened or low cuboidal. Activity low.
Spleen:	
No alterations observed.	Slight to moderate extramedullary hematopoietic activity. Minimal pigment within red pulp.
Liver:	
No alterations observed.	Minimal nonsuppurative hepatitis.
Bone Marrow:	
No alterations observed.	Numerous megakaryocytes. Considerable numbers of maturing erythroid and myeloid cells. Activity moderate.
The following organ was not altered grossly or microscopically: kidney.	

249

GROUP NO. 2
Male Rat No. 82-717

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Small-, medium-, and large-sized follicles. Epithelium lining the follicles chiefly low cuboidal. Activity low.
Lung:	
Small consolidated areas.	Moderate interstitial pneumonitis.
Spleen:	
Appeared enlarged.	Slight extramedullary hematopoietic activity.
Liver:	
No alterations observed.	Slight nonsuppurative hepatitis. Occasional chronic pericholangitis.
Kidney:	
No alterations observed.	Slight chronic interstitial nephritis. Occasional foci of regenerative tubular epithelium. Small focus of chronic inflammation seen in perirenal fat.
Bone Marrow:	
No alterations observed.	Numerous megakaryocytes. Several numbers of maturing erythroid and myeloid cells. Activity moderately high.

250

GROUP NO. 2
Male Rat No. 82-718

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium chiefly low cuboidal or cuboidal.

Activity low.

Lung:

Dark red areas in all lobes.

Moderate interstitial pneumonitis.

Moderate perivascular cuffs of lymphocytic
cells.

Large areas of focal hemorrhage.

Some bronchi contained aspirated blood.

Spleen:

Appeared enlarged.

Slight to moderate extramedullary hematopoietic
activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Kidney:

No alterations observed.

Moderate chronic interstitial nephritis.

In some areas, mild dilatation of some cortical
tubules.

These tubules usually empty but, in some cases
contained very small amounts of granular
eosinophilic material.

Slight to moderate tubular regenerative changes.

Slight chronic pyelitis.

251

GROUP NO. 2
Male Rat No. 82-718 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Numerous megakaryocytes seen.

Considerable numbers of maturing erythroid and
myeloid cells.

Activity moderate.

GROUP NO. 2
Male Rat No. 82-719

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, small-, and medium-sized follicles.

Epithelium lining the follicles varied from

cuboidal to high cuboidal.

Activity moderately high.

Spleen:

No alterations observed.

Moderately high extramedullary hematopoietic
activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Kidney:

Speckled surface pale

yellowish brown.

Moderate chronic interstitial nephritis
involving cortex and medulla.Focal areas of tubular regeneration, moderate
in extent, and sometimes accompanied by slightly
dilated tubules.

Cervical Lymph Node:

Appeared enlarged and dark
pink.Lymphoid follicles very active and merged one
with another.Many plasma cells present in the medullary
sinusoids.

Node congested.

253

GROUP NO. 2
Male Rat No. 82-719 (Continued)

GROSS

MICROSCOPIC

Some large sections of salivary glands submitted
along with lymph node section, these sections
not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderate.

254

GROUP NO. 2
Male Rat No. 82-721

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium flattened to low cuboidal.

Activity low.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Kidney:

No alterations observed.

Some tubules in medulla appeared dilated.

Otherwise, not remarkable.

Small Intestine:

Wall appeared thickened.

Not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderate.

The following organ was not altered grossly or microscopically: liver.

255

GROUP NO. 3
Male Rat No. 82-736

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Small-, medium-, and large-sized follicles. Epithelium lining the follicles flattened or low cuboidal. Activity low.
Lung:	
Small, gray, cyst-like areas in all lobes.	Slight interstitial pneumonitis. Slight perivascular lymphocytic infiltration. Large areas of congestion in focal pattern.
Spleen:	
No alterations observed.	Slight extramedullary hematopoietic activity. Minimal pigment within red pulp.
Liver:	
Small, firm, yellow area in median lobe. Section preserved.	Area seen grossly represented by a focus of chronic inflammation and fibrosis with bile duct hyperplasia. Minimal focal nonsuppurative hepatitis.
Kidney:	
No alterations observed.	Very minimal tubular regenerative changes.
Bone Marrow:	
No alterations observed.	Numerous megakaryocytes. Numerous maturing erythroid and myeloid cells. Activity moderately high.

256

GROUP NO. 3
Male Rat No. 82-738

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, small- and medium-sized follicles.

Epithelium lining the follicles cuboidal or
plump cuboidal.

Activity moderately high.

Lung:

Consolidated area in
left lobe.

Slight interstitial pneumonitis.

Slight bronchiectasis with purulent exudate
in a few bronchi and bronchioles.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal amount of pigment in red pulp.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Minimal chronic pericholangitis.

Kidney:

No alterations observed.

Very minimal interstitial nephritis.

Otherwise, not remarkable.

Stomach:

Walls thickened.

Slight chronic gastritis.

Focal collections of chronic inflammatory cells
in the submucosa.

257

GROUP NO. 3
Male Rat No. 82-738 (Continued)

GROSS

MICROSCOPIC

Small Intestine:

Walls thickened and yellow

foci in lining.

Not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Considerable numbers of maturing erythroid

and myeloid cells.

Activity moderately high.

258

GROUP NO. 3
Male Rat No. 82-739

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles chiefly cuboidal
in nature.

Activity moderate.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Minimal chronic pericholangitis.

Small Intestine:

Small, white foci in
lining.

Not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

The following organ was not altered grossly or microscopically: kidney.

259

GROUP NO. 3
Male Rat No. 82-743

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Many small- and medium-sized follicles.

Epithelium lining the follicles chiefly
cuobidal in type.

Activity moderate.

Lung:

Consolidated areas in
all lobes.

Moderate interstitial pneumonitis.

Peribronchiolar and perivascular lymphoid
proliferation.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment in red pulp.

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Minimal chronic pericholangitis.

Kidney:

No alterations observed.

Slight interstitial nephritis involving cortex
and medulla.

Minimal numbers of regenerating tubules.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

260

GROUP NO. 3
Male Rat No. 82-744

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles chiefly
flattened or low cuboidal.

Activity moderate.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Kidney:

Greenish tinge.

Very mild nonsuppurative pyelitis.

Otherwise, not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

261

GROUP NO. 4
Male Rat No. 82-758

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Chiefly, large- and medium-sized follicles. Epithelium lining follicles flattened or low cuboidal in type. Activity low.
Lung:	
No alterations observed.	Slight interstitial pneumonitis.
Spleen:	
No alterations observed.	Slight to moderate extramedullary hematopoietic activity.
Small Intestine:	
Duodenum walls thickened with small, yellow foci.	Not remarkable.
Kidney:	
No alterations observed.	Slight tubular regenerative activity.
Prostate:	
No alterations observed.	Slight suppurative prostatitis with accumulations of purulent exudate within some prostatic glands.

262

GROUP NO. 4
Male Rat No. 82-758 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Moderate numbers of maturing erythroid and
myeloid cells.

Activity moderate.

The following organs were not altered grossly or microscopically: brain,
spinal cord, pituitary, adrenal, eye, heart, liver, stomach, pancreas, large
intestine, urinary bladder, mesenteric lymph node, testis, and bone.

263

GROUP NO. 4
Male Rat No. 82-759

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Large- and medium-sized follicles predominated.
Epithelium varied from flattened to cuboidal.
Activity judged to be low.

Eye:

No alterations observed.

Many artifacts present.
Portions of retina, ciliary processes, iris
and cornea, missing.

Lung:

Dark red areas in all lobes.

Slight interstitial pneumonitis.
Moderate cuffs of lymphocytic cells around
blood vessels and bronchioles.

Spleen:

No alterations observed.

Minimal extramedullary hematopoietic activity.

Prostate:

No alterations observed.

Section not available for examination.

Bone Marrow:

No alterations observed.

Moderate numbers of megakaryocytes.
Moderate numbers of maturing erythroid and
myeloid cells.
Activity moderate.

The following organs were not altered grossly or microscopically: brain,
spinal cord, pituitary, adrenal, heart, liver, kidney, stomach, pancreas, small
intestine, large intestine, urinary bladder, mesenteric lymph node, testis, and
bone.

264

GROUP NO. 4
Male Rat No. 82-760

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles chiefly low

cuboidal or cuboidal.

Activity moderate.

Heart:

No alterations observed.

Minimal focal chronic myocarditis.

Lung:

Dark red areas in all lobes.

Minimal interstitial pneumonitis.

Large foci of hemorrhage and pulmonary edema.

Some bronchi and alveolar lumens contained
aspirated blood.

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic
activity.

Liver:

No alterations observed.

Slight chronic pericholangitis.

Minimal nonsuppurative hepatitis.

Kidney:

No alterations observed.

Occasional foci of chronic interstitial nephritis.

Minimal nonsuppurative pyelitis.

Pancreas:

No alterations observed.

Minimal chronic interstitial pancreatitis.

Mesenteric Lymph Node:

No alterations observed.

No section available for examination.

265

GROUP NO. 4

Male Rat No. 82-760 (Continued)

GROSS

MICROSCOPIC

Urinary Bladder:

No alterations observed.

Minimal focal nonsuppurative cystitis.

Testis:

No alterations observed.

Minimal nonsuppurative epididymis with small collections of chronic inflammatory cells in the interstitium.

Bone Marrow:

No alterations observed.

Marrow section insufficient for critical evaluation.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, eye, stomach, small intestine, large intestine, prostate, and bone.

266

GROUP NO. 4
Male Rat No. 82-764

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Small-, medium-, and large-sized follicles. Epithelium lining follicles chiefly low cuboidal. Activity moderate.
Heart:	
No alterations observed.	Minimal chronic myocarditis.
Lung:	
Small, gray, cyst-like areas in all lobes.	Slight chronic interstitial pneumonitis. Bronchioles appeared widely dilated. Some collapse of the pulmonary parenchyma.
Spleen:	
No alterations observed.	Very minimal extramedullary hematopoietic activity.
Kidney:	
Pale yellowish brown cortex.	
Dark pink outer medulla.	Not remarkable.
Testis:	
No alterations observed.	Minimal nonsuppurative epididymitis.
Bone Marrow:	
No alterations observed.	Moderate numbers of megakaryocytes. Moderate numbers of maturing erythroid and myeloid cells. Activity moderate.

267

GROUP NO. 4

Male Rat No. 82-764 (Continued)

GROSS

MICROSCOPIC

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, eye, liver, stomach, pancreas, small intestine, large intestine, urinary bladder, mesenteric lymph node, prostate, and bone.

268

GROUP NO. 4
Male Rat No. 82-765

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles flattened or
low cuboidal.

Activity low.

Lung:

Gray, cyst-like areas
in all lobes.

Slight interstitial pneumonitis.

Slight peribronchiolar lymphoid hyperplasia.

Spleen:

No alterations observed.

Slight extramedullary hematopoietic activity.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Kidney:

Small, yellowish brown
cortex.

Dark red medulla.

Minimal tubular regeneration.

Otherwise, not remarkable.

Bone Marrow:

No alterations observed.

Moderate numbers of megakaryocytes.

Moderate numbers of maturing erythroid and
myeloid cells.

Activity moderate.

269

GROUP NO. 4

Male Rat No. 82-765 (Continued)

GROSS

MICROSCOPIC

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, eye, heart, stomach, pancreas, small intestine, large intestine, urinary bladder, mesenteric lymph node, testis, prostate, and bone.

270

GROUP NO. 5
Male Rat No. 82-776

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Chiefly, moderate-sized follicles. Epithelium lining follicles chiefly low cuboidal. Activity low.
Adrenal:	
No alterations observed.	Medulla not included in section. Moderate vacuolation of cells in zona fasciculata.
Eye:	
No alterations observed.	Optic nerve not included in section. Otherwise, not remarkable.
Lung:	
No alterations observed.	Slight interstitial pneumonitis. Moderate peribronchial lymphoid hyperplasia.
Spleen:	
No alterations observed.	Slight to moderate extramedullary hematopoietic activity.
Liver:	
No alterations observed.	Minimal chronic pericholangitis.
Kidney:	
No alterations observed.	Slight chronic interstitial nephritis with accompanying slight tubular regeneration.
Small Intestine:	
No alterations observed.	Section not available for examination.

271

GROUP NO. 5
Male Rat No. 82-776 (Continued)

GROSS

MICROSCOPIC

Mesenteric Lymph Node:

No alterations observed.

Activity appeared to be within normal limits.

Cervical Lymph Node:

Enlarged.

Slight follicular hyperplasia.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous, maturing erythroid and myeloid cells.

Activity moderate.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, stomach, pancreas, large intestine, urinary bladder, testis, prostate, and bone.

GROUP NO. 5
Male Rat No. 82-778

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Mild nonsuppurative meningitis of the cerebellar
cortex.

Pituitary:

No alterations observed.

Not remarkable.

Small section; pars nervosa and pars intermedia
missing.

Thyroid:

No alterations observed.

Chiefly, medium- and large-sized follicles.

Epithelium lining follicles chiefly cuboidal or
high cuboidal.

Activity moderately high.

Adrenal:

No alterations observed.

Moderate vacuolation of zona fasciculata.

Eye:

No alterations observed.

Lens badly shattered.

Optic nerve not included in section.

Otherwise, not remarkable.

Heart:

No alterations observed.

Slight focal myocarditis and epicarditis.

Lung:

No alterations observed.

Minimal interstitial pneumonitis.

Slight peribronchial lymphoid hyperplasia.

Moderate alveolar expansion.

GROUP NO. 5
Male Rat No. 82-778 (Continued)

GROSS

MICROSCOPIC

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic activity.

Kidney:

No alterations observed.

Slight focal, chronic interstitial nephritis.
Slight focal pyelitis.

Cervical Lymph Node:

Enlarged.

Cervical lymph nodes not found in section, but sections of salivary gland present.

Urinary Bladder:

No alterations observed.

Poor histologic section.
Mucosa very folded.
Slight focal nonsuppurative cystitis.

Liver:

No alterations observed.

Slight chronic pericholangitis.
Occasional focus of nonsuppurative hepatitis with a few necrotic hepatocytes.

Prostate:

No alterations observed.

Section not available for examination.

Bone Marrow:

No alterations observed.

Moderate numbers of megakaryocytes.
Considerable numbers of maturing erythroid and myeloid cells.
Activity moderate.

The following organs were not altered grossly or microscopically: spinal cord, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, testis, and bone.

274

GROUP NO. 5
Male Rat No. 82-780

GROSS	MICROSCOPIC
Brain:	
No alterations observed.	Mild nonsuppurative meningocephalitis characterized by small foci of gliosis, collections of small numbers of lymphocytes within the meninges, and occasional cuffing of intracerebral vessels by chronic inflammatory cells.
Thyroid:	
No alterations observed.	Small-, medium-, and large-sized follicles. Epithelium lining follicles chiefly cuboidal. Activity moderate.
Adrenal:	
No alterations observed.	Slight vacuolation of cells in zona fasciculata.
Eye:	
No alterations observed.	Portions of the anterior segment of eye missing; iris and cornea cannot be evaluated microscopically. Other segments of eye normal.
Heart:	
No alterations observed.	Minimal focal, chronic myocarditis. Chronic inflammatory cells occurred in interstitial locations of the myocardium.

275

GROUP NO. 5
Male Rat No. 82-780 (Continued)

GROSS	MICROSCOPIC
Lung:	
Dark red areas on all lobes.	Mild interstitial pneumonitis. Mild peribronchial lymphoid hyperplasia.
Spleen:	
No alterations observed.	Activity appeared within normal limits.
Liver:	
No alterations observed.	Minimal focal chronic pericholangitis.
Kidney:	
No alterations observed.	Minimal focal chronic pyelitis.
Pancreas:	
No alterations observed.	Minimal focal chronic pancreatitis.
Small Intestine:	
No alterations observed.	The superficial mucosal epithelium missing.
Urinary Bladder:	
No alterations observed.	No section available for examination.
Mesenteric Lymph Node:	
No alterations observed.	Small section submitted. Activity appeared within normal limits.
Testis:	
No alterations observed.	Activity appeared within normal limits.
Prostate:	
No alterations observed.	No section available for examination.

GROUP NO. 5
Male Rat No. 82-780 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Cytologic staining poor, probably due to
over decalcification.

Numerous numbers of megakaryocytes.

Poor cytologic detailed prevents a definitive
evaluation of hematogenic activity.

The marrow, however, appeared very cellular.

The following organs were not altered grossly or microscopically: spinal cord,
pituitary, adrenal, stomach, large intestine, and bone.

GROUP NO. 5
Male Rat No. 82-782

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Minimal nonsuppurative meningoencephalitis.

Focal glial nodules within brain.

Minimal numbers of intracerebral vessels
cuffed by lymphocytes.Small numbers of lymphocytes present in
the meninges.

Pituitary:

No alterations observed.

Small section included.

Only pars distalis included on section.

Otherwise, not remarkable.

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles chiefly cuboidal in
type.

Activity moderate.

Adrenal:

No alterations observed.

only small section of medullary area included.

Slight vacuolation of cells in zona fasciculata.

Eye:

No alterations observed.

Minimal chronic dacryoadenitis.

Otherwise, not remarkable.

GROUP NO. 5
Male Rat No. 82-782 (Continued)

GROSS	MICROSCOPIC
Heart:	
No alterations observed.	Minimal nonsuppurative myocarditis.
Lung:	
No alterations observed.	Minimal interstitial pneumonitis and peri- bronchial lymphoid hyperplasia.
Spleen:	
Appeared enlarged.	Moderate extramedullary hematopoiesis.
Liver:	
No alterations observed.	Mild chronic pericholangitis.
Kidney:	
No alterations observed.	Occasional foci of chronic interstitial nephritis. Small numbers of regenerating tubules in affected areas.
Pancreas:	
No alterations observed.	Minimal chronic pancreatitis with focal acinar atrophy.
Mesenteric Lymph Node:	
No alterations observed.	Activity appeared within normal limits. Adventitia of one artery in mesenteric fat was segmentally infiltrated with collections of mononuclear inflammatory cells and a few polymorphs.
Testis:	
No alterations observed.	Activity appeared within normal limits.

279

GROUP NO. 5
Male Rat No. 82-782 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Moderately high numbers of megakaryocytes.

Moderately high numbers of maturing erythroid
and myeloid cells.

Activity moderately high.

Prostate:

No alterations observed.

Section not available for examination.

The following organs were not altered grossly or microscopically: spinal cord,
stomach, small intestine, large intestine, urinary bladder, and bone.

280

GROUP NO. 5
Male Rat No. 82-785

GROSS	MICROSCOPIC
Brain:	
No alterations observed.	Mild nonsuppurative meningitis. Rarely, a small focus of gliosis.
Pituitary:	
No alterations observed.	Section incomplete. Only the pars distalis included. Otherwise, not remarkable.
Thyroid:	
No alterations observed.	Small-, medium-, and large-sized follicles. Epithelium lining follicles chiefly cuboidal in size. Activity moderate.
Adrenal:	
No alterations observed.	Medulla not included on section. Low level of vacuolation of cells in zona fasciculata.
Heart:	
No alterations observed.	Minimal chronic myocarditis.
Lung:	
No alterations observed.	Minimal interstitial pneumonitis and peribronchial lymphoid hyperplasia.
Spleen:	
Appeared enlarged.	Moderate extramedullary hematopoietic activity.
Liver:	
No alterations observed.	Minimal chronic pericholangitis.

GROUP NO. 5
Male Rat No. 82-785 (Continued)

GROSS

MICROSCOPIC

Kidney:

No alterations observed.

Minimal chronic interstitial nephritis and
focal chronic pyelitis.

Pancreas:

No alterations observed.

Minimal chronic pancreatitis.

Mesenteric Lymph Node:

No alterations observed.

Small section submitted.

Activity appeared to be within normal limits.

One mesenteric artery had infiltrations of
mononuclear cells and polymorphs in the
adventitia in a segmental distribution.

Testis:

No alterations observed.

Activity appeared within normal limits.

Bone Marrow:

No alterations observed.

Moderately high numbers of megakaryocytes.

Moderately high numbers of maturing erythroid
and myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: spinal cord,
eye, stomach, small intestine, large intestine, urinary bladder, prostate, and
bone.

GROUP NO. 1
Female Rat No. 82-706

GROSS	MICROSCOPIC
Brain:	
No alterations observed.	Slight nonsuppurative meningocephalitis, perivascular cuffing, and focal gliosis.
Spinal Cord:	
No alterations observed.	Minimal nonsuppurative meningomyelitis.
Thyroid:	
No alterations observed.	Section not available for examination.
Adrenal:	
No alterations observed.	Medulla not included. Moderate vacuolation of cells in the zona fasciculata.
Heart:	
No alterations observed.	Minimal nonsuppurative myocarditis and epicarditis.
Lung:	
No alterations observed.	Slight interstitial pneumonitis. Slight perivascular lymphoid hyperplasia.
Spleen:	
No alterations observed.	Slight to moderate extramedullary hematopoietic activity. Pigment in red pulp minimal in amount.
Liver:	
No alterations observed.	Slight nonsuppurative hepatitis.
Kidney:	
No alterations observed.	Minimal tubular dilatation of medullary tubule.

GROUP NO. 1
Female Rat No. 82-706 (Continued)

GROSS

MICROSCOPIC

Urinary Bladder:

No alterations observed.

Minimal nonsuppurative cystitis.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared to be within normal limits.

Ovary:

No alterations observed.

Activity appeared to be within normal limits.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes present.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: pituitary, eye, stomach, pancreas, small intestine, large intestine, uterus, and bone.

284

GROUP NO. 1
Female Rat No. 82-707

GROSS

MICROSCOPIC

Pituitary:

No alterations observed.

Pars nervosa and pars intermedia not included
in section.

Pars distalis, not remarkable.

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles varied from flattened
to cuboidal.

Activity low.

Adrenal:

No alterations observed.

Moderate diffuse vacuolation of zona
fasciculata.

Eye:

No alterations observed.

Cornea and parts of retina and iris are missing.
Section does not include optic nerve.
Otherwise, not remarkable.

Lung:

No alterations observed.

Slight interstitial pneumonitis.
Slight perivascular lymphoid hyperplasia.

Spleen:

No alterations observed.

Minimal extramedullary hematopoietic activity.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared within normal limits.

285

GROUP NO. 1

Female Rat No. 82-707 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Complete maturation of myeloid and erythroid
cells.

Numerous megakaryocytes.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain,
spinal cord, heart, liver, kidney, stomach, pancreas, small intestine, large
intestine, urinary bladder, ovary, uterus, and bone.

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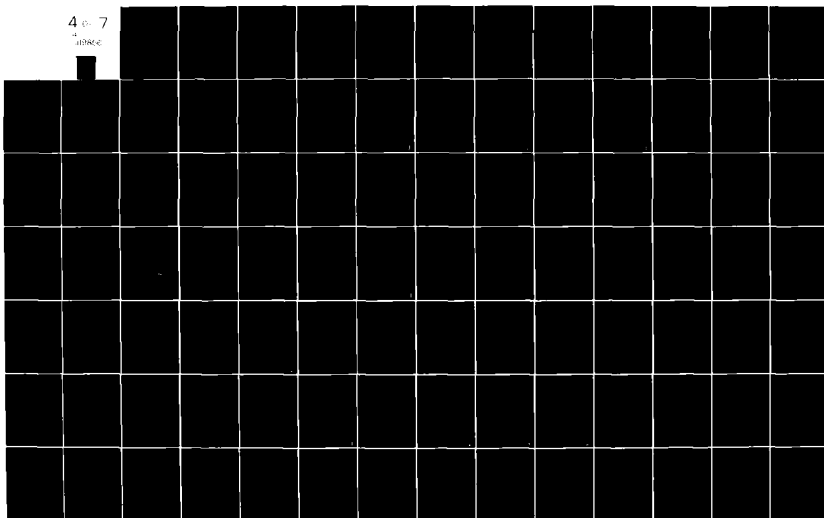
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GROUP NO. 1
Female Rat No. 82-708

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, small- and medium-sized follicles.

Epithelium lining follicles predominantly
flattened or low cuboidal.

Activity low.

Adrenal:

No alterations observed.

Moderate diffuse vacuolation of cells of zona
fasciculata.

Heart:

No alterations observed.

Slight chronic myocarditis.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

A large component of eosinophils present in
inflammatory response.

Spleen:

No alterations observed.

Minimal extramedullary hematopoietic activity.

Liver:

No alterations observed.

Many artifacts present making interpretation
difficult.

Slight nonsuppurative hepatitis.

Slight chronic pericholangitis.

Pancreas:

No alterations observed.

Slight chronic pancreatitis and focal acinar
atrophy.

287

GROUP NO. 1
Female Rat No. 82-708 (Continued)

GROSS

MICROSCOPIC

Mesenteric Lymph Node:

No alterations observed.

Activity appeared within normal limits.

Bone Marrow:

No alterations observed.

Small section included for examination.

Many megakaryocytes.

Maturing erythroid and myeloid cells seen in
moderate numbers.

Activity moderate.

The following organs were not altered grossly or microscopically: brain, spinal
cord, pituitary, eye, kidney, stomach, small intestine, large intestine, urinary
bladder, ovary, uterus, and bone.

288

GROUP NO. 1
Female Rat No. 82-709

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles chiefly flattened
or cuboidal in size.

Activity moderate.

Adrenal:

No alterations observed.

Slight vacuolation of cells in zona fasciculata.

Eye:

No alterations observed.

Section of optic nerve not included.

Lens shattered.

Otherwise, not remarkable.

Lung:

No alterations observed.

Moderate interstitial pneumonitis.

Moderate perivascular lymphoid hyperplasia.

Spleen:

No alterations observed.

Slight extramedullary hematopoietic activity.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Minimal chronic pericholangitis.

Kidney:

No alterations observed.

Rarely, a focus of chronic interstitial
nephritis.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared within normal limits.

GROUP NO. 1
Female Rat No. 82-709 (Continued)

GROSS

MICROSCOPIC

Ovary:

Left Ovary - Surrounded with
dark red cyst.

Not remarkable.
Cyst observed grossly not seen microscopically.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.
Numerous maturing erythroid and myeloid
cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain,
spinal cord, pituitary, heart, stomach, pancreas, small intestine, large intestine,
urinary bladder, uterus, and bone.

290

GROUP NO. 1
Female Rat No. 82-714

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Minimal nonsuppurative meningocephalitis.

Slight focal gliosis.

Thyroid:

No alterations observed.

Medium- and large-sized follicles predominated.

Epithelium lining follicles chiefly flattened.

Activity very low.

Adrenal:

No alterations observed.

Moderate vacuolation of cells in zona fasciculata.

Eye:

No alterations observed.

Optic nerve section missing.

Center of lens missing.

Otherwise, not remarkable.

Heart:

No alterations observed.

Infrequent foci of chronic myocarditis.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Slight perivascular lymphocytic response.

Spleen:

Appeared enlarged.

Moderate extramedullary hematopoietic activity.

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Slight pericholangitis.

Kidney:

No alterations observed.

Rarely, a tiny focus of chronic interstitial
nephritis.

Minimal renal tubular regeneration.

291

GROUP NO. 1
Female Rat No. 82-714 (Continued)

GROSS

MICROSCOPIC

Pancreas:

No alterations observed.

Slight nonsuppurative pancreatitis with slight
ductal hyperplasia.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared to be within normal limits.

Ovary:

No alterations observed.

Activity appeared to be within normal limits.

Uterus:

Distended with clear
fluid.

Lumen distended.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid
cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: spinal cord,
pituitary, stomach, small intestine, large intestine, urinary bladder, and bone.

292

GROUP NO. 2
Female Rat No. 82-726

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium varied from a low cuboidal to a
plump cuboidal.

Activity moderately high.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal amount of pigment within red pulp.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Uterus:

Distended with clear fluid.

Uterine lumen distended.

Otherwise, not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderate.

The following organ was not altered grossly or microscopically: kidney.

293

GROUP NO. 2
Female Rat No. 82-727

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles chiefly

flattened or low cuboidal in type.

Activity moderate.

Spleen:

Appeared enlarged.

Many artifacts from histologic preparation

makes interpretation difficult.

Slight extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Kidney:

Both pelves dilated.

Slight to moderate chronic interstitial

nephritis involving cortex and medulla.

Minimal regenerative tubular epithelial changes

associated with these inflammatory foci.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderate.

The following organ was not altered grossly or microscopically: liver.

294

GROUP NO. 2
Female Rat No. 82-729

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles chiefly flattened
or low cuboidal.

Activity low.

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic
activity.

Slight pigment within red pulp.

Kidney:

Dark red outer medulla.

Congestion in outer medulla.

Otherwise, not remarkable.

Bone Marrow:

No alterations observed.

Considerable numbers of megakaryocytes.

Considerable numbers of maturing erythroid and
myeloid cells.

Activity moderate.

The following organ was not altered grossly or microscopically: liver.

295

GROUP NO. 2
Female Rat No. 82-733

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, medium- and large-sized follicles.

Epithelium lining the follicles flattened

or low cuboidal.

Activity low.

Lung:

Small, cyst-like areas.

Marked bronchial dilatation.

Moderate interstitial pneumonitis.

Minimal lymphocytic perivascular infiltration.

Spleen:

Appeared enlarged.

Moderate extramedullary hematopoietic activity.

Slight amount of pigment within red pulp.

Liver:

No alterations observed.

Slight extramedullary hematopoietic activity.

Minimal nonsuppurative hepatitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis involving
cortex and medulla.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderate.

296

GROUP NO. 2
Female Rat No. 82-735

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium chiefly flattened or low cuboidal
in type.

Activity low.

Spleen:

Appeared enlarged.

Some artifacts due to histologic preparation.

Slight to moderate extramedullary hemopoietic
activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Slight pericholangitis.

Minimal nonsuppurative hepatitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis involving
cortex and medulla.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

297

GROUP NO. 3
Female Rat No. 82-747

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Medium- and large-sized follicles predominated. Epithelium lining the follicles chiefly flattened or low cuboidal. Activity low.
Lung:	
Median lobe consolidated.	Severe interstitial pneumonitis with wide- spread consolidation of pulmonary parenchyma. Moderately large peribronchial lymphocytic aggregates. One large area of pulmonary emphysema present.
Spleen:	
No alterations observed.	Minimal extramedullary hematopoietic activity and minimal pigment within red pulp.
Liver:	
No alterations observed.	Slight nonsuppurative hepatitis. Otherwise, not remarkable.
Kidney:	
No alterations observed.	Very minimal chronic interstitial nephritis.
Bone Marrow:	
No alterations observed.	Section too small and not adequate for evaluation; however, activity appeared to be within normal limits.

GROUP NO. 3
Female Rat No. 82-748

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Small-, medium-, and large-sized follicles. One small focus of lymphocytic infiltration. Epithelium lining the follicles flattened or low cuboidal. Activity judged to be low.
Spleen:	
No alterations observed.	Moderate extramedullary hematopoietic activity. Minimal pigment in red pulp.
Liver:	
No alterations observed.	Slight nonsuppurative hepatitis.
Kidney:	
No alterations observed.	Slight chronic interstitial nephritis involving medulla.
Small Intestine:	
Duodenal lining thickened and contained small, yellow foci.	Not remarkable.
Bone Marrow:	
No alterations observed.	Numerous megakaryocytes. Numerous maturing erythroid and myeloid cells. Activity moderately high.

299

GROUP NO. 3
Female Rat No. 82-750

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles varied from
flattened to cuboidal.

Activity low.

Lung:

Dark red areas in all
lobes.

Rather large areas of pulmonary congestion and
edema as well as hemorrhage.

Slight to moderate interstitial pneumonitis.

Moderate perivascular lymphoid infiltration
present.

Slight alveolar emphysema.

Spleen:

No alterations observed.

Slight extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Bone Marrow:

No alterations observed.

Small section.

Many megakaryocytes present.

Many maturing erythroid and myeloid cells.

Activity moderate.

The following organs were not altered grossly or microscopically: liver and kidney.

300

GROUP NO. 3
Female Rat No. 82-752

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly medium- and large-sized follicles.

Epithelium lining the follicles flattened or
low cuboidal, chiefly.

Activity judged to be low.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Slight pigment in red pulp.

Liver:

Yellowish tinge.

Infrequent foci of nonsuppurative hepatitis.

Otherwise, not remarkable.

Kidney:

No alterations observed.

Minimal tubular regeneration in cortex.

Small Intestine:

In duodenum; small, yellow
foci.

Walls appeared thickened.

Not remarkable.

Uterus:

Walls distended with clear
fluid.

Uterine lumen moderately distended.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

301

GROUP NO. 3
Female Rat No. 82-755

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Small-, medium-, and large-sized follicles. Epithelium lining the follicles flattened or low cuboidal in type. Activity low.
Spleen:	
No alterations observed.	Slight extramedullary hematopoietic activity. Minimal pigment within red pulp.
Kidney:	
No alterations observed.	Very minimal chronic interstitial nephritis.
Bone Marrow:	
No alterations observed.	Only a small section included for examination. Marrow appeared well populated with erythroid and myeloid cells and megakaryocytes.
Skin:	
Severe alopecia on body.	Possibly, a slight hyperkeratosis. Inflammatory changes not observed.
The following organ was not altered grossly or microscopically: liver.	

GROUP NO. 4
Female Rat No. 82-766

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles varied from

a flattened to plump cuboidal.

Activity moderate.

Pituitary:

No alterations observed.

Solitary cyst involving the pars distalis
containing eosinophilic secretory material
and calcareous bodies.

Heart:

No alterations observed.

Slight chronic myocarditis and epicarditis.

Lung:

Distended with abscessed
areas.

Severe bronchiectasis.

Bronchi wildly dilated and filled with purulent
exudate.

Dense zones of chronic inflammatory tissue
surrounding the effected bronchi.

Spleen:

No alterations observed.

Some tearing of tissues due to histologic
preparation.

Slight extramedullary hematopoietic activity.

Slight to moderate amounts of pigment in red
pulp.

GROUP NO. 4
Female Rat No. 82-766 (Continued)

GROSS

MICROSCOPIC

Liver:

Lobes thickened and pale
yellowish brown.

Slight pericholangitis.

In some areas, hepatocytes had vacuolated,
swollen cytoplasm.

Kidney:

Pale yellowish brown
cortex.

Not remarkable.

Bone Marrow:

No alterations observed.

Numerous maturing erythroid and myeloid
cells.

Numerous megakaryocytes.

Activity moderately high.

Small Intestine:

Walls appeared thickened.

Entire circumference of the intestine not
included on this section.

Artifactual disruption of villi.

Vacuolation of cells in lamina propria.

The following organs were not altered grossly or microscopically: brain, spinal
cord, adrenal, eye, stomach, pancreas, large intestine, urinary bladder,
mesenteric lymph node, ovary, uterus, and bone.

304

GROUP NO. 4
Female Rat No. 82-768

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles chiefly flattened
or low cuboidal.

A few cystic follicles seen.

One cystic follicle filled with colloid the others
filled with cellular debris resembling
keratinaceous material.

Activity moderate.

Two large foci of lymphocytic infiltration.

Eye:

No alterations observed.

Artifacts present, otherwise, not remarkable.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Perivascular aggregates of lymphocytes and
plasma cells.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Rare focus of nonsuppurative hepatitis.

Slight irregularity in cords of cells.

GROUP NO. 4
Female Rat No. 82-768 (Continued)

GROSS

MICROSCOPIC

Stomach:

Walls appeared thickened.

Not remarkable.

Bone Marrow:

No alterations observed.

Many megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, heart, kidney, pancreas, small intestine, large intestine, urinary bladder, mesenteric lymph node, ovary, uterus, and bone.

GROUP NO. 4
Female Rat No. 82-770

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small- and medium-sized follicles predominated.

Epithelium lining the follicles chiefly

low cuboidal or cuboidal.

Activity moderate.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Slight perivascular aggregates of lymphocytes
and plasma cells.

Spleen:

No alterations observed.

Slight extramedullary hematopoietic activity.

Minimal pigment in red pulp.

Stomach:

Walls thickened.

Focal nonsuppurative gastritis seen with very
small numbers of chronic inflammatory cells
in submucosa.

Small Intestine:

Duodenum wall thickened

with small, yellow foci.

Not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Considerable numbers of maturing erythroid
and myeloid cells.

Activity moderately high.

307

GROUP NO. 4

Female Rat No. 82-770 (Continued)

GROSS

MICROSCOPIC

Skin:

Alopecia on body.

Section of skin preserved.

Not remarkable.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, eye, heart, liver, kidney, pancreas, large intestine, urinary bladder, mesenteric lymph node, ovary, uterus, and bone.

308

GROUP NO. 4
Female Rat No. 82-771

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles either flattened
or low cuboidal in type.

Activity low.

Heart:

No alterations observed.

Minimal focal chronic myocarditis.

Lung:

Distended with consolidated
areas.

Minimal interstitial pneumonitis.

Slight perivascular and peribronchiolar lymphoid
infiltration.

Spleen:

Appeared slightly enlarged.

Moderate extramedullary hematopoietic activity.

Minimal pigment in red pulp.

Liver:

Yellowish tinge.

Slight nonsuppurative hepatitis.

Minimal chronic pericholangitis.

GROUP NO. 4
Female Rat No. 82-771 (Continued)

GROSS

MICROSCOPIC

Kidney:

Yellowish brown cortex.

Dark red outer medulla.

Moderate interstitial nephritis with
infiltrations of chronic inflammatory cells.
Inflammatory changes involved both cortex
and medulla.
Slight tubular dilatation and regenerative
tubular changes.

Small Intestine:

Lining of the duodenum
contained small, yellow
foci; walls appeared
thickened.

Not remarkable.

Urinary Bladder:

No alterations observed.

No section available for examination.

Mesenteric Lymph Node:

No alterations observed.

In the perinodal fat, a small focus of
chronic inflammation.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.
Considerable numbers of maturing erythroid and
myeloid cells.
Activity moderate to moderately high.

310

GROUP NO. 4
Female Rat No. 82-771 (Continued)

GROSS

MICROSCOPIC

The following organs were not altered grossly or microscopically: brain,
spinal cord, pituitary, adrenal, eye, stomach, pancreas, large intestine, ovary,
uterus, and bone.

311

GROUP NO. 4
Female Rat No. 82-772

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles cuboidal or
high cuboidal.

Activity moderate to moderately high.

Eye:

No alterations observed.

Staining artifacts present, otherwise, not
remarkable.

Lung:

No alterations observed.

Foci of chronic interstitial pneumonitis.

Small leukocytic cuffs evident around some
blood vessels.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Kidney:

No alterations observed.

Very minimal cast formation in some cortical
tubules.

Uterus:

Distended with clear
fluid.

Lumen slightly distended.

Mild dilatation of a few uterine glands.

GROUP NO. 4

Female Rat No. 82-772 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, adrenal, liver, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, ovary, and bone.

3/3

GROUP NO. 5
Female Rat No. 82-786

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Most follicles lined by cuboidal epithelium.

Minimal focal chronic thyroiditis and

fibrosis in association with cystic follicles.

Adrenal:

No alterations observed.

Only small section of medulla included.

Not remarkable.

Lung:

No alterations observed.

Minimal interstitial pneumonitis and

lymphoid hyperplasia.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Moderate amount of golden brown pigment

within red pulp.

Liver:

No alterations observed.

Poor histologic section.

Otherwise, not remarkable.

314

GROUP NO. 5

Female Rat No. 82-786 (Continued)

GROSS

MICROSCOPIC

Kidney:

Pelvis dilated and contained small, firm, sand-like granules.

Severe pyelonephritis with ulceration of the epithelium lining the renal pelvis. Renal pelvis and adjacent medulla are diffusely infiltrated with chronic inflammatory cells.

Many polymorphs infiltrate the pelvic mucosa. Tubules in affected areas widely separated by inflammatory exudate.

Occasional tubules have small numbers of neutrophils in their lumens.

Cortex only minimally effected.

Urinary Bladder:

Walls thickened, dark pink, and rough.

Contained numerous, firm, white stones measuring approximately 1 x 0.5 cm. to small granules.

Mucosa greatly thickened and thrown up into tortuous folds.

Within lamina propria collections of acute and chronic inflammatory cells, including plasma cells.

GROUP NO. 5
Female Rat No. 82-786 (Continued)

GROSS

MICROSCOPIC

Edematous separation of the muscle layers and infiltrations of chronic inflammatory cells and pigment containing macrophages.

Histopathologic changes correspond to a moderately severe, chronic hyperplastic cystitis.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared to be within normal limits.

Ovary:

No alterations observed.

Activity appeared to be within normal limits.

Bone Marrow:

No alterations observed.

Moderately high numbers of megakaryocytes.

Considerable numbers of maturing erythroid and myeloid elements.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, eye, heart, stomach, pancreas, small intestine, large intestine, uterus, and bone.

GROUP NO. 5
Female Rat No. 82-791

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, medium- and large-sized follicles.
Follicles lined by flattened or low cuboidal
epithelium.
Activity low.

Adrenal:

No alterations observed.

Adrenal medulla not included for examination.
Moderately high vacuolation of cells in zona
fasciculata.

Eye:

No alterations observed.

Lenses shattered and displaced.
Section does not include optic nerve.
Otherwise, not remarkable.

Lung:

No alterations observed.

Slight interstitial pneumonitis.
Minimal peribronchial lymphoid hyperplasia.

Spleen:

Appeared enlarged.

Slight extramedullary hematopoietic activity.

Liver:

No alterations observed.

Slight chronic pericholangitis.

Kidney:

No alterations observed.

Minimal chronic interstitial nephritis.

317

GROUP NO. 5
Female Rat No. 82-791

GROSS	MICROSCOPIC
Pancreas:	
No alterations observed.	Minimal chronic pancreatitis.
Large Intestine:	
No alterations observed.	Lumen distended. Otherwise, not remarkable.
Mesenteric Lymph Node:	
No alterations observed.	Small section represented. Activity appeared within normal limits.
Ovary:	
No alterations observed.	Activity appeared within normal limits.
Bone Marrow:	
No alterations observed.	Numerous megakaryocytes. Considerable numbers of maturing erythroid and myeloid cells. Activity moderate.
The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, stomach, small intestine, urinary bladder, uterus, and bone.	

318

GROUP NO. 5
Female Rat No. 82-792

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, small- and medium-sized follicles.

Epithelium lining follicles flattened to cuboidal.

Activity moderate.

Adrenal:

No alterations observed.

Moderately high degree of vacuolation of cells in zona fasciculata.

Eye:

No alterations observed.

Optic nerve not represented on section.

Otherwise, not remarkable.

Lung:

Abscessed areas.

Moderate interstitial pneumonitis and moderate lymphoid peribronchial hyperplasia.

Areas of bronchiectasis also seen.

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic activity.

Pigment minimal in red pulp.

Liver:

No alterations observed.

Minimal focal areas of necrosis seen with a mononuclear inflammatory cell infiltration.

319

GROUP NO. 5
Female Rat No. 82-792 (Continued)

GROSS

MICROSCOPIC

Kidney:

No alterations observed.

A very few foci of chronic interstitial
nephritis associated with infrequent
tubules showing regenerative changes.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared to be within normal limits.

Uterus:

No alterations observed.

Lumen appeared slightly distended.
Otherwise, not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.
Considerable numbers of maturing erythroid and
myeloid cells.
Activity moderately high.

The following organs were not altered grossly or microscopically: brain,
spinal cord, pituitary, heart, stomach, pancreas, small intestine, large intestine,
urinary bladder, ovary, and bone.

GROUP NO. 5
Female Rat No. 82-793

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Medium- and large-sized follicles predominated.

Epithelium lining follicles a flattened or
low cuboidal type.

Activity low.

Adrenal:

No alterations observed.

Low level of vacuolation of cells in zona
fasciculata.

Eye:

No alterations observed.

Anterior segments missing including cornea,
iris, and ciliary processes.

Lenses shattered and displaced.

Section does not include optic nerve.

Retina and coroid, not remarkable.

Heart:

No alterations observed.

Minimal nonsuppurative myocarditis.

Lung:

No alterations observed.

Moderate interstitial pneumonitis and
moderate peribronchial lymphoid hyperplasia.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Liver:

No alterations observed.

Infrequent foci of mononuclear cell infiltration
seen.

GROUP NO. 5
Female Rat No. 82-793 (Continued)

GROSS

MICROSCOPIC

Kidney:

No alterations observed.

Infrequent foci of chronic interstitial
nephritis.

Minimal areas of regenerating tubular
epithelium in cortex.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared within normal limits.

Uterus:

Distended with clear
fluid.

Lumens distended.

Mild cystic endometrial hyperplasia.

Bone Marrow:

No alterations observed.

Moderate numbers of megakaryocytes.

Considerable numbers of maturing erythroid
and myeloid cells.

Moderately high activity.

The following organs were not altered grossly or microscopically: brain,
spinal cord, pituitary, stomach, pancreas, small intestine, large intestine,
urinary bladder, ovary, and bone.

GROUP NO. 5
Female Rat No. 82-795

GROSS

MICROSCOPIC

Pituitary:

No alterations observed.

Only pars distalis represented on the section.

Otherwise, not remarkable.

Thyroid:

No alterations observed.

Section not available for examination.

Adrenal:

No alterations observed.

Moderate degree of vacuolation of cells in
zona fasciculata.

Lung:

No alterations observed.

Moderate interstitial pneumonitis and
peribronchial lymphoid hyperplasia.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Liver:

Mottled surface.

Slight chronic pericholangitis.

Kidney:

No alterations observed.

Occasional small foci of chronic interstitial
nephritis.

A few tubules in medulla distended.

One dilated tubule surrounded by amorphous
pink material.

Pancreas:

No alterations observed.

One dilated pancreatic duct surrounded by
a small zone of chronic inflammation.

GROUP NO. 5
Female Rat No. 82-795 (Continued)

GROSS

MICROSCOPIC

Ovary:

No alterations observed.

Activity appeared within normal limits.

Uterus:

No alterations observed.

Slight cystic endometritis.

Bone Marrow:

No alterations observed.

Considerable numbers of megakaryocytes.

Considerable numbers of maturing erythroid and
myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal
cord, eye, heart, stomach, small intestine, large intestine, urinary bladder,
mesenteric lymph node, and bone.

SUMMARY

One hundred healthy albino rats of the Charles River Caesarean-derived strain (50 males and 50 females) were divided by stratified randomization into five groups of 10 males and 10 females each. Group No. 1 served as the vehicle control. Groups No. 2, No. 3, No. 4, and No. 5 received the test compound, WR-2823 (AU 69115), via intravenous injection at the rates of 30, 60, 120, and 15 mg/kg/day, respectively, administered in a vehicle of 0.9% sterile saline. The first five rats in each group received 16 injections, and the last five in each group received 15 injections. Rats were killed on the day following the last dose. The following tissues were collected in 10% buffered formalin from Group No. 1 (control), Group No. 5 (low level), and Group No. 4 (high level) and examined microscopically: brain, pituitary, eye, spinal cord (three levels), thyroid, lung, heart, spleen, liver, kidney, adrenal, stomach, pancreas, small intestine, large intestine, urinary bladder, mesenteric lymph node, testis, ovary, prostate, uterus, bone marrow, bone, and unusual lesions. Eyes were fixed in alcoholic formalin. From male and female rats in Groups No. 2 and No. 3, sections of thyroid, liver, spleen, kidney, and unusual lesions were examined.

Definite, compound-related changes were not observed in this study. Rare histopathologic findings in the treated groups consisted of: dacryoadenitis, focal thyroiditis, gastritis (two animals), pyelonephritis, prostatitis, and severe chronic cystitis in one Group No. 5 rat (low level). Sections of spinal cord, pituitary, and eye were unremarkable from the treated groups. The histologic appearance of the pituitary, adrenal, spleen, mesenteric lymph node, and bone marrow were comparable between the control and treated rats.

Histopathologic findings which were comparable in incidence and severity in control and treated animals included: chronic interstitial nephritis, pyelitis, chronic nonsuppurative meningoencephalitis, myocarditis and epicarditis, chronic murine pneumonia complex, nonsuppurative hepatitis and pericholangitis, non-suppurative pancreatitis, and mild nonsuppurative cystitis.

Sections of pituitary, eye, stomach, and prostate from control animals were not considered remarkable. Other histopathologic changes listed in the incidence table or mentioned in the detailed pathology section and not mentioned in this summary are considered incidental findings not related to the compound administration.

In summary, the intravenous injection of the compound, WR-2823 (AU 69115), at levels of 15, 30, 60, and 120 mg/kg/day for two weeks did not produce compound-related, histopathologic changes in any of the tissues examined.

KEY TO DETAILED HISTOPATHOLOGY INCIDENCE TABLE

N = No Section

X = Not Remarkable

A = Autolysis

P or ✓ = Present or Taken

0 = Absent

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderate to Severe

5 = Severe

DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS	ANIMAL NUMBER	MALES									
		GROUP NUMBER									
		1					2				
		82-696	82-700	82-702	82-703	82-704	82-716	82-717	82-718	82-719	82-721
BRAIN			X								
Nonsuppurative Meningitis											
Perivascular Cuffing				2							
Glial Nodules		P		P	P						
Meningoencephalitis		2		2	2	2					
SPINAL CORD			X		X	X					
Focal Gliosis		P									
Nonsuppurative Meningitis				P							
Meningomyelitis											
PITUITARY		X		X	X	X					
THYROID											
Level of Activity		3	4	3	3	2	2	2	2	4	2
EYE		X	X	X	X						
Dacryoadenitis											
Myositis						2					
HEART											
Epicarditis			2	2	2						
Focal Myocarditis		1	3	2	2	1					
Endocarditis			3	2							
LUNG											
Bronchiectasis											
Emphysema											
Interstitial Pneumonitis		2	2	3	2	2		3	3		
Peribronchial Lymphoid											
Hyperplasia		1	3	2		2					
SPLEEN											
Extramedullary Hematopoiesis		2	2	2-3	2-3	3-4	2-3	2	2-3	4	3
LIVER											X
Nonsuppurative Hepatitis		2	2	2	2	2	1	2	1	2	
Necrosis											
Pericholangitis		1		2	2	2		2			
KIDNEY			X				X				
Interstitial Nephritis		2		2	2	2		2	3	3	
Pyelitis				2					2		
Regenerative Epithelium		2		2				2	2-3	3	

HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

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Date: September 28, 1970

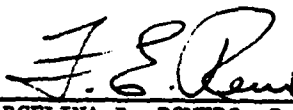
Material: WR-2823 (AU 69115)

Subject: REPORT NO. 37
Pathology Report
Two-Week Intravenous Toxicity Study - Dogs
Project No. 193-411

This pathology report is a supplement to Report No. 29 dated, January 14, 1970, entitled "Two-Week Intravenous Toxicity Study - Dogs" on compound, WR-2823 (AU 69115). In that report the results were reported without the histopathologic evaluation of tissues.

Submitted by

for


MARCELINA B. POWERS, D.V.M., M.S.
Director, Drugs and
Industrial Chemicals Department
Toxicology-Biosciences Laboratory

Pathology by


ROBERT P. KWAPIEN, D.V.M., Ph.D.
Staff Pathologist

saw

HISTOPATHOLOGICAL EVALUATION FOR MALE AND FEMALE BEAGLE DOGS
SACRIFICED AT TERMINATIONGROUP NO. 1
Male Dog No. 14121

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Moderate- to large-sized follicles predominated. Follicles lined by low cuboidal or flattened epithelium. Activity judged moderate by microscopic appearance.
Spleen:	
No alterations observed.	A few megakaryocytes scattered throughout red pulp. Small amount of brown, granular pigment in red pulp.
Urinary Bladder:	
No alterations observed.	One small area of ulceration infiltrated by polymorphonuclear leukocytes and hemorrhage. Inflammatory response spreads only a short distance into the submucosa.
The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, eye, heart, lung, gallbladder, liver, kidney, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, prostate, testis with epididymis, nerve with muscle, and rib (bone).	

GROUP NO. 1
Male Dog No. 14125

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Moderate- to large-sized follicles predominated. Follicles lined by low cuboidal or flattened epithelium. Follicular epithelium moderate in amount. Activity judged to be moderate based on microscopic appearances.
Adrenal:	
No alterations observed.	Cells of the zona fasciculata diffusely vacuolated.
Kidney:	
No alterations observed.	Occasional glomeruli in which the glomerular tuft was shrunken and a pink, amorphous sediment existed within the glomerular space along with small quantities of brown pigment.
Prostate:	
No alterations observed.	In one area, a focus of lymphocytic infiltration.
Nerve with Muscle:	
No alterations observed.	Section missing.

GROUP NO. 1
Male Dog No. 14125 (Continued)

GROSS	MICROSCOPIC

Bone Marrow:

No alterations observed.

Complete maturation of erythroid and myeloid elements.

Low number of megakaryocytes.

Small amounts of pigment within macrophages.

Activity low.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, eye, heart, lung, gallbladder, liver, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testis with epididymis, and bone.

GROUP NO. 2
Male Dog No. 14251

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Follicles predominantly large or medium size. Colloid brightly eosinophilic. Follicles lined by flattened or low cuboidal epithelium. Activity judged to be low by histologic criteria.
Spleen:	
No alterations observed.	Lymphoid follicles appeared normal. Greater abundance of red pulp than white pulp. Megakaryocytes rare. Pigment within red pulp present in very low quantities.
Kidney:	
No alterations observed.	Minimal, very infrequent areas of chronic interstitial nephritis, tubular regeneration, and tubular dilatation.
Urinary Bladder:	
Contains single, hemorrhagic-appearing area.	Slight acute inflammatory changes with hemorrhage, edema, and infiltrations of polymorphonuclear leukocytes. A few arterioles in the submucosa had fibrinoid changes.

GROUP NO. 2
Male Dog No. 14251 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Complete maturation of erythroid and myeloid
elements.

Megakaryocytes few in number.

Small amount of pigment in red pulp.

Activity judged to be low.

The following organs were not altered grossly or microscopically: liver and
pancreas.

334

GROUP NO. 2
Male Dog No. 14253

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Medium- and large-sized follicles. Colloid brightly eosinophilic. Follicles lined by flattened or low cuboidal epithelium. Activity judged to be low.
Spleen:	
No alterations observed.	Proportion of reticuloendothelial tissue to lymphoid tissue, high. Megakaryocytes infrequent. Pigment within red pulp very low.
Liver:	
No alterations observed.	Many hepatocytes, often swollen with a vacuolated cytoplasm.
Kidney:	
No alterations observed.	Few glomeruli had shrunken glomerular tufts with the presence of pink, proteinaceous exudate within the glomerular space.
Bone Marrow:	
No alterations observed.	Hematopoietic cells very scarce. Section composed mainly of fat. Minimal numbers of megakaryocytes.

335

GROUP NO. 2
Male Dog No. 14253 (Continued)

GROSS

MICROSCOPIC

Erythroid and myeloid cell maturation complete.

Amount of pigment within bone marrow very low.

Activity of marrow appeared low.

The following organ was not altered grossly or microscopically: urinary bladder.

GROUP NO. 3
Male Dog No. 14366

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Thyroid follicles predominantly medium to large
in size.

Colloid brightly eosinophilic.

Follicles lined by flattened or low cuboidal
epithelium.

Overall activity of thyroid judged to be low.

Spleen:

No alterations observed.

Lymphoid follicles appeared normal with a
preponderance of immature lymphocytic cells.

Ratio of reticuloendothelial tissue to lymphoid
tissue, high.

Kidney:

No alterations observed.

Minimal small foci of chronic interstitial
nephritis at corticomedullary junction.

Bone Marrow:

No alterations observed.

Erythroid and myeloid maturation appeared
complete.

Very few megakaryocytes present.

Presence of hemosiderin pigment very low.

Overall activity of the marrow low.

The following organs were not altered grossly or microscopically: liver,
urinary bladder, and pancreas.

GROUP NO. 3
Male Dog No. 14389

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Large- and medium-sized follicles predominated. Colloid brightly eosinophilic. Thyroid follicles lined by flattened or low cuboidal epithelium. Overall activity of thyroid judged to be low.
Gallbladder:	
Moderately distended.	Very few lymphoid follicles found in submucosa.
Spleen:	
No alterations observed.	Lymphoid follicles appeared normal. Quantity of reticuloendothelial tissue to lymphoid tissue, high. Minimal pigment within red pulp.
Kidney:	
Capsules appeared slightly rough.	
Medulla reddened.	Moderate changes primarily involving the cortex and consisting of focal areas of tubular dilatation; chronic interstitial nephritis; and tubular regeneration. Only occasionally did the dilated tubules contain any material. Small amounts of eosinophilic proteinaceous sediment were seen in some tubules.

GROUP NO. 3
Male Dog No. 14389 (Continued)

GROSS	MICROSCOPIC
	Dilated tubules lined by flattened or low cuboidal epithelium.
	Sparse infiltration by chronic inflammatory cells.
	Tubular regeneration and dilated tubules most conspicuous features.
	Often in regenerating tubules, intracytoplasmic brown, granular pigment.
	Similar pigment found in some unaffected convoluted tubules.
Pancreas:	
No alterations observed.	Minimal chronic interstitial pancreatitis.
Urinary Bladder:	
Mucosal surface appeared hemorrhagic.	Mucosal epithelium absent in some areas.
	In focal areas, mucosal epithelium appeared vacuolated, and small numbers of polymorphs infiltrated the epithelium.
	Within the submucosa, infiltrations by polymorphs and lymphocytic cells.
	Submucosal vessels markedly congested with small areas of hemorrhage in submucosa.
	Histologic changes correspond to a subacute cystitis.

GROUP NO. 3
Male Dog No. 14389 (Continued)

GROSS	MICROSCOPIC
Bone Marrow:	
No alterations observed.	Erythroid and myeloid cell maturation appeared complete.
	Moderate numbers of megakaryocytes.
	Minimal pigment.
	Activity low.
The following organ was not altered grossly or microscopically: liver.	

340

GROUP NO. 4
Male Dog No. 14494

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Follicles of moderate size predominated.

Follicles lined by low cuboidal or flattened epithelium.

Thyroid activity on the basis of histologic criteria judged to be low.

Gallbladder:

No alterations observed.

A few lymphocytic aggregates in submucosa.

Spleen:

No alterations observed.

Lymphoid follicles appeared normal.

Lymphoid follicles had a predominance of immature lymphocytic cells.

In a few cases, lymphoid follicles replaced by an acellular, and homogeneous eosinophilic material.

Liver:

Markedly distended (three times normal).

Centrilobular congestion noted.

Cells in centrilobular portions of the lobules had a decreased staining intensity.

Cord-like arrangement of hepatocytes in centrilobular areas slightly disorganized.

341

GROUP NO. 4
Male Dog No. 14494 (Continued)

GROSS

MICROSCOPIC

Kidney:

Capsular surface covered
with what appeared to be
gray, pitted areas.

Irregularities in capsular surface characterized
by small depressions.

Moderately great numbers of dilated tubules.

Dilated tubules often empty or contained a
small quantity of pale-staining eosinophilic
material.

Slight inflammatory cell infiltration.

Moderately large numbers of regenerating
tubules.

Numerous tubules in cortex both within and outside
these areas of hypercellularity contained
intracytoplasmic, brown, granular pigment.

Glomeruli, chiefly in affected areas, appeared
to show a thickening of basement membrane of
glomerular tufts.

Rarely, mineralized tubules in the medulla.

342

GROUP NO. 4
Male Dog No. 14494

GROSS	MICROSCOPIC
Adrenal:	
No alterations observed.	Activity within normal limits.
Eye:	
No alterations observed.	Slight acute conjunctivitis. Slight acute superficial keratitis. The inflammatory process extends only a short distance from the limbus margin.
Heart:	
No alterations observed.	In the epicardium near the larger coronary vessels, there was an area of acute inflammation chiefly within the fatty layer. The inflammatory process also extended a short distance into the myocardium. Involvement of the myocardium minimal.
Pancreas:	
No alterations observed.	Discrete interstitial alterations. Histologic changes, in most cases, involved the interlobular interstitial areas of acinar pancreas with small nests and bands of elongated cells which often contained a single discrete cytoplasmic vacuole. The type of cell showing these vacuolar changes could not be identified with certainty. In some cases, the vacuolated cells appeared to be exocrine cells or ductular cells. Inflammatory cells not observed.

343

GROUP NO. 4
Male Dog No. 14494 (Continued)

GROSS	MICROSCOPIC
Urinary Bladder:	
Walls slightly thickened and the mucosa appeared hemorrhagic.	Acute cystitis. Focal vacuolation of the mucosal epithelial cells. Infiltration of polymorphonuclear leukocytes into the mucosal epithelium. Focal infiltration of polymorphonuclear leukocytes into the submucosa and small areas of hemorrhage. Submucosal vessels congested.
Prostate:	
No alterations observed.	Minimal acute prostatitis with infiltrations of polymorphs in the interstitium and in the capsule. Collections of purulent exudate in the lumen of some prostatic gland.
Testis:	
No alterations observed.	Slight testicular degeneration, with the presence in seminiferous tubules of giant cells and other abnormal forms.

344

GROUP NO. 4
Male Dog No. 14494 (Continued)

GROSS	MICROSCOPIC
	Nuclei of some spermatogonia very large and vacuolated.
	In the head of the epididymis, there was pronounced vacuolar change of the epithelial cells lining the epididymal duct.
	To a marked degree, there was phagocytosis of spermatozoal precursor cells by the epididymal duct epithelium.
Bone Marrow:	
No alterations observed.	Normal maturation of erythroid and myeloid elements.
	Megakaryocytes in small numbers.
	Activity judged to be moderate.
The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, lung, stomach, small intestine, large intestine, mesenteric lymph node, nerve with muscle, and rib (bone).	

345

GROUP NO. 4
Male Dog No. 14502

GROSS

MICROSCOPIC

Thyroid:

Right thyroid 2 x 3 mm.; cyst-
like formations on anterior
end.

Thyroid follicles moderate or large in size.
Follicles at periphery of thyroid gland
distended with colloid and probably represent
cyst-like formations seen grossly.
Parafollicular tissue moderate in amount.
Thyroid follicles lined by low cuboidal or
flattened epithelium.
Activity low.

Gallbladder:

Distended approximately two
times normal size.

Few lymphoid follicles in submucosa.

Spleen:

No alterations observed.

Lymphoid follicles relatively large with
moderate numbers of mitotic figures evident
within their centers.
Immature lymphocytic cell predominated.
Minimal pigment within macrophages of red pulp.
Megakaryocytes infrequently observed.

Liver:

No alterations observed.

At peripheral portions of the lobule, liver
cells vacuolated and slightly swollen.
Pigment within Kupffer cells minimal.

346

GROUP NO. 4
Male Dog No. 14502 (Continued)

GROSS	MICROSCOPIC
Kidney:	
Capsule white and pitted.	
Medulla and hilus of	
kidney reddened.	Linear streaks of hypercellularity in cortex. Moderate numbers of lymphocytic cells and few plasma cells infiltrated affected areas. Many tubules in affected areas closely packed, small with increased basophilic. Moderate regenerative changes. Moderate numbers of tubules in areas dilated and contained small amount of pink, protein- aceous sediment. Tubules both within and outside affected areas contained small, brown, granules of intracytoplasmic pigment. Moderate numbers of glomeruli showed thickening of the basement membrane of the tuft as well as the basement membrane of Bowman's capsule. Fibrosis minimal. Medulla rarely involved, but small areas of inflammatory cell infiltration and regenerative tubules occasionally seen in outer medulla. Rarely, mineralized tubules in medulla. Rarely, polymorphs within a few dilated tubules.

347

GROUP NO. 4
Male Dog No. 14502 (Continued)

GROSS	MICROSCOPIC
Adrenal:	
No alterations observed.	Activity within normal limits.
Prostate:	
No alterations observed.	Moderate suppurative prostatitis with purulent exudate in many glandular lumens. Affected tubules surrounded by small numbers of acute and chronic inflammatory cells.
Urinary Bladder:	
Walls thickened.	
Mucosal surface hemorrhagic.	Bladder mucosa varied markedly in thickness. Bladder mucosa completely denuded in some areas. Mucosal epithelium rather generally infiltrated with neutrophils, with focal epithelial vacuolation. Within the submucosa many large areas of hemorrhage, infiltrations of polymorphs, and mononuclear inflammatory cells. Basal layers of the submucosa quite edematous. Mild leukocytic infiltration also seen within superficial muscle layers.
Testis:	
Odd, brown tinge evident grossly.	Moderately large numbers of spermatozoa in epididymal ducts.

34/8

GROUP NO. 4
Male Dog No. 14502 (Continued)

GROSS

MICROSCOPIC

Seminiferous tubules exhibited a moderate
to high level of activity.

Bone Marrow:

No alterations observed.

Myeloid and erythroid maturation complete.

Megakaryocytes few in numbers.

Overall activity judged to be slight.

The following organs were not altered grossly or microscopically: brain,
spinal cord, pituitary, eye, heart, lung, stomach, pancreas, small intestine,
large intestine, mesenteric lymph node, nerve with muscle, and rib (bone).

349

GROUP NO. 5
Male Dog No. 14504

GROSS	MICROSCOPIC
Brain:	
No alterations observed.	Mild autolysis.
Pituitary:	
No alterations observed.	Autolytic changes evident with individualization of cells in pars distalis.
Thyroid:	
Enlarged.	Many large- and medium-sized follicles. Colloid richly eosinophilic. Epithelial cells lining follicles predominantly low cuboidal or cuboidal. Desquamation of some follicular epithelial cells into the centers of thyroid follicles, and probably represented an artifact. Activity low.
Adrenal:	
No alterations observed.	Autolytic changes, especially in adrenal medulla. Occasional foci of cellular vacuolation in zona glomerulosa. Cells within the zona fasciculata appeared rather uniformly vacuolated.
Eye:	
No alterations observed.	Poor histologic preparation. Cornea folded.

350

GROUP NO. 5
Male Dog No. 14504 (Continued)

GROSS	MICROSCOPIC
	Retina detached and choroid disrupted.
	Retina showed evidence of postmortem autolysis.
	Mild chronic conjunctivitis of palpebral conjunctiva.
Lung:	
No alterations observed.	Pronounced congestion.
	Significant autolytic changes.
Gallbladder:	
No alterations observed.	Advanced autolysis.
	Impossible to evaluate histologically.
Spleen:	
Enlarged.	Advanced autolysis.
	A critical histopathologic evaluation impossible.
Liver:	
Enlarged.	Areas of autolysis present.
	Marked congestion.
	Much acid hematin pigment distributed throughout liver tissue.
Kidney:	
No alterations observed.	Autolytic changes present which made critical evaluation impossible.
	Cortex and medulla markedly congested.

GROUP NO. 5
Male Dog No. 14504 (Continued)

GROSS	MICROSCOPIC
	Epithelium lining renal pelvis quite vacuolated and infiltrated by small numbers of polymorphs.
Stomach:	
No alterations observed.	Autolytic changes.
Small Intestine:	
No alterations observed.	Extensive autolysis.
Large Intestine:	
No alterations observed.	Extensive autolysis.
Mesenteric Lymph Node:	
No alterations observed.	Autolytic changes.
Urinary Bladder:	
No alterations observed.	Much of the mucosal epithelium had undergone postmortem desquamation; otherwise, not remarkable. Inflammatory changes not evident in submucosa.
Prostate:	
No alterations observed.	Poor cytological detail due to postmortem autolytic changes.
Testis:	
No alterations observed.	Normal spermatozoa formation. Spermatozoa present within epididymal ducts. Overall spermatozoa formation judged to be low.

352

GROUP NO. 5
Male Dog No. 14504 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Many artifacts of histologic preparation.

Poor cytologic detail prevents an adequate
appraisal of hematogenic activity.

The following organs were not altered grossly or microscopically: heart, pancreas,
nerve with muscle, and bone.

GROUP NO. 5
Male Dog No. 14515

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Follicles predominantly large or medium size. Colloid brightly eosinophilic. Follicles for the most part lined by flattened or low cuboidal epithelium. Parafollicular tissue very scant in amount.
Adrenal:	
No alterations observed.	Cells of the zona fasciculata rather uniformly and finely vacuolated.
Eye:	
No alterations observed.	Many artifacts (folded cornea, shattered lens, detached retina, and disrupted choroid). Otherwise, histologic appearance not remarkable.
Gallbladder:	
No alterations observed.	Autolytic changes present.
Spleen:	
Enlarged.	Collections of polymorphs generally distributed throughout red pulp. Autolytic changes make interpretation difficult.
Liver:	
No alterations observed.	Congestion. Focal hepatic cell vacuolation.

354

GROUP NO. 5
Male Dog No. 14515 (Continued)

GROSS	MICROSCOPIC
Kidney:	
No alterations observed.	Great numbers of dilated tubules in cortex and medulla. Tubules essentially devoid of any sediment or foreign material, but a few contained small amount of eosinophilic, granular sediment. Affected tubules appeared to be mainly distal convoluted tubules and collecting tubules. Dilated tubules lined by an intact epithelial layer, which is attenuated. Proteinaceous cast present in small numbers in collecting tubules near the renal papilla. A few recent soft thrombi seen in veins in the medulla. Only infrequent foci of chronic inflammatory cells were seen in the cortex.
Stomach:	
No alterations observed.	Section not present.
Small Intestine:	
No alterations observed.	Autolysis of the superficial mucosa.
Prostate:	
No alterations observed.	Section missing.

355

GROUP NO. 5
Male Dog No. 14515 (Continued)

GROSS

MICROSCOPIC

Testis:

No alterations observed.

Spermatogenic activity very low.

Very low number of mature spermatozoa within
epididymis.

Spermatozoal precursors found within some
epididymal ducts.

It was possible that the dog was just approaching
sexual maturity.

Bone Marrow:

No alterations observed.

Complete maturation of erythroid and
myeloid cells.

Megakaryocytes present in low numbers.

Very low amount of pigment present.

Overall activity of the marrow judged to be
moderate.

The following organs were not altered grossly or microscopically: brain,
pituitary, heart, lung, pancreas, large intestine, mesenteric lymph node,
urinary bladder, nerve with muscle, and bone.

356

GROUP NO. 1
Female Dog No. 14333

GROSS	MICROSCOPIC
Brain:	
No alterations observed.	At the level of the pons, one capillary in the white matter cuffed by a small number of lymphocytes and microglial cells; not a significant alteration.
Thyroid:	
No alterations observed.	A predominance of moderate-sized follicles. Follicles lined for the most part by a low cuboidal or flattened epithelium. Moderate parafollicular tissue. Overall activity judged to be low.
Adrenal:	
No alterations observed.	Moderate vacuolation of cells in zona fasciculata.
Spleen:	
No alterations observed.	A tip of splenic parenchyma exhibited postmortem autolysis. Lymphoid follicles of normal size and distribution with a predominance of immature forms present. Megakaryocytes seen rarely. Adjacent to one of the large arterioles in the splenic trabeculum; loosening of the smooth

357

GROUP NO. 1
Female Dog No. 14333 (Continued)

GROSS	MICROSCOPIC
	muscle fibers, with concomitant hemorrhage and, deposition of hemosiderin pigment. Hemosiderin pigment rarely seen in red pulp.
Liver:	
No alterations observed.	Slight vacuolation of hepatocytes near periportal areas.
Pancreas:	
No alterations observed.	Minimal focal chronic pancreatitis.
Small Intestine:	
No alterations observed.	A few glands cystic-filled with a mucous-appearing substance, a few desquamated epithelial cells, and a few leukocytes.
Urinary Bladder:	
No alterations observed.	The mucosal epithelium intact and regular in thickness. Polymorphs rather generally infiltrated the mucosal epithelium. Focal areas of hemorrhage into the mucosal epithelium. Submucosa congested, edematous in places, and rather diffusely infiltrated with, mononuclear inflammatory cells, and polymorphs. Changes corresponded to an acute cystitis of moderate degree.

358

GROUP NO. 1
Female Dog No. 14333 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Erythroid maturation of cells complete.

Moderately high numbers of meagkaryocytes.

Quantity of pigment very low.

Hematogenic activity moderately high.

The following organs were not altered grossly or microscopically: pituitary, eye, heart, lung, gallbladder, kidney, stomach, large intestine, mesenteric lymph node, uterus, ovary, nerve with muscle, and bone.

359

GROUP NO. 1
Female Dog No. 14348

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Majority of thyroid follicles large and medium size and lined by flattened or low cuboidal epithelium. Numerous parafollicular cells. Overall activity of thyroid judged to be low.
Adrenal:	
No alterations observed.	Moderate vacuolation of cells within the zona fasciculata.
Eye:	
No alterations observed.	Poor histologic preparation. Cornea markedly folded and retina detached. Choroid disrupted in some places. Intraocular structures were poorly fixed, infiltrated, and impossible to evaluate critically.
Lung:	
No alterations observed.	A few areas of alveolar thickening in focal locations by lymphocytes, erythrocytes, and a few polymorphs.

360

GROUP NO. 1
Female Dog No. 14348 (Continued)

GROSS	MICROSCOPIC
Spleen:	
No alterations observed.	Splenic follicles normal in size and distribution. Megakaryocytes infrequent. Minimal pigment within macrophages of red pulp.
Liver:	
No alterations observed.	Many hepatocytes slightly swollen and vacuolated. Very small foci of leukocytic infiltration in periportal areas.
Kidney:	
No alterations observed.	Infrequent glomeruli were sclerotic and surrounded by a small rim of chronic inflammatory cells.
Urinary Bladder:	
No alterations observed.	Tissue poorly stained, probably the result of poor fixation. Areas of cystitis not seen.
Uterus:	
No alterations observed.	Section poorly stained. Otherwise, not remarkable.
Ovary:	
No alterations observed.	Section poorly stained.

361

GROUP NO. 1
Female Dog No. 14348 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Myeloid and erythrocytic maturation complete.

Megakaryocytes relatively numerous.

Activity moderate.

Minimal pigment present in red pulp.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, nerve with muscle, and bone.

362

GROUP NO. 2
Female Dog No. 14355

GROSS

MICROSCOPIC

Pituitary:

Small cyst in base.

One large cyst and a few smaller cysts involving the pars anterior.

The larger cysts filled by fine, fibrillar, eosinophilic material, with occasional globules, and cysts lined by flattened or columnar epithelium.

Some of the columnar cells resemble goblet cells, and had a brush border.

Thyroid:

No alterations observed.

Medium-sized with large-sized follicles predominated.

Colloid brightly eosinophilic.

Follicles lined by flattened or low cuboidal epithelium.

Functional activity of the thyroid appeared to be low.

Spleen:

No alterations observed.

Lymphoid follicles appeared normal.

Proportion of reticuloendothelial tissue to lymphoid tissue, high.

Megakaryocytes infrequent.

Occasional pigment within red pulp.

343

GROUP NO. 2
Female Dog No. 14355 (Continued)

GROSS	MICROSCOPIC
Liver:	
No alterations observed.	Hepatocytes in centrilobular and midzonal portions of lobules much lighter in staining intensity than those at the periphery. A few areas of fibrosis and chronic inflammation in subcapsular locations.
Kidney:	
No alterations observed.	One tiny area of chronic interstitial nephritis. No tubular dilatation.
Bone Marrow:	
No alterations observed.	Low numbers of megakaryocytes. Erythroid and myeloid maturation complete. Small amounts of pigment. Activity moderate.

364

GROUP NO. 2
Female Dog No. 14457

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Medium- and large-sized follicles predominated. Colloid bright eosinophilic. Follicles lined by flattened to low cuboidal epithelium. Functional activity judged to be low.
Gallbladder:	
Could not be located grossly.	Section not available for microscopic examination.
Spleen:	
No alterations observed.	Follicles appeared normal. Much greater abundance of reticuloendothelial tissue than lymphoid tissue. Megakaryocytes infrequently seen. Occurrence of pigment within red pulp very low.
Liver:	
No alterations observed.	Mild chronic pericholangitis. Very slight amount of periportal fibrosis.
Kidney:	
No alterations observed.	Minimal areas of chronic interstitial nephritis and tubular dilatation in cortex. In one of the affected areas, dilated tubules lined by flattened or low cuboidal epithelium and devoid of any material in their lumens. Slight chronic pyelitis.

365

GROUP NO. 2
Female Dog No. 14457 (Continued)

GROSS	MICROSCOPIC
Urinary Bladder:	
Neck of bladder red.	Not remarkable.
Bone Marrow:	
No alterations observed.	Erythroid and myeloid maturation complete.
	Small numbers of megakaryocytes.
	Very little pigment present.
	Activity of the marrow appeared to be low.

366

GROUP NO. 3
Female Dog No. 14417

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Moderate- or large-sized follicles predominated.

Colloid predominantly brightly eosinophilic.

Follicles lined by flattened or low cuboidal
epithelium.

Functional activity of thyroid based on
histologic criteria was low.

Spleen:

No alterations observed.

Lymphoid follicles appeared normal.

The bulk of the splenic tissue composed of
reticuloendothelial tissues.

Megakaryocytes occasionally seen.

Minimal of pigment within red pulp.

Kidney:

No alterations observed.

Very minimal chronic interstitial nephritis.

Areas of tubular regeneration or tubular
dilatation not seen.

Bone Marrow:

No alterations observed.

Erythroid and myeloid maturation appeared
complete.

Erythroid hyperplasia present.

Red blood cell precursors very numerous.

367

GROUP NO. 3
Female Dog No. 14417 (Continued)

GROSS

MICROSCOPIC

Numbers of megakaryocytes very numerous.

Small amount of pigment.

The following organs were not altered grossly or microscopically: liver and urinary bladder.

GROUP NO. 3
Female Dog No. 14435

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Large- or medium-sized follicles predominated. Colloid brightly eosinophilic. Thyroid follicles lined by low or flattened cuboidal epithelium. Activity of thyroid low as judged by histologic criteria.
Gallbladder:	
Distended.	Scattering of lymphocytes and plasma cells in the submucosa, but no well-defined follicles.
Spleen:	
No alterations observed.	Lymphoid follicles normal. Reticuloendothelial tissue much more abundant than white pulp. Occasional megakaryocytes. Slight amounts of pigment within red pulp.
Kidney:	
No alterations observed.	Moderate tubular regeneration and tubular dilatation, primarily, involving the cortex. Occasional foci of chronic interstitial nephritis. Occasional glomeruli appeared sclerotic.

369

GROUP NO. 3
Female Dog No. 14435 (Continued)

GROSS	MICROSCOPIC
	Transitional epithelium lining the renal pelvis, vacuolated in focal areas, with infiltrations of neutrophils, and chronic inflammatory cells.
	Within the submucosa diffuse collections of acute and chronic inflammatory cells and some lymph follicle formations.
	Changes correspond to a subacute pyelitis.
Urinary Bladder:	
No alterations observed.	Moderate chronic cystitis.
	Mucosal epithelium was vacuolated with focal infiltrations by polymorphonuclear leukocytes.
	Within the submucosa were many foci of chronic inflammatory cells.
	Many vessels in submucosa were congested.
Bone Marrow:	
No alterations observed.	Erythroid and myeloid maturation appeared complete.
	Only a few megakaryocytes seen.
	Small amounts of pigment present.
	Activity of the marrow appeared to be very low.
The following organs were not altered grossly or microscopically: liver and pancreas.	

GROUP NO. 4
Female Dog No. 14458

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Moderate-sized follicles predominated. Follicles lined by flattened or low cuboidal epithelium. Activity low.
Gallbladder:	
Distended approximately four times normal size.	Chronic cholecystitis with generalized infiltration of the tunic propria with lymphocytes and plasma cells. Infiltration extended into superficial muscular tunics.
Spleen:	
No alterations observed.	Lymphoid follicles normal in appearance. Reticuloendothelial tissue predominated. Amount of pigment in red pulp very low. Megakaryocytes seen infrequently.
Kidney:	
Capsular surface appeared rough with some gray discoloration. Medulla reddened.	Slight chronic interstitial nephritis involving the cortex with the presence of lymphocytes and plasma cells.

371

GROUP NO. 4
Female Dog No. 14458 (Continued)

GROSS	MICROSCOPIC
	In affected areas, moderate numbers of cortical tubules dilated, but essentially devoid of proteinaceous sediment.
	Moderate numbers of tubules in affected areas showed regenerative activity.
	Fibrosis appeared minimal.
	Intracytoplasmic, brown pigment found in very low quantities within cytoplasm of cortical tubules.
	Minimal cast formation in medullary tubules.
Liver:	
No alterations observed.	Focal chronic hepatitis in sections of liver adjacent to gallbladder section.
	Mild periportal chronic inflammation.
Eye:	
No alterations observed.	Severe conjunctivitis with focal ulceration of conjunctival epithelium.
	Large lymphoid follicle formations in the sub-epithelial tissues of the palpebral conjunctiva near the limbus inflammatory cell adhered to the cornea.
	Other structures not remarkable.
Pancreas:	
No alterations observed.	Vacuolar pancreatopathy similar to that described in male Dog No. 14494.

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GROUP NO. 4
Female Dog No. 14458 (Continued)

GROSS	MICROSCOPIC
Urinary Bladder:	
No alterations observed.	Slight congestion of the submucosal vessels; otherwise, not remarkable.
Ovary:	
No alterations observed.	Many oocytes within small follicles in the cortex. Corpora lutea not seen.
Uterus:	
No alterations observed.	Small section included for examination not remarkable.
The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, heart, lung, stomach, large intestine, mesenteric lymph node, nerve with muscle, and rib (bone).	

GROUP NO. 4
Female Dog No. 14468

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Small- and medium-sized follicles predominated. Colloid within follicles brightly eosinophilic. Follicles lined by flattened or low cuboidal epithelium. Activity moderate.
Gallbladder:	
No alterations observed.	No section available for examination.
Spleen:	
No alterations observed.	Lymphoid follicles appeared normal. Reticuloendothelial tissues comprised the bulk of the organ. Very few megakaryocytes. Small amount of pigment in red pulp.
Liver:	
No alterations observed.	Minimal vacuolation of hepatocytes in periportal locations.
Kidney:	
No alterations observed.	Moderate areas of interstitial nephritis chiefly in cortex. In these areas, small numbers of dilated tubules which occasionally contained a small amount of eosinophilic granular sediment.

374

GROUP NO. 4
Female Dog No. 14468 (Continued)

GROSS	MICROSCOPIC
	Moderate numbers of tubules undergoing regeneration, small with closely crowded nuclei. Small amounts of lymphocytes and plasma cells infiltrated affected areas. Small amount of brown, granular pigment in some tubules in affected areas. Small numbers of glomeruli in which basement membrane of glomerular tuft thickened. Other glomeruli atrophic.
Urinary Bladder:	
No alterations observed.	Slight congestion of submucosal vessels; other- wise, not remarkable.
Uterus:	
No alterations observed.	Minimal focal endometritis with small numbers of polymorphs within uterine glands. Affected glands surrounded by small numbers of reticuloendothelial and lymphocytic cells.
Ovary:	
No alterations observed.	Many oocytes within small follicles occupying the cortex. Corpora lutea not seen.

375

GROUP NO. 4
Female Dog No. 14468 (Continued)

GROSS	MICROSCOPIC
Bone Marrow:	
No alterations observed.	Erythroid and myeloid maturation of cells complete.
	Megakaryocytes numerous.
	Pigment moderate in amount.
	Hematogenic activity moderately high.
The following organs were not altered grossly or microscopically: brain spinal cord, pituitary, liver, adrenal, eye, heart, lung, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, nerve with muscle, and rib (bone).	

GROUP NO. 5
Female Dog No. 14470

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Majority of follicles large or medium size. Colloid brightly eosinophilic. Follicles lined by flattened or low cuboidal epithelium. Thyroid activity according to histologic criteria appeared to be low.
Eye:	
No alterations observed.	Globe partially collapsed. Cornea wrinkled. Lens badly shattered. Parts of retina and choroid disrupted or detached.
Lung:	
No alterations observed.	Artifactual compression of alveolar septa.
Spleen:	
Enlarged.	Autolysis; impossible to evaluate.
Liver:	
Pale appearance.	Diffuse, fine vacuolation of hepatocytes. Congestion. Autolysis.

377

GROUP NO. 5
Female Dog No. 14470 (Continued)

GROSS	MICROSCOPIC
Kidney:	
No alterations observed.	Large numbers of dilated tubules within cortex and outer medulla. Dilated tubules for the most part empty, but occasionally a small amount of pink, granular, exudate within lumens. Dilated tubules lined by flattened or low cuboidal epithelium. Occasional minute foci of chronic interstitial nephritis. In inner medulla, the presence of pink, proteinaceous cast within tubules was more apparent.
Mesenteric Lymph Node:	
No alterations observed.	Section missing.
Bone Marrow:	
No alterations observed.	Normal erythroid and myeloid cell maturation. Megakaryocytes moderately numerous. Presence of pigment very low. Overall activity of marrow judged to be low.
The following organs were not altered grossly or microscopically: brain, pituitary, adrenal, heart, gallbladder, stomach, small intestine, large intestine, pancreas, urinary bladder, ovary, nerve with muscle, and bone.	

GROUP NO. 5
Female Dog No. 14471

GROSS	MICROSCOPIC
Thyroid:	
No alterations observed.	Thyroid follicles predominantly large or medium size. Colloid brightly eosinophilic. Follicles lined, for the most part, by flattened or low cuboidal epithelium. Overall activity judged to be low.
Adrenal:	
No alterations observed.	In focal areas, cells of the zona glomerulosa very vacuolated. In a few cases, it appeared that continuous cell borders had ruptured, leaving small cystic areas.
Eye:	
No alterations observed.	Artifacts present. Globe partially collapsed. Cornea wrinkled. Lens badly shattered. Segments of retina detached. Significant histopathologic changes not observed.

GROUP NO. 5
Female Dog No. 14471 (Continued)

GROSS	MICROSCOPIC
Spleen:	
Enlarged.	Lymphoid follicles few in number. Moderate numbers of polymorphs distributed throughout red pulp. Amount of pigment within red pulp very low.
Liver:	
No alterations observed.	Generalized congestion; otherwise, not remarkable.
Kidney:	
No alterations observed.	Moderately great numbers of dilated tubules predominantly in cortex but to a lesser extent within medulla. These tubules, for the most part, are empty but occasionally contained small amounts of pink, granular material within lumen. Very minimal areas of chronic interstitial nephritis seen. Dilated tubules lined by an intact, flattened or low cuboidal epithelium. Granular and hyaline casts more numerous in tubules in the inner medulla.

380

GROUP NO. 5
Female Dog No. 14471 (Continued)

GROSS	MICROSCOPIC

Bone Marrow:

No alterations observed.

Myeloid and erythroid maturation complete.

Megakaryocytes moderately numerous.

Only small amounts of pigment.

Activity moderate.

The following organs were not altered grossly or microscopically: brain, pituitary, heart, lung, gallbladder, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, uterus, ovary, nerve with muscle, and bone.

SUMMARY

Twenty clinically healthy beagle dogs (10 males and 10 females) were divided randomly into five groups and administered the compound (WR 2823) intravenously once daily for 14 days at levels of 20 mg/kg (Group No. 2), 40 mg/kg (Group No. 3), 80 mg/kg (Group No. 4), and 160 mg/kg (Group No. 5). Dogs in Group No. 1 served as untreated controls and received only saline injections. After 14 days, the dogs in Groups No. 1, No. 2, No. 3, and No. 4 were necropsied. All of the Group No. 5 animals died following three or four doses of the compound. Designated tissues were collected and placed in 10% buffered formalin, except for testes which were placed in Bouin's fluid, and eyes which were usually placed in alcoholic formalin. The eyes from Group No. 5 dogs were preserved in 10% neutral formalin. The following tissues were examined microscopically from two males and two females in each of Groups No. 1, No. 4, and No. 5: brain, pituitary, eye, thyroid, lung, heart, spleen, liver, gallbladder, kidney, adrenal, stomach, pancreas, small intestine, large intestine, urinary bladder, mesenteric lymph node, testis, ovary, prostate, uterus, rib (bone), and bone marrow. Sections of thoracic spinal cord from Groups No. 1 and No. 4 were also examined microscopically. From the dogs in Groups No. 2 and No. 3, the thyroid, liver, spleen, kidney, bone marrow, and unusual lesions were examined microscopically. Except for the Group No. 5 animals, all the dogs were catheterized, and a urine sample collected on the day before euthanasia.

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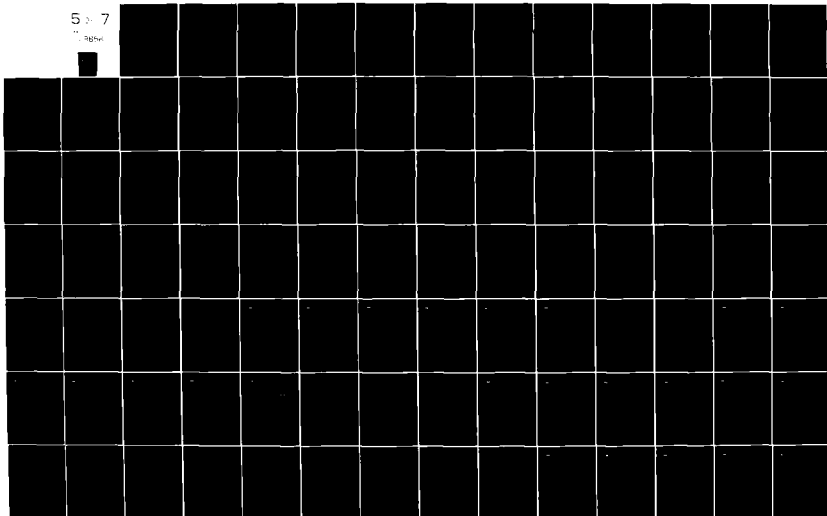
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A definite, compound-associated nephropathy was seen in Groups No. 3 and No. 4 animals. The typical triad of changes consisted of chronic interstitial nephritis, tubular regeneration, and tubular dilatation and were seen in all Group No. 4 dogs and from two dogs in Group No. 3. In some cases, the regenerating tubules contained an increased amount of brown, intracytoplasmic pigment. In three of the Group No. 2 animals, one or more of these same histopathologic changes were seen, but the lesions were very minimal. There is a good likelihood that the renal lesions in Group No. 2 dogs were compound related, especially since they resembled the triad of histopathologic changes which occurred in Groups No. 3 and No. 4 dogs, and also because there was an absence of histopathologic changes in the kidneys of the control dogs. Histopathologic interpretation was difficult in the Group No. 5 animals, since they died after receiving two or three injections of the compound; and the tissues, in some cases, showed autolytic changes. In three of the five kidney sections from the Group No. 5 animals, there were pronounced tubular dilatation and the presence of renal tubular cast formation. Given sufficient time, these renal lesions may have progressed to the spectrum of histopathologic changes seen in Groups No. 3 and No. 4 dogs. There were neither significant inflammatory changes nor unequivocal nephrotic lesions in the kidneys of Group No. 5 dogs. The occurrence of acute cystitis and hemorrhage in urinary bladders from dogs in Groups No. 1 (two dogs), No. 2 (two dogs), and No. 4 (two dogs) was probably due to the catheterization procedure on the day preceding on the termination of the experiment. Two Group No. 3 dogs and one Group No. 4 dog had subacute or chronic cystitis which also appeared to be unrelated to the compound administration.

The compound-related conjunctivitis seen grossly was confirmed microscopically. Incidental findings in Group No. 4 dogs (not compound related) consisted of endometritis (one dog), prostatitis (two dogs), and testicular degeneration (one dog). Pancreatic acinar changes in two Group No. 4 animals were unusual and difficult to characterize histopathologically. These changes consisted of a slight interstitial thickening or prominence with discrete cytoplasmic vacuolation. The vacuolated cells frequently occurred as discrete small nests or thin bands of cells in the interlobular areas of the acinar pancreas. The cell-type showing this vacuolation could not be identified with certainty. The significance of this histologic change was difficult to assess, since similar pancreatic alterations were seen infrequently in control dogs.

Incidental findings in tissues from control dogs consisted of cystic glands in the small intestine, hepatic cell vacuolation, and focal pancreatitis. Rare or incidental histopathologic findings in the treated animals which were not believed to be compound induced included pituitary cyst, pulmonary congestion, chronic coleocystitis, pericholangitis, hepatic congestion, hepatocytic vacuolation, slight hepatic fibrosis, and chronic inflammation.

The microscopic appearances of the spleen, bone marrow, ovary, testis, pituitary, thyroid, adrenal, and mesenteric lymph node were comparable between control and treated groups. Sections of eye, heart, lung, gallbladder, small intestine, large intestine, nerve with muscle, rib bone, and stomach were not remarkable in the control or treated groups.

In the summary section of the Project No. 193-406 study, a compound-related enlargement of the spleen was reported in the Group No. 5 dogs. However, the presence of autolytic changes in the spleen prevented a detailed microscopic appraisal. Congestion of the spleen was observed microscopically in the Group No. 5 dogs, but this most probably does not represent a compound effect since these animals died and, further, were not exsanguinated as were the other dogs in the study.

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KEY TO DETAILED HISTOPATHOLOGY INCIDENCE TABLE

N = No Section

X = Not Remarkable

A = Autolysis

P or ✓ = Present or Taken

0 = Absent

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderate to Severe

5 = Severe

DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS	ANIMAL NUMBER	MALES									
		GROUP NUMBER									
		1		2		3		4		5	
		14121	14125	14251	14253	14366	14389	14494	14502	14504	14515
BRAIN		X	X					X	X	A	X
PITUITARY Cysts		X		X				X	X	A	X
THYROID											
Level of Activity		3	3	2	2	2	2	2	2	2	2
Epithelial Height		2	2	2	2	2	2	2	2	2-3	2
Follicular Size		4	4	4	4	4	4	3	4	4	4
ADRENAL										A	
Normal Activity		P	P					P	P	P	P
EYE		X	X						X	A	X
Conjunctivitis								2		2	
Artifact											
HEART		X	C						X	X	X
Epicarditis & Myocarditis								P			
LUNG		X	X						X	A	X
Congestion										P	
GALLBLADDER		X	X			X	X	X	X	A	A
Cholecystitis											
SPLEEN		X	X	X	X	X	X	X	X	A	A
Congestion										P	P
LIVER		X	X	X		X	X			A	
Hepatitis											
Pericholangitis											
Fibrosis of Chronic Inflammation											
Vacuolation											
Congestion					P			P	P		P
STOMACH		X	X						X	A	N

DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS	ANIMAL NUMBER	MALES									
		GROUP NUMBER									
		1		2		3		4		5	
		14121	14125	14251	14253	14366	14389	14494	14502	14504	14515
URINARY BLADDER											
Acute Cystitis	P	X		X		X				A	X
Subacute or Chronic Cystitis							P		P		
Ulcerations	P										
Hemorrhage	P			P			P	P	P		
KIDNEY											
Interstitial Nephritis	X	X		X						A	
Tubular Regeneration				1		1	3	2	3		1
Tubular Dilatation				1			3	4	3		
Cast Formation				1			3	4	3		5
Pigment											P
Pyelitis								P	P	1	

DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS	ANIMAL NUMBER	FEMALES									
		GROUP NUMBER									
		1		2		3		4		5	
		14333	14348	14355	14457	14417	14435	14458	14468	14470	14471
BRAIN		X	X					X	X	X	X
PITUITARY		X	X					X	X	X	X
Cysts				P							
THYROID											
Level of Activity		2	2	2	2	2	2	2	3	2	2
Epithelial Height		2	2	2	2	2	2	2	2-3	2	2
Follicular Size		3	4	4	4	4	4	3	2-3	4	4
ADRENAL											
Normal Activity		P	P					P	P	P	P
EYE		X	A						X		
Conjunctivitis								5			
Artifact										P	P
HEART		X	X					X	X	X	X
Epicarditis & Myocarditis											
LUNG		X						X	X	X	X
Congestion											
GALLBLADDER		X	X		N		X		N	X	X
Cholecystitis								P			
SPLEEN		A	X	X	X	X	X	X	X	A	X
Congestion										P	P
LIVER						X	X				X
Hepatitis								P			
Pericholangitis					2						
Fibrosis of Chronic Inflammation				2	2						
Vacuolation		P	P					P		P	
Congestion											
STOMACH		X	X					X	X	X	X

DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS	ANIMAL NUMBER	FEMALES									
		GROUP NUMBER									
		1		2		3		4		5	
		14333	14348	14355	14457	14417	14435	14458	14468	14470	14471
PANCREAS			X						X	X	X
Vacuolated Interstitial								P			
Pancreatopathy											
Pancreatitis		1				1					
SMALL INTESTINE			X						X	X	X
Cystic glands		P									
LARGE INTESTINE		X	X					X	X	X	X
MESENTERIC LYMPH NODE		X	X					X	X	N	X
PROSTATE											
Prostatitis											
UTERUS		X						X			X
Artifact			P								
Endometritis									1		
TESTIS											
Testicular Degeneration											
OVARY		X						X	X	X	X
Artifact			P								
NERVE WITH MUSCLE		X	X					X	X	X	X
RIB		X	X					X	X	X	X
BONE MARROW											
Hematogenic Activity		4	3	3	2		2	4		2	3
Numbers of Megakaryocytes		4	3	2	2	4	3	2	3	3	3
Erythroid Hyperplasia						4					

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DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS	ANIMAL NUMBER	FEMALES									
		GROUP NUMBER									
		1		2		3		4		5	
		14333	14348	14355	14457	14417	14435	14458	14468	14470	14471
URINARY BLADDER											
Acute Cystitis	P	X		X		X		X	X	X	X
Subacute or Chronic Cystitis							P				
Ulcerations											
Hemorrhage	P										
KIDNEY											
Interstitial Nephritis	X	X									
Tubular Regeneration				1	1	1	2	2	3	1	1
Tubular Dilatation				1			3	3	3		
Cast Formation					1		3	3	2	5	4
Pigment								P	P	P	P
Pyelitis						P	5	P	P		

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Sponsor: Walter Reed Army Institute of Research

Date: September 30, 1970

Material: WR 2823 AC (AU 69115)
WR 2823 AB

Lot No: WR 8-55D
BV-WR-01

Subject: REPORT NO. 38
Two-Week Intravenous Toxicity Study - Rats
Project No. 193-412

SUMMARY OF FINDINGS

This study was conducted to evaluate and compare the effects of short term intravenous administration of WR 2823 AC (AU 69115) and WR 2823 AB in male and female albino rats.

Criteria evaluated for compound effect were physical appearance and behavior, body weight gains, food consumption, survival, clinical laboratory results, and gross and microscopic findings at necropsy.

The following signs were observed in the test rats after the daily dose: depression, watery eyes, sleepy appearance, and a heart beat of normal rate but increased depth or intensity. Group No. 3 (WR 2823 AB) rats also exhibited cold extremities.

Growth and food consumption were depressed in test males, but were generally comparable between test and control females.

Except for higher blood sugar values obtained for the male and female test groups at one and two weeks, the results of the clinical laboratory values for the test groups were generally comparable with those for the control rats.

At necropsy the following observations were made: dark red areas on the lobes of the lungs (nine controls, four Group No. 2 rats, and eight Group No. 3 rats); small abscessed and/or consolidated areas on the lobes of the lungs (three controls, two Group No. 2 rats, and two Group No. 3 rats); dark pink lungs (one Group No. 2 rat); gray, cyst-like areas on the lungs (one Group No. 3 rat); dark pink, red, or brown outer renal medullas (four controls, nine Group No. 2 rats, and 11 Group No. 3 rats); dilated renal pelves (two controls and two Group No. 2 rats); dark red zone between renal cortices and medullas (two Group No. 2 rats); pale, gray-brown, green-brown, or yellow-brown renal cortices (four Group No. 2 rats and two Group No. 3 rats); thick, yellow substance in the renal pelves (one Group No. 2 rat); yellow foci in the duodenal lining (one Group No. 3 rat); and distended uterine horns filled with clear fluid (two controls and one Group No. 3 rat).

Statistical analysis of terminal body weights, organ weights, and organ/body weight ratios revealed significantly lower terminal body weights for test males than for controls, significantly lower heart weights for test males than for controls, significantly lower testes weights for Group No. 2 males than for controls, and a significantly higher adrenal/body weight ratio for Group No. 2 males than for controls.

Histopathological examination of selected tissues failed to show any distinct, compound-related alterations; and no significant differences were observed in rats treated with the two samples of WR 2823.

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MATERIALS

Identification

WR 2823 AC (AU 69115): Lot No. WR 8-55D.

WR 2823 AB: Lot No. BV-WR-01.

Description

WR 2823 AC (AU 69115): A fine, white powder; no odor noted.

WR 2823 AB: White, solid material in sterile, sealed vials.

Receipt Both from Walter Reed Army Institute of Research on June 11, 1970.

Purity Considered 100% active ingredient.

METHODS

Experimental Animals Seventy-two healthy albino rats, 36 males and 36 females,
of Charles River Caesarean-derived strain.

Weight Range at Initiation: For the males from 180 to 205 grams and for
the females from 162 to 190 grams.

Housing: Individually in elevated wire mesh cages.

Diet: Purina Laboratory Chow and water available ad libitum.

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Animal Groups and Dosage Levels

Method of Grouping: Stratified randomization.

<u>Group No.</u>	<u>No. of Animals</u>		<u>Treatment</u>	<u>Dosage Level</u> mg/kg/day
	<u>male</u>	<u>female</u>		
1 (Vehicle Control)	12	12	Saline	-
2	12	12	WR 2823 AC	60
3	12	12	WR 2823 AB	60

Preparation of Solutions

Vehicle: 0.9% sterile saline.

Concentration: 60 mg. of the test compound per milliliter of vehicle for Groups No. 2 and No. 3. The solution of saline and compound WR 2823 AC which was administered to Group No. 2 animals was kept refrigerated and allowed to warm to room temperature before dosing. The solution of saline and WR 2823 AB which was administered to Group No. 3 animals was prepared fresh daily, and the test powder was kept in the freezer.

Drug Administration

Each test rat received a daily intravenous injection via the lateral tail vein of 60 mg. of test compound per kilogram of body weight at a volume of 0.1 ml. per 100 grams of body weight. Dosages were adjusted daily on the basis of individual body weights. Control animals were dosed with a volume of saline equivalent to that received by the treated groups.

All rats received 15 consecutive daily injections. Seven males and seven females from the control and high level groups were sacrificed on the second day following the last dose. The other 44 animals were sacrificed on the day following the last dosage; no dosages were administered on the day of sacrifice.

Observations and Records

Daily: For signs of toxic or pharmacologic effect with special attention to heart rate, body temperature, and coloration.

Weekly: Food consumption. Individual body weights were taken daily for the purpose of dosage adjustment but are recorded weekly in this report.

Clinical Laboratory Studies

Intervals: Initially, at one week, and at two weeks (terminal).

Methods: Performed on five rats of each sex from each group; blood samples were obtained from the tail vein (from the abdominal aorta for biochemical studies at sacrifice). Urine samples were collected from rats housed overnight in individual metabolism cages and pooled by groups.

Hematology: Erythrocyte count, total and differential leukocyte counts, hematocrit, hemoglobin, and prothrombin and coagulation time determinations.

Biochemistry: Fasting blood sugar, blood urea nitrogen, serum glutamic-pyruvic transaminase, and alkaline phosphatase determinations.

Urine Analysis: Appearance, pH, specific gravity, sugar, protein, bilirubin, occult blood, and microscopic examination of the sediment.

Ophthalmologic Examinations Conducted on all rats assigned to the study initially and at termination, prior to sacrifice, using "Mydriacyl" (Alcon) and a binocular, indirect ophthalmoscope.

Terminal Studies

Terminal Sacrifice: Performed on each rat one day (five males and five females from controls and Group No. 3 and all Group No. 2 rats) or two days (seven males and seven females from controls and Group No. 3) after the last injection (the 15th dose).

Method - Exsanguination under Diabutal anesthesia.

Gross Observations - Recorded at necropsy for each rat.

Organ Weights (Determined For Each Rat) - Thyroids, liver, kidneys, spleen, heart, adrenal, testes with epididymis, and ovaries. (Thyroids and adrenals weighed after fixation.)

Tissues Preserved From Each Rat:

In 10% Neutral Buffered Formalin - Brain, pituitary, spinal cord, thyroid, lung, heart, liver, spleen, kidney, ureter, urinary bladder, adrenal, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, testis, prostate, ovary, uterus, bone marrow, bone, and injection site.

In Alcoholic Formalin - Eyes.

Histopathological Examination: From five males and five females in each group, all tissues listed above under "Tissues Preserved From Each Rat," with special attention to the kidney, ureter, bladder, and cornea.

All tissues are being held at Hazleton Laboratories, Inc., for possible future reference.

Statistical Evaluation

Criteria: Terminal body weights, organ weights, and organ/body weight ratios.

Method: Analysis of variance, or F-test, at the 5.0% probability level; preliminary tests (where applicable) by methods of Bartlett, Scheffe, and Fisher-Behrens (modified t-test).

RESULTS

Gross Appearance and Behavior

Transient signs included urine stains in one Group No. 2 male and female and one Group No. 3 male, wheezing in one control male and female and in two males and two females from Group No. 2, nasal discharge in one control female and one Group No. 3 male, soft feces in one control male, and bloody crust on the eyes or nose of two Group No. 3 males.

One male and six females from Group No. 2 and one male and two females from Group No. 3 exhibited alopecia after approximately one week of dosing. One Group No. 1 female, one male and six females from Group No. 2, and two Group No. 3 females exhibited hunched posture, generally toward the end of the study.

A few minutes after they were dosed, Groups No. 2 and No. 3 rats showed depression, watery eyes, and sleepy behavior. The heartbeat of these rats continued at a normal rate after dosing, but the beat was noticeably deeper or stronger. In addition, Group No. 3 rats exhibited cold extremities shortly after dosing.

Growth, Food Consumption, and Survival

Mean weekly body weight and food consumption data are presented in Table No. 1.

Weight gains and food consumption for Groups No. 2 and No. 3 males were lower than those for control males. Body weight gain and food consumption were comparable among female control and test groups. Survival was 100%.

Results of Ophthalmoscopic Examination

Gross ophthalmoscopic examinations were performed on all rats at initiation and prior to sacrifice. At initiation, no gross abnormalities were observed in any rat. At termination a small, corneal opacity adjacent to the nasal canthus was observed in the right eye of female Rat No. 86-586 from Group No. 1 (control) and the left eye of female Rat No. 86-613 from Group No. 2. The eyes of the remaining 70 rats appeared grossly normal at termination.

Clinical Laboratory Studies

The results of these studies are presented in Tables No. 2 (hematology), No. 3 (biochemical values), and No. 4 (urine analyses).

The hematological values determined at one and two weeks for the male and female test groups showed no significant differences from control values, and no dose-related trends were apparent. Except for a few slightly decreased or elevated individual values obtained for control and test rats, all values were comparable among the test and control groups.

A trend toward higher blood sugar values was evident at Week 1 and Week 2 in the male and female test groups when compared with control rats. The two-week blood sugar values showed an overall increase in all groups including controls when compared with the blood sugar values at Week 1.

Other biochemical values and the results of urine analysis were comparable among the test and the respective control groups.

Gross Observations at Necropsy

The following gross alterations were observed at necropsy: dark red areas on the lobes of the lungs were observed in four control males and five control females, two males and two females from Group No. 2, and four males and four females from Group No. 3. Small, abscessed and/or consolidated areas on the lobes of the lungs were noted in one control male and two control females, two Group No. 2 males, and one male and one female from Group No. 3. The lungs of one Group No. 2 female were dark pink; and the lungs of one Group No. 3 male contained gray, cyst-like areas. None of the above findings are considered compound related.

Dark pink, red, or brown outer renal medullas were noted in three control males and one control female, four males and five females from Group No. 2, and six males and five females from Group No. 3. Dilated renal pelves were observed in one male and one female each from Groups No. 1 and No. 2. A dark red zone was observed between the renal cortices and medullas of one male and one female from Group No. 2. Pale, gray-brown, green-brown, or yellow-brown renal cortices were noted in two males and two females from Group No. 2 and one male and one female from Group No. 3. The renal pelves of one Group No. 2 female contained a thick, yellow-green substance.

Yellow foci were observed in the duodenal lining of one Group No. 3 male. The horns of the uterus were distended with clear fluid in two control females and one Group No. 3 female.

Organ Weights

Mean terminal body weights, organ weights, organ/body weight ratios, and their standard deviations for all males and females are presented in Table No. 5.

Statistical analysis revealed the following values for the rats in the test groups to be significantly different from values for the control animals.

Summary of Table No. 5
Significantly Different Values For Test Groups
As Compared to Control Group

Organ	Males	
	Group No. 2	Group No. 3
	Receiving WR 2823 AC	Receiving WR 2823 AB
Terminal body weight	S-	S-
Heart weight	S-	S-
Testes weight	S-	
Adrenal/body weight ratio	S+	

S- = Significantly lower than control

S+ = Significantly higher than control

Histopathological Examination of Tissues

Unequivocal, compound-induced changes were not seen in the study. Histopathologic findings among control and treated groups which did not vary significantly in their incidence or severity were chronic murine pneumonia, nonsuppurative epididymitis, nonsuppurative hepatitis and pericholangitis, and focal pancreatitis. Rare lesions in control or treated groups consisted of mild chronic interstitial nephritis, Harderian gland adenitis, and prostatitis. The occurrence of epicarditis and focal myocarditis were considered spontaneous lesions unrelated to the compound administration. The occurrence of glial nodules, nonsuppurative meningitis, and perivascular lymphocytic cuffs in the brain resemble those lesions described in murine nose matosis, a latent, clinical occult infection in this species.

An extracellular vacuolation in spinal cord and brain was seen in some control and treated animals. The vacuoles either appeared empty or contained gray, birefringent, granular material. These changes probably represent histologic artifacts.

Sections of spleen, ureter, urinary bladder, stomach, small intestine, large intestine, mesenteric lymph node, and bone were generally not remarkable. Sections of bone marrow, thyroid, and adrenal appeared comparable microscopically in control and treated groups. Other cytologic changes described in the detailed pathology, protocol, or listed on the incidence tables are considered incidental findings and not related to administration of the compound. Examination of the injection site revealed no marked or consistent differences between the treated and control animals.

In summation, the administration of compounds WR 2823 AC and WR 2823 AB to male and female rats for two weeks by intravenous injection did not produce unequivocal, compound-induced changes in the tissues examined.

The incidence tables are presented as an addendum. The detailed histologic findings are on file at Hazleton Laboratories, Inc.

Submitted by

MB Powers

MARCELINA B. POWERS, D.V.M., M.S.
Director, Drugs and
Industrial Chemicals Department
Toxicology-Biosciences Laboratory

Pathology by

Robert P. Kwapien

ROBERT P. KWAPIEN, D.V.M., Ph.D.
Staff Pathologist

Report Preparation: Spruill
Supervision: Elliott

gbb

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EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

T = trace ($\pm$)

0 = negative

1 = slight (+)

2 = moderate (++)

3 = marked (+++)

4 = severe (++++)

V T YEL = very turbid yellow

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Table No. 1 - Mean body weights, weight ranges, food consumption, and survival data for (☒ male, ☐ female) albino rats.

ALLOCATION RATES OF 2 NO-CLIMING BY 2023 AC & GR 5 P-CHEMLOG IN 2023 AG FOR TOL + CHN

TIME INTERVAL weeks	Group 1				Group 2				Group 3			
	WT. g.	WT. RANGE	FOOD g.	SURV.	WT. g.	WT. RANGE	FOOD g.	SURV.	WT. g.	WT. RANGE	FOOD g.	SURV.
0	241	225-294	0	12/12	240	214-282	0	12/12	241	215-266	0	12/12
1	250	262-307	176	12/12	262	233-280	139	12/12	277	256-300	153	12/12
2	333	305-360	172	12/12	297	259-325	151	12/12	311	279-337	141	12/12

TABLE NO. 2 - INDIVIDUAL BIOLOGICAL VALUES
 ALLISON RATS OR 2 RECEIVING GR 2123 AC 8 GR 3 RECEIVING GR 2123 AC FOR 100 WEEKS
 TOTAL

GROUP	INDIVIDUAL	SEX	AGE	WGT	HGT	KID	KID	TUS	DIFFERENTIAL						WASH
									WTA	LAND	SEG	LYOPH	MURD	ROSTU	
1	00560	F	42.0	11.9	11.9	6.05	24.6	24.6	0	0	10	38	0	2	0
1	00567	F	40.0	13.4	13.4	4.76	17.7	17.7	0	2	17	31	0	0	0
1	00563	F	41.5	13.2	13.2	4.93	22.6	22.6	0	2	25	73	0	0	0
1	00569	F	42.5	12.7	12.7	4.89	31.1	31.1	0	0	21	69	0	0	0
1	00570	F	44.0	12.5	12.5	4.90	31.1	31.1	0	1	16	33	0	0	0
GROUP TOTAL			42.0	12.7	12.7	5.04	25.4	25.4							
2	00590	F	38.0	12.7	12.7	4.65	24.5	24.5	0	1	15	33	0	1	0
2	00591	F	40.0	12.1	12.1	4.62	15.5	15.5	0	0	12	37	0	1	0
2	00592	F	42.0	12.5	12.5	5.23	19.0	19.0	0	1	16	32	0	1	0
2	00593	F	42.5	12.7	12.7	5.41	19.5	19.5	0	0	22	70	0	0	0
2	00594	F	47.0	14.2	14.2	5.38	29.8	29.8	0	0	13	36	1	0	0
GROUP TOTAL			41.9	12.8	12.8	4.96	22.2	22.2							
3	00614	F	38.0	11.9	11.9	5.03	12.0	12.0	0	2	29	69	0	0	0
3	00615	F	41.0	12.8	12.8	4.40	26.3	26.3	0	0	33	65	2	0	0
3	00616	F	40.0	11.8	11.8	4.61	21.8	21.8	0	1	25	76	2	0	0
3	00617	F	39.5	12.7	12.7	4.87	16.5	16.5	0	0	27	72	1	0	0
3	00618	F	41.0	12.7	12.7	5.27	18.4	18.4	0	1	21	77	1	0	0
GROUP TOTAL			39.9	12.4	12.4	4.65	19.5	19.5							

TABLE NO. 2 - INDIVIDUAL ORNITHOLOGICAL VALUES
 ALBUQUERQUE GR 2 RECEIVING TO 2023 AC & GR 3 RECEIVING TO 2023 AC POP 100 CRIES
 OVER 1

GROUP	ACTUAL F	HCT	HGO	RDC	ORC	DIFFERENTIAL						LASH
						DATA	DATA	SEG	LY PH	POP	CRS	
POP	CRS	3ER	X	S	THS	3	3	3	3	3	3	3
1	06576	F	41.5	13.6	5.14	23.6	0	15	83	0	2	0
1	06579	F	45.0	12.0	6.08	21.1	0	9	91	0	0	0
1	06580	F	45.5	15.2	6.19	22.4	0	6	91	0	3	0
1	06581	F	42.5	13.0	5.76	29.8	0	7	93	0	0	0
1	06582	F	43.0	13.4	5.40	23.5	0	14	85	0	1	0
GROUP TOTAL			43.5	14.1	5.72	24.1						
2	06602	F	44.0	14.2	5.76	32.7	0	17	83	0	0	0
2	06603	F	46.0	15.2	6.32	19.5	0	17	82	0	1	0
2	06604	F	43.0	14.2	5.76	19.5	0	16	82	0	2	0
2	06605	F	43.0	15.0	5.83	27.7	0	7	91	0	2	0
2	06606	F	44.5	15.0	5.81	24.0	0	22	73	0	3	2
GROUP TOTAL			44.1	14.7	5.69	24.7						
3	06626	F	49.5	14.6	5.69	27.9	0	12	86	1	1	0
3	06627	F	45.5	12.4	5.77	19.6	0	17	82	0	1	0
3	06628	F	43.0	14.2	5.63	27.6	0	10	90	0	0	0
3	06629	F	48.0	14.5	6.10	24.8	0	15	83	0	1	0
3	06630	F	45.0	14.6	6.06	19.5	0	13	85	0	2	0
GROUP TOTAL			45.6	14.7	5.65	23.7						

	1906	1907	1908	1909	1910	1911	1912	1913	1914	1915	1916	1917	1918	1919	1920	1921	1922	1923	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2423	2424	2425	2426	2427	2428	2429	2430	2431	2432	2433	2434	2435	2436	2437	2438	2439	2440	2441	2442	2443	2444	2445	2446	2447	2448	2449	2450	2451	2452	2453	2454	2455	2456	2457	2458	2459	2460	2461	2462	2463	2464	2465	2466	2467	2468	2469	2470	2471	2472	2473	2474	2475	2476	2477	2478	2479	2480	2481	2482	2483	2484	2485	2486	2487	2488	2489	2490	2491	2492	2493	2494	2495	2496	2497	2498	2499	2500	2501	2502	2503	2504	2505	2506	2507	2508	2509	2510	2511	2512	2513	2514	2515	2516	2517	2518	2519	2520	2521	2522	2523	2524	2525	2526	2527	2528	2529	2530	2531	2532	2533	2534	2535	2536	2537	2538	2539	2540	2541	2542	2543	2544	2545	2546	2547	2548	2549	2550	2551	2552	2553	2554	2555	2556	2557	2558	2559	2560	2561	2562	2563	2564	2565	2566	2567	2568	2569	2570	2571	2572	2573	2574	2575	2576	2577	2578	2579	2580	2581	2582	2583	2584	2585	2586	2587	2588	2589	2590	2591	2592	2593	2594	2595	2596	2597	2598	2599	2600	2601	2602	2603	2604	2605	2606	2607	2608	2609	2610	2611	2612	2613	2614	2615	2616	2617	2618	2619	2620	2621	2622	2623	2624	2625	2626	2627	2628	2629	2630	2631	2632	2633	2634	2635	2636	2637	2638	2639	2640	2641	2642	2643	2644	2645	2646	2647	2648	2649	2650	2651	2652	2653	2654	2655	2656	2657	2658	2659	2660	2661	2662	2663	2664	2665	2666	2667	2668	2669	2670	2671	2672	2673	2674	2675	2676	2677	2678	2679	2680	2681	2682	2683	2684	2685	2686	2687	2688	2689	2690	2691	2692	2693	2694	2695	2696	2697	2698	2699	2700	2701	2702	2703	2704	2705	2706	2707	2708	2709	2710	2711	2712	2713	2714	2715	2716	2717	2718	2719	2720	2721	2722	2723	2724	2725	2726	2727	2728	2729	2730	2731	2732	2733	2734	2735	2736	2737	2738	2739	2740	2741	2742	2743	2744	2745	2746	2747	2748	2749	2750	2751	2752	2753	2754	2755	2756	2757	2758	2759	2760	2761	2762	2763	2764	2765	2766	2767	2768	2769	2770	2771	2772	2773	2774	2775	2776	2777	2778	2779	2780	2781	2782	2783	2784	2785	2786	2787	2788	2789	2790	2791	2792	2793	2794	2795	2796	2797	2798	2799	2800	2801	2802	2803	2804	2805	2806	2807	2808	2809	2810	2811	2812	2813	2814	2815	2816	2817	2818	2819	2820	2821	2822	2823	2824	2825	2826	2827	2828	2829	2830	2831	2832	2833	2834	2835	2836	2837	2838	2839	2840	2841	2842	2843	2844	2845	2846	2847	2848	2849	2850	2851	2852	2853	2854	2855	2856	2857	2858	2859	2860	2861	2862	2863	2864	2865	2866	2867	2868	2869	2870	2871	2872	2873	2874	2875	2876	2877	2878	2879	2880	2881	2882	2883	2884	2885	2886	2887	2888	2889	2890	2891	2892	2893	2894	2895	2896	2897	2898	2899	2900	2901	2902	2903	2904	2905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TABLE 2. - INDIVIDUAL PHYSIOLOGICAL VALUES
 RECEIVING GP 2823 AC & GP 3 RECEIVING GP 2823 AT PM 100 YEARS
 IN 11100

GROUP	APICAL	5	PERCENTAGE	CONCENTRATION	
NO.	NUMBER	X	SECONDS	OF	SEC
1	66566	0	13.5	1	05
1	66567	0	12.8	1	02
1	66568	0	12.9	1	11
1	66569	0	13.3	0	56
1	66570	0	16.3	0	50
GROUP	66571		13.9	1	01
2	66590	0	12.5	1	15
2	66591	0	12.3	1	13
2	66592	0	12.7	0	50
2	66593	1	13.9	1	07
2	66594	1	14.0	0	53
GROUP	66595		13.1	1	05
3	66614	0	14.5	1	23
3	66615	0	12.1	1	04
3	66616	0	14.9	0	53
3	66617	1	12.4	1	16
3	66618	0	13.4	1	30
GROUP	66619		13.5	1	14

TABLE NO. 2 - INDIVIDUAL PHYSIOLOGICAL VALUES
 ALBINO RATIS GR 2 RECEIVING GR 2623 AC & GR 3 RECEIVING GR 2623 w/ FOR TOP OF 65
 WEEK 1

GROUP	ANIMAL NUMBER	5 PROTHROMBIN X	5 PROTHROMBIN SEC	5 COAGULATION TIME SEC
GROUP 1	1	86566 n	11.8	1 06
	1	86567 n	14.0	1 08
	1	86568 n	18.4	1 13
	1	86569 n	19.7	0 56
	1	86570 n	16.4	1 06
GROUP 1	1	16.2	1 05	
GROUP 2	2	86590 n	15.7	1 12
	2	86591 n	14.4	1 04
	2	86592 n	15.2	1 09
	2	86593 n	15.0	1 05
	2	86594 n	15.1	1 01
GROUP 2	2	15.1	1 06	
GROUP 3	3	86614 n	18.2	1 37
	3	86615 n	13.9	1 11
	3	86616 n	12.7	1 06
	3	86617 n	16.9	1 07
	3	86618 n	15.2	1 23
GROUP 3	3	15.4	1 17	

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1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100

TABLE NO. 2 - INDIVIDUAL DECODED LOGICAL VALUES
 ADDRESS RATS OR 2 RECEIVING ON 2623 AC & GR 3 RECEIVING ON 2623 AB FOR THE OTHERS

GROUP	ADDRESS	S	PROTHROPEIN	COAGUL	TIME
NUMBER	NUMBER	X	SECONDS	TIME	SEC
1	86576	F	12.1	1	34
1	86579	F	13.8	1	24
1	86580	F	19.9	0	51
1	86581	F	11.8	1	19
1	86582	F	14.6	1	01
GROUP	MEAN		14.4	1	14
2	86602	F	13.3	1	15
2	86603	F	13.6	0	52
2	86604	F	12.2	1	19
2	86605	F	13.6	0	51
2	86606	F	15.8	0	53
GROUP	MEAN		13.7	1	03
3	86626	F	13.7	0	59
3	86627	F	15.8	1	07
3	86628	F	11.9	1	03
3	86629	F	14.7	1	02
3	86630	F	14.3	0	52
GROUP	MEAN		13.7	1	01

TABLE NO. 2 - INDIVIDUAL DECAFOLOGICAL VALUES
 ALLELO RATS GR 2 RECEIVING GR 2823 AC 8 OR 3 RECEIVING GR 2823 AR FOR 100 WEEKS
 PER 1

GROUP	ANIMAL	S	PROTHROMBIN	COAGULATION
NUMBER	NUMBER	X	SECONDS	TIME SEC
1	86578	F	16.6	0 55
1	86579	F	14.4	0 50
1	86580	F	17.1	1 03
1	86581	F	15.1	1 25
1	86582	F	13.0	1 09
GROUP MEAN			15.2	1 04
2	86602	F	13.4	1 25
2	86603	F	13.1	1 10
2	86604	F	12.9	1 34
2	86605	F	14.8	1 12
2	86606	F	13.3	1 15
GROUP MEAN			13.5	1 19
3	86626	F	18.2	1 07
3	86627	F	18.5	1 29
3	86628	F	15.7	1 16
3	86629	F	12.8	1 07
3	86630	F	13.9	1 23
GROUP MEAN			15.4	1 19

[illegible]

TABLE NO. 3 - INDIVIDUAL ALBINO COLUMBISTRY VALUES
 PLODD RATS GR 2 RECEIVING GR 2623 AC R GR 3 RECEIVING GR 2623 AC FOR 100 CUBES
 I. TOTAL

GROUP NUMBER	ANTIAL PUBER X	S	GLUCOSE MG%	GUH MG%	SGPT R-F.	ALK. PHOS K-A. UNITS
1	86571	0	56.0	17.0	41.0	70.4
1	86572	0	44.0	16.0	38.0	76.4
1	86573	0	42.0	17.0	38.0	60.0
1	86574	0	52.0	16.0	39.0	68.4
1	86575	0	41.0	12.0	38.0	69.2
GROUP MEAN			46.6	15.6	38.8	68.9
2	86595	0	75.0	15.0	41.0	52.0
2	86596	0	86.0	14.0	29.0	63.2
2	86597	0	88.0	18.0	36.0	60.0
2	86598	0	80.0	13.0	38.0	53.2
2	86599	0	82.0	15.0	35.0	66.4
GROUP MEAN			82.2	15.0	35.8	59.0
3	86619	1	50.0	13.0	41.0	50.4
3	86620	1	65.0	16.0	38.0	87.6
3	86621	1	62.0	18.0	35.0	51.2
3	86622	0	61.0	16.0	41.0	38.4
3	86623	1	37.0	13.0	38.0	39.2
GROUP MEAN			59.6	15.2	38.6	53.4

ALBINO RATS GR 2 RECEIVING OR 2023 AC & GR 3 RECEIVING OR 2025 AC FOR 100 WEEKS

GROUP	INDIVIDUAL	GLUCOSE	BUN	S6PT	ALKALPHOS
NUMBER	NUMBER	MG	MG	R-F	R-A, UNITS
1	86571	43.0	16.0	41.0	60.4
1	86572	42.0	17.0	34.0	56.0
1	86573	25.0	14.0	36.0	34.4
1	86574	37.0	15.0	39.0	46.8
1	86575	36.0	15.0	47.0	52.0
GROUP MEAN		36.6	15.6	39.6	49.9
2	86595	86.0	16.0	39.0	41.6
2	86596	73.0	16.0	44.0	61.2
2	86597	75.0	17.0	46.0	56.6
2	86598	92.0	16.0	36.0	43.2
2	86599	71.0	16.0	39.0	38.8
GROUP MEAN		79.4	16.2	40.8	48.3
3	86619	66.0	13.0	41.0	44.6
3	86620	77.0	19.0	36.0	62.8
3	86621	62.0	16.0	44.0	46.0
3	86622	72.0	16.0	42.0	33.2
3	86623	76.0	14.0	41.0	61.2
GROUP MEAN		70.6	16.0	40.8	53.6

TABLE 40. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 ALBINO RATS GR 2 RECEIVING GR 2823 AC & GR 3 RECEIVING GR 2823 AC FOR TWO WEEKS
 TOTAL

GROUP	ANIMAL	SEX	GLUCOSE	RBC	SGPT	ALK. PHOS
NUMBER	NUMBER	X	MG%	MG%	R-F	K-A, UNITS
1	86563	F	127.0	20.0	41.0	39.2
1	86564	F	85.0	22.0	38.0	33.2
1	86565	F	85.0	21.0	32.0	60.8
1	86586	F	92.0	16.0	38.0	26.0
1	86587	F	86.0	17.0	38.0	24.4
GROUP	MEAN		95.0	19.2	37.4	32.7
2	86607	F	96.0	29.0	39.0	61.2
2	86608	F	99.0	20.0	38.0	60.0
2	86609	F	87.0	21.0	41.0	68.0
2	86610	F	69.0	20.0	35.0	60.0
2	86611	F	70.0	20.0	42.0	53.2
GROUP	MEAN		86.2	22.0	39.0	60.5
3	86631	F	84.0	37.0	38.0	63.2
3	86632	F	73.0	22.0	35.0	50.4
3	86633	F	86.0	27.0	32.0	47.6
2	86634	F	79.0	32.0	50.0	54.8
3	86635	F	83.0	23.0	32.0	33.6
GROUP	MEAN		81.0	28.2	37.4	49.9

TABLE NO. 3 - INDIVIDUAL LABORATORY VALUES
ALBINO RATS GR 2 RECEIVING GR 2023 AC & GR 3 RECEIVING GR 2023 AC FOR 100 DAYS
PER 1

GROUP NUMBER	ACTUAL EPOXY INDEX	S	GLUCOSE mg.	PHOSPHORUS mg.	SGPT R-F.	ALKALINE PHOSPHATASE R-A. Units
1	86503	F	65.0	26.0	62.0	28.8
1	86504	F	52.0	21.0	44.0	21.6
1	86505	F	50.0	18.0	36.0	24.4
1	86506	F	53.0	15.0	39.0	20.0
1	86507	F	49.0	17.0	46.0	22.4
GROUP MEAN			49.6	19.4	45.4	23.4
2	86607	F	61.0	23.0	38.0	21.6
2	86608	F	100.0	20.0	39.0	28.8
2	86609	F	103.0	17.0	47.0	36.8
2	86610	F	126.0	27.0	53.0	56.0
2	86611	F	96.0	18.0	46.0	16.8
GROUP MEAN			97.6	22.0	44.6	28.4
3	86631	F	112.0	24.0	62.0	22.4
3	86632	F	86.0	20.0	49.0	35.2
3	86633	F	72.0	17.0	42.0	26.0
3	86634	F	74.0	18.0	46.0	19.6
3	86635	F	75.0	20.0	41.0	52.0
GROUP MEAN			93.4	19.8	46.0	30.6

TABLE NO. 4 - ORDER ANALYSIS
 ALGONQUATS GR 2 RECEIVING GR 2823 AC & GR 3 RECEIVING GR 2823 AB FOR YOU DEERS
 INITIAL

GROUP OF ORDER TOTALS	NUMBER OF APPEAR.	H	P	SP. GR.	GAB	TFL	RUBIE	BLD	OCC	MICROSCOPIC FINDINGS		
										RBC	DEC	EPITH ALORPH CRYS BACT SPERG
1	5*	T YFL	7	1.018	0	0	0	0	0	2-3	LOUCH	LOUCH LOUCH
2	5*	T YFL	7	1.013	0	0	0	0	0	0-1		LOUCH LOUCH
3	5*	T YFL	7	1.013	0	0	0	0	0		LOUCH	LOUCH LOUCH

* = POOLED SAMPLES

TABLE NO. 4 - URINE ANALYSIS
ALBINO RATS GR 2 RECEIVING UR 2823 AC & GR 3 RECEIVING UR 2823 AB FOR TWO WEEKS
WEEK 1

GROUP NUMBER	NUMBER OF ANALYSES	NUMBER OF ANALYSES X APPEAR.	P	SP. GR.	SID- GAR	PRO- TET	BILI- RUB	UCC BLD	-----MICROSCOPIC FINDINGS----- DEC DEC EPI TH AMORPH CRYST BACT SPEC	
1	5*	11	7	1.008	0	0	0	0	2-3 3-4 0-3	DAILY DAILY
2	5*	11	6	1.004	0	0	0	0	0-2 4-5 3-5	DAILY DAILY
3	5*	11	7	1.009	0	1	0	0	1-3 2-3 2-3	DAILY DAILY

* = POOLED SAMPLES

TABLE NO. 4 - URINE ANALYSIS
ALBINO RATS GR 2 RECEIVING PK 2623 AC & GR 3 RECEIVING DR 2823 AP FOR TWO WEEKS
INITIAL

GROUP	ORDER	SEX	AGE	APPEAR.	P	SP.GR.	GAR	TEIR	ROBIE	BLO	DCC	ROC	YBC	EPITH	AMORPH	CRYS	FACT	SPEC	
1	53	F	M	T	YEL	6	1.018	0	0	0	0								EMPTY URINE
2	53	F	M	T	YEL	8	1.020	0	0	0	0			1-2					EMPTY URINE
3	53	F	T	YEL	7	1.016	0	0	0	0	0								EMPTY URINE

* = POOLED SAMPLES

NUMBER OF GROUP	OF AG- F	SUB- PROD- BIL- OCC	-----MICROSCOPIC FINDINGS-----
		P	RBC EPOCH ADORPH CrYS DACT SPHL
		H	SP.GR. GAR TITP RUBIN BLD
			APPEAR.
			TOTALS X

1	5*	F	T	YFL	7	1.00	6	0	0	0	0-1	0-2	10A ₁ ⁺ Y	10A ₁ ⁺ Y
2	5*	F	T	YFL	7	1.00	5	0	0	0	1-2	2-3	10A ₁ ⁺ Y	10A ₁ ⁺ Y
3	5*	F	T	YFL	6	1.00	4	0	0	0	0-2	1-3	10A ₁ ⁺ Y	10A ₁ ⁺ Y

ST-17015 = *17114

1. The first of these is the fact that the number of years of life expectancy at birth is increasing in all countries.

2. The second is the fact that the number of years of life expectancy at birth is increasing in all countries.

3. The third is the fact that the number of years of life expectancy at birth is increasing in all countries.

4. The fourth is the fact that the number of years of life expectancy at birth is increasing in all countries.

5. The fifth is the fact that the number of years of life expectancy at birth is increasing in all countries.

6. The sixth is the fact that the number of years of life expectancy at birth is increasing in all countries.

7. The seventh is the fact that the number of years of life expectancy at birth is increasing in all countries.

8. The eighth is the fact that the number of years of life expectancy at birth is increasing in all countries.

9. The ninth is the fact that the number of years of life expectancy at birth is increasing in all countries.

10. The tenth is the fact that the number of years of life expectancy at birth is increasing in all countries.

11. The eleventh is the fact that the number of years of life expectancy at birth is increasing in all countries.

12. The twelfth is the fact that the number of years of life expectancy at birth is increasing in all countries.

13. The thirteenth is the fact that the number of years of life expectancy at birth is increasing in all countries.

14. The fourteenth is the fact that the number of years of life expectancy at birth is increasing in all countries.

15. The fifteenth is the fact that the number of years of life expectancy at birth is increasing in all countries.

16. The sixteenth is the fact that the number of years of life expectancy at birth is increasing in all countries.

17. The seventeenth is the fact that the number of years of life expectancy at birth is increasing in all countries.

18. The eighteenth is the fact that the number of years of life expectancy at birth is increasing in all countries.

19. The nineteenth is the fact that the number of years of life expectancy at birth is increasing in all countries.

20. The twentieth is the fact that the number of years of life expectancy at birth is increasing in all countries.

193412

TABLE NO. 5- MEAN TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, ORGAN/BODY WEIGHT RATIOS, AND STANDARD DEVIATIONS FOR MALE AND FEMALE ALBINO RATS.

ALBINO RATS GR 2 RECEIVING WR2823 AC & GR 3 RECEIVING WR2823 AB FOR TWO WEEKS

GROUP NUMBER	SEX	BODY WEIGHT			THYROID				HEART			
		N	WEIGHT G.	S G.	WEIGHT G.	S G.	RATIO %	S %	WEIGHT G.	S G.	RATIO %	S %
1	M	12	304	14	0.023	0.005	0.0076	0.0015	1.30	0.11	0.430	0.041
2	M	12	268 ^{S-}	15	0.020	0.004	0.0076	0.0013	1.13 ^{S-}	0.16	0.423	0.050
3	M	12	285 ^{S-}	15	0.020	0.003	0.0070	0.0008	1.16 ^{S-}	0.12	0.409	0.046
1	F	12	213	10	0.020	0.003	0.0096	0.0014	0.95	0.09	0.45	0.04
2	F	12	211	15	0.020	0.004	0.0094	0.0019	0.89	0.19	0.43	0.06
3	F	12	211	13	0.019	0.003	0.0088	0.0012	0.92	0.08	0.44	0.04

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S- = SIGNIFICANTLY LOWER THAN CONTROL

TABLE NO. 5- MEAN TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, ORGAN/BODY WEIGHT RATIOS, AND STANDARD DEVIATIONS FOR MALE AND FEMALE ALBINO RATS.

ALBINO RATS GR 2 RECEIVING WR2823 AC & GR 3 RECEIVING WR2823 AB FOR TWO WEEKS

GROUP NUMBER	SEX	BODY WEIGHT			LIVER			SPLEEN		
		N	WEIGHT G.	S G.	WEIGHT G.	S G.	RATIO %	WEIGHT G.	S G.	RATIO %
1	M	12	304	14	11.53	2.12	3.78	0.83	0.18	0.27
2	M	12	268 ^{S-}	15	10.28	1.95	3.83	0.74	0.18	0.26
3	M	12	285 ^{S-}	15	10.27	1.13	3.60	0.72	0.22	0.25
1	F	12	213	10	7.88	1.21	3.71	0.64	0.18	0.30
2	F	12	211	15	8.70	1.87	4.09	0.58	0.12	0.28
3	F	12	211	13	8.43	1.18	4.01	0.67	0.22	0.32

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S- - SIGNIFICANTLY LOWER THAN CONTROL

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TABLE NO. 5- MEAN TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, ORGAN/BODY WEIGHT RATIOS, AND STANDARD DEVIATIONS FOR MALE AND FEMALE ALBINO RATS.

ALBINO RATS GR 2 RECEIVING WR2823 AC & GR 3 RECEIVING WR2823 AB FOR TWO WEEKS

GROUP NUMBER	SEX	N	BODY WEIGHT			KIDNEYS				ADRENALS			
			WEIGHT G.	S G.	WEIGHT G.	S G.	RATIO %	S %	WEIGHT G.	S G.	RATIO %	S %	
1	M	12	304	14	2.87	0.34	0.944	0.090	0.060	0.011	0.020	0.003	
2	M	12	268 S-	15	2.50 S-	0.30	0.933	0.081	0.068	0.011	0.025 S+	0.003	
3	M	12	285 S-	15	2.70	0.27	0.945	0.059	0.063	0.011	0.022	0.004	
1	F	12	213	10	1.90	0.19	0.895	0.080	0.069	0.010	0.032	0.004	
2	F	12	211	15	1.86	0.19	0.879	0.065	0.070	0.013	0.033	0.005	
3	F	12	211	13	1.88	0.19	0.894	0.074	0.078	0.012	0.037	0.004	

S- = SIGNIFICANTLY LOWER THAN CONTROL
 S+ = SIGNIFICANTLY HIGHER THAN CONTROL

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193412

TABLE NO. 5- MEAN TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, ORGAN/BODY WEIGHT RATIOS, AND STANDARD DEVIATIONS FOR MALE AND FEMALE ALBINO RATS.

ALBINO RATS GR 2 RECEIVING WR2823 AC & GR 3 RECEIVING WR2823 AB FOR TWO WEEKS

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GROUP NUMBER	SEX	N	BODY WEIGHT			TESTES			OVARIES		
			WEIGHT G.	S	WEIGHT G.	S	RATIO %	S %	WEIGHT G.	S G.	RATIO %
1	M	12	304	14	4.43	0.29	1.46	0.11			
2	M	12	268 ^{S-}	15	4.08 ^{S-}	0.43	1.53	0.15			
3	M	12	285 ^{S-}	15	4.23	0.26	1.49	0.10			
1	F	12	213	10					0.123	0.023	0.0577
2	F	12	211	15					^{11/} 0.120	^{11/} 0.017	^{11/} 0.0566
3	F	12	211	13					0.123	0.016	0.0582
											0.0058

S- = SIGNIFICANTLY LOWER THAN CONTROL
 / = MEAN FOR NUMBER DESIGNATED

KEY TO DETAILED HISTOPATHOLOGY INCIDENCE TABLE

N = No Section

X = Not Remarkable

A = Autolysis

P or ✓ = Present or Taken

0 = Absent

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderate to Severe

5 = Severe

IT = Insufficient Tissue

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DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS	ANIMAL NUMBER	MALES														
		GROUP NUMBER														
		1					2					3				
		86-566	86-567	86-568	86-569	86-570	86-590	86-591	86-592	86-593	86-594	86-614	86-615	86-616	86-617	86-618
SPINAL CORD																
Extracellular Vacuolation		P	P	P	X	N	X	X	X	X	X	X	X	P	X	N
BRAIN																
Glial Nodules						X	X		X			X	X		X	X
Perivascular Lymphoid Cuffing									P	P						
Nonsuppurative Meningitis									1	1						
Extracellular Vacuolation		P	P	P	P			P	1	1				P		
PITUITARY		X	X	N	N	X	N	X	X	X	X	X	X	X	X	X
THYROID																
Level of Activity		3	3	3		IT						IT				
Epithelial Height		2-3	2-3	2-3		3	2	2-3	3-4	3	2-3		3	4	2	3
Follicular Size		2-3	2-3	2-3		2-3	4	2-3	2-3	3	2-3		2-3	2-3	4	2-
ADRENAL																
Vacuolation of Zona Fasciculata		1	1	1	1	1	2		1	1	1	1	1	1	1	1
HEART																
Epicarditis			X	X	X	X	X	X								
Focal Myocarditis		1								1	1	1		1		1
Valvulitis											1				1	
LUNG																
Peribronchial Lymphoid Hyperplasia																
Perivascular Lymphoid Infiltration		2	2		3	3		1	2		1		2	3	2	2
Interstitial Pneumonitis				2	5		1	1	2	2	1	1	2	3	1	1
LIVER		X	X		X	X	X	X				X	X	X	X	
Nonsuppurative Hepatitis									1	2	2					
Pericholangitis										2						2
KIDNEY		X	X	X	X	X		X				X	X	X	X	
Epithelial Hyperplasia																
Interstitial Nephritis									1	1	1					1
Regenerative Epithelium							1			1						2
Pyelitis										1						
PANCREAS		X	X	X	X	X	X				X	X	X	X	X	X
Pancreatitis								1	1	1						

DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS		MALES (CONTINUED)														
		ANIMAL NUMBER	GROUP NUMBER													
			1 (Continued)					2 (Continued)					3 (Continued)			
			86-566	86-567	86-568	86-569	86-570	86-590	86-591	86-592	86-593	86-594	86-614	86-615	86-616	86-617
TESTIS																
Nonsuppurative Epididymitis	1	X		X	X	X		X		1	1	1	X	1	1	X
PROSTATE																
Prostatitis	X	X	X	X	X	X	X	X	X	X	X	X	X			X
URINARY BLADDER																
Artifact	X	X	X		X	X	X	X		X	X	X	X	X	X	X
BONE MARROW																
Hematogenic Activity	3	3	3	4	4	3	3	3	3	4	3	3	3	3	3	3
Number of Megakaryocytes	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Number of Erythroid and Myeloid Cells	5	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
INJECTION SITE (TAIL)																
Focal Inflammation in Dermo	P	P	P	P	P	P	N	P	P	P	P		P	P	P	

DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS	ANIMAL NUMBER	FEMALES														
		GROUP NUMBER														
		1					2					3				
		86-578	86-579	86-580	86-581	86-596	86-602	86-603	86-604	86-605	86-613	86-626	86-627	86-628	86-629	86-630
SPINAL CORD		X	N	X	X	X	X	X	X	X	X	X	X	X	X	X
Extracellular Vacuolation																
BRAIN		X	N	X			X	X	X		X	X	X	X	X	
Glial Nodules					P					P						
Perivascular Lymphoid Cuffing					1					1						
Nonsuppurative Meningitis					1	1				1						
Extracellular Vacuolation						P										P
PITUITARY		X	N	N	X	X	X	N	X	X	N	X	N	X	X	X
THYROID			N	N							N		N	N		
Level of Activity		3			2	3	3	3	3	3		3			3	3
Epithelial Height		2			2	3	2-3	3	3	3		3			3	3
Follicular Size		2-3			2-3	2-3	2-3	2-3	2-3	2-3		2-3			2-3	2-
EYE		X	X	X	X	X	N	X		X		X	N	X	X	X
Harderian Adenitis									P		P					
HEART			X	X			X	X	X			X	X	X		X
Epicarditis		1			1					1					1	
Focal Myocarditis					1	1				1	1				1	
Valvulitis					1											
LUNG																
Peribronchial Lymphoid																
Hyperplasia			1		1		2	1	2	1	1	2	2	1	1	2
Perivascular Lymphoid																
Infiltration		1	1	2	2	2	3	1	2	3	3	1	2	1	3	2
Interstitial Pneumonitis		1	1	1	1	1	1	1	2	2	2		1	1	1	1
LIVER			X			X	X	X	X			X		X		X
Nonsuppurative Hepatitis					1						1				1	
Pericholangitis		2		1	2					1					1	
KIDNEY		X	X	X	X	X			X	X	X		X	X		X
Interstitial Nephritis							1	1				1			1	
Regenerative Epithelium												1				
PANCREAS		X	X	X		X	X	X	X		X		X	X	X	X
Pancreatitis					1					1		1				

DETAILED HISTOPATHOLOGY INCIDENCE TABLE

		FEMALES (CONTINUED)														
		GROUP NUMBER														
		1 (Continued)					2 (Continued)					3 (Continued)				
		86-578	86-579	86-580	86-581	86-596	86-602	86-603	86-604	86-605	86-613	86-626	86-627	86-628	86-629	86-630
ORGANS	ANIMAL NUMBER															
URINARY BLADDER		X	X	X	X	X	X	X	X	X	X	N	N	X	X	X
Mucosal Epithelial Vacuolation													P			
BONE MARROW																
Hematogenic Activity		4	4	4	4	4	3	3	4	3	3	4	3	4	3	3
Number of Megakaryocytes		4	4	4	4	4	3	3	4	3	3	4	3	4	3	3
Number of Erythroid and Myeloid Cells		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
INJECTION SITE (TAIL)							N									
Focal Inflammation in Derma		P	P	P	P	P	P		P	P	P		P	P	P	P

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TRW/

HAZLETON LABORATORIES

SPONSOR: Walter Reed Army Institute of Research

DATE: July 6, 1971

MATERIAL: WR 149,024 AD (AX 67287)

LOT NO: 308/422

SUBJECT: REPORT NO. 39

Acute Intravenous Toxicity Study - Rats and Mice

Acute Intraperitoneal Toxicity Study - Guinea Pigs

Project No. 193-413

SUMMARY

WR 149,024 AD (AX 67287) was evaluated for acute intravenous toxicity in male albino rats and mice and for acute intraperitoneal toxicity in male albino guinea pigs. The acute intravenous LD₅₀ in rats is 41.7 mg/kg of body weight (confidence limits, 39.3 to 44.2 mg/kg) and in mice is 35.5 mg/kg of body weight (no confidence limits due to all-or-none response). The acute intraperitoneal LD₅₀ in guinea pigs is 204 mg/kg of body weight (confidence limits, 169 to 247 mg/kg).

Test Material WR 149,024 AD (AX 67287); Lot No: 308/422.

Procedures

Animals: Seven groups for each species, each composed of 10 males. Rats weighed from 89 to 175 grams, mice from 20 to 37 grams. and guinea pigs from 325 to 530 grams at initiation.

Drug Administration: By intravenous injection via the lateral tail vein in the rats and mice, and by intraperitoneal injection in the guinea pigs. Concentrations were adjusted so that mice were dosed with a total volume of 10 ml. of compound and vehicle per kg. of body weight. Rats and guinea pigs were dosed with a total volume of five ml. of compound and vehicle per kg. of body weight. The vehicle, normal saline, was administered to control animals in volumes equal to those for their respective test groups.

Dosage Levels:

Mice - 10.0, 15.9, 20.0, 25.1, 31.6, and 39.8 mg/kg of body weight.

Rats - 25.1, 31.6, 39.8, 44.7, 50.1, and 63.1 mg/kg of body weight.

Guinea Pigs - 25.1, 39.8, 63.1, 100, 159, and 251 mg/kg of body weight.

Observations: For mortality and pharmacotoxic effect immediately after dosing, frequently on the day of dosing, and daily thereafter, for a total of 14 days. Gross necropsies were performed on all animals which died or were sacrificed at termination.

Statistical Analysis: Mortality data were analyzed by the method of Litchfield, J. T., and Wilcoxon, F., J. Pharmacol. Exptl. Therap. 96, 99, 1949.

Results

Mortality Data: Values below represent the number of animals dead per number of animals tested, cumulative.

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TRW/**HAZLETON LABORATORIES**

<u>Dose</u> mg/kg	<u>Concentration</u> %	<u>Time of Death - Mice</u>		
		<u>Immediate</u>	<u>Hours</u> 24	<u>Days</u> 2 - 14
10.0	0.10	0/10	0/10	0/10
15.9	0.16	0/10	0/10	0/10
20.0	0.20	0/10	0/10	0/10
25.1	0.25	0/10	0/10	0/10
31.6	0.32	0/10	0/10	0/10
39.8	0.40	10/10		

LD₅₀, mg/kg - 35.5 (No confidence limits due to all-or-none response.)

<u>Dose</u> mg/kg	<u>Concentration</u> %	<u>Time of Death - Rats</u>		
		<u>Immediate</u>	<u>Hours</u> 24	<u>Days</u> 2 - 14
25.1	0.50	0/10	0/10	0/10
31.6	0.63	0/10	0/10	0/10
39.8	0.80	1/10	1/10	1/10
44.7	0.89	9/10	9/10	9/10
50.1	1.0	10/10		
63.1	1.3	10/10		

LD₅₀, mg/kg - 41.7

Confidence Limits (95%), mg/kg - 39.3 to 44.2

Slope - 1.116

Graphical presentation of the dose-response evaluations is appended to this report.

Dose mg/kg	Concentration %	Time of Death - Guinea Pigs				
		Immediate	Hours	Days		
			24	2-9	10	11-14
25.1	2.5	0/10	0/10	0/10	2/10	2/10*
39.8	4.0	0/10	0/10	0/10	1/10	1/10*
63.1	6.3	0/10	0/10	0/10	0/10	0/10
100	10.0	0/10	0/10	0/10	0/10	0/10
159	15.9	0/10	1/10	1/10	1/10	1/10
251	25.1	0/10	8/10	8/10	8/10	8/10

LD₅₀, mg/kg - 204

Confidence Limits, (95%), mg/kg - 169 to 247

Slope - 1.375

Graphical presentation of the dose-response evaluation is appended to this report.

* Death considered due to spontaneous causes; not included in calculation of LD₅₀.

Principal Toxic Effects:

Following Intravenous Injection in Mice - Sores were observed on the tails of nine control mice from Day 7 through Day 14. Slight depression was noted in all mice from Groups No. 5 (25.1 mg/kg) and No. 6 (31.6 mg/kg) immediately after dosing.

Following Intravenous Injection in Rats - Fecal stains were observed on from one to four rats from Group No. 2 (25.1 mg/kg) from Day 6 through Day 14, and on from one to three rats from Group No. 4 (39.8 mg/kg) from Day 5 through Day 14. One Group No. 5 (44.7 mg/kg) rat showed fecal stains on Day 5. Slight depression

was seen within 30 minutes postdose and for the remainder of the day in all rats from Group No. 3 (31.6 mg/kg) and in eight Group No. 4 rats. One Group No. 5 rat was slightly depressed on Day 1. Ten Group No. 3 rats and eight Group No. 4 rats exhibited decreased activity, limb weakness, and irregular respiration immediately after dosing, and one Group No. 5 rat showed prostration, momentary lapses of respiration (apnea), and decreased activity immediately after dosing. All Group No. 3 rats lost the righting reflex and were ataxic immediately after dosing. Decreased activity and irregular respiration were noted within 30 minutes postdose and for the remainder of the day in one Group No. 5 rat.

Following Intraperitoneal Injection in Guinea Pigs - One Group No. 2 (25.1 mg/kg) animal exhibited irregular respiration on Day 1 and labored respiration on Day 6, Day 7, and Day 9. One Group No. 2 animal showed alopecia, ataxia, thinness, sneezing, and nasal discharge on Day 8 and Day 9. One or two Group No. 3 (39.8 mg/kg) animals showed the following signs from Day 5 or Day 6 through Day 8 or Day 9: slight depression, alopecia, anorexia, nasal discharge, hunched posture, and emaciation. One Group No. 3 animal also showed alopecia from Day 12 through Day 14, and another Group No. 3 animal exhibited ptosis, with exudate from one eye on Day 5.

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TRW/

HAZLETON LABORATORIES

Major Necropsy Findings:

Following Intravenous Injection in Mice - One Group No. 3 (15.9 mg/kg)

mouse exhibited a lesion on the liver following sacrifice.

Following Intravenous Injection in Rats - No gross pathology was noted

at death or sacrifice.

Following Intraperitoneal Injection in Guinea Pigs - One Group No. 6

(159 mg/kg) guinea pig showed pale tan kidneys at sacrifice.

Submitted by

Frederick E. Reno

FREDERICK E. RENO, Ph.D.
Project Manager, Drugs and
Industrial Chemicals Department
Toxicology-Biosciences Laboratory

Report Preparation: Spruill

Supervision: Minner

sad

Project No. 193-413
WR 149,024 AD (AX 67287)

I.V.
Male Rats Adult

Endpoint - mortality

LD₅₀ = 41.6
(39.3 - 44.2)

99.9

99.0

90.0

70.0

50.0

30.0

10.0

1.0

0.1

0

Percent response

Dose level - mg/kg

100

10

1000

Probit

0

-1

-2

-3

+1

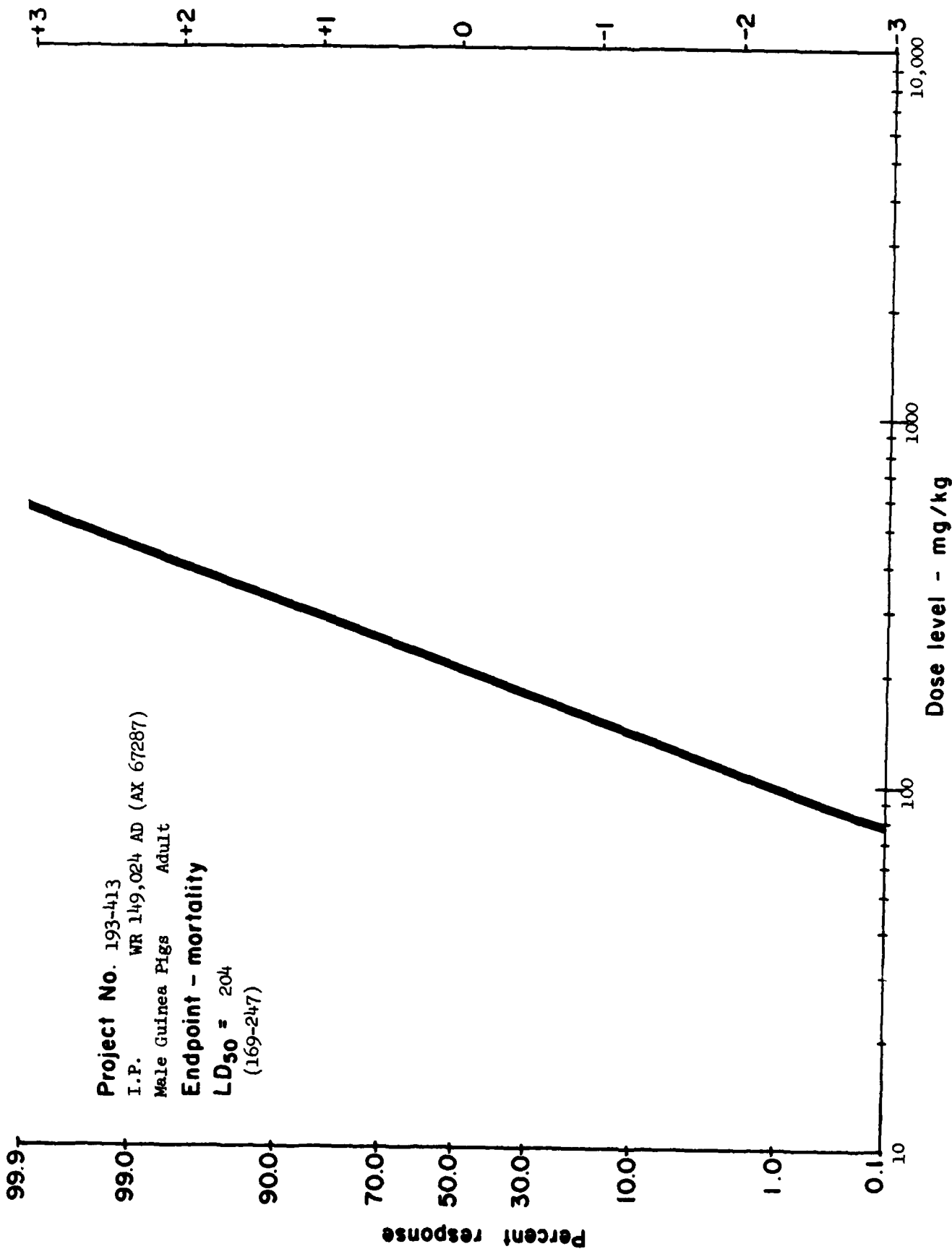
+2

+3

446

447

Probit



Project No. 193-413
 I.P. WR 149,024 AD (AX 67287)
 Male Guinea Pigs Adult
 Endpoint - mortality
 LD₅₀ = 204
 (169-247)

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TRW**HAZLETON LABORATORIES****SPONSOR:** Walter Reed Army Institute of Research**DATE:** September 15, 1971**MATERIAL:** WR 149,024 AD (AX 67287)**LOT NO:** 308/422**SUBJECT:** REPORT NO. 41
Acute Intravenous Toxicity Study - Dogs
Project No. 193-414**SUMMARY**

WR 149,024 AD was evaluated for acute intravenous toxicity in male purebred beagles at seven dosage levels ranging from 3.2 to 150 mg/kg of body weight. Observations for toxic and/or pharmacologic effect were recorded for seven days postdose, at which time the surviving animals were sacrificed. Representative tissues were preserved and sections of liver and kidneys were examined microscopically from each animal sacrificed at termination.

Dosage levels of 150 and 75 mg/kg produced death within three minutes postdose in the single animal treated at each level. Immediate respiratory arrest, cyanosis, rapid heart rates, salivation, retching, and cutaneous twitching were observed prior to death. Dose-related signs observed at the five lower dosage levels tested (37.5, 18.75, 9.38, 4.69, and 3.2 mg/kg) included rapid heart rates, deepened or depressed respiratory activity, pink or reddened mucous membranes, retching, emesis, quivering, pupillary dilation, salivation, temporary absence of reflexes, and cyanosis. Each of the animals at the five lower dosage levels recovered.

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Gross Pathology and microscopic examination of sections of liver and kidney for the animals sacrificed at termination revealed no compound-related alterations.

Therefore, the maximum nonlethal dose level tested was 37.5 mg/kg.

OBJECTIVE

The purpose of this study was to evaluate the toxicity of WR 149,024 AD (AX 67287) following a single intravenous dose to adult purebred beagles.

MATERIAL

Identification WR 149,024 AD (AX 67287); Lot No. 308/422.

Description A white powder with a faint odor.

Receipt Date May 12, 1971.

Purity Assumed 100% active ingredient.

METHODS

Experimental Animals

Breed: Young adult purebred beagles.

Number: Seven males.

Body Weight Range: At initiation from 9.3 to 14.5 kg.

Housing: Individually in metal cages.

Diet: Ground Wayne Dog Meal and water ad libitum.

Groups and Dosage Levels

<u>Group No.</u>	<u>No. of Animals</u>	<u>Dosage Level</u> mg/kg
1	1	3.20
2	1	4.69
3	1	9.38
4	1	18.75
5	1	37.50
6	1	75.00
7	1	150.00

Compound Administration and Preparation

The test material was mixed with isotonic saline at a concentration of 500 mg/ml and injected once at the specified dose levels into the cephalic vein of the forepaw at a rate of 0.1 ml. per 10 seconds.

Observations and Records

Mortality and Toxic Effects: Immediately, frequently on the day of dosing and daily thereafter for seven days.

Body Weights: Initially and terminally.

Terminal Studies

Terminal Sacrifice: By exsanguination under Surital anesthesia after a seven-day observation period.

Gross Necropsy: Performed on all animals sacrificed at termination.

Tissue Preservation: The following tissues from each animal sacrificed at termination were preserved in 10% neutral buffered formalin: brain, pituitary, thoracic spinal cord, eye, thyroids, lung, heart, liver (two lobes), gallbladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, prostate, skin, rib junction, bone marrow, and nerve with muscle.

The testes with epididymis were preserved in Bouin's fixative.

Histopathological Examination

One section from each of two lobes of the liver and three sections from the kidneys were examined microscopically from each animal sacrificed at termination.

RESULTS

Appearance, Behavior, Body Weight Changes, and Signs of Compound Effect

Individual body weights and compound administration are presented in Table No. 1.

3.2 mg/kg Level: The predose heart rate of 108/minute reached a peak of 172/minute at one minute postdose. The predose respiratory rate of 32/minute reached a peak of 36/minute at one minute postdose. Recovery to predose levels occurred three minutes postdose, and the animal appeared normal.

- 4.69 mg/kg Level: The predose heart rate of 132/minute reached 192/minute immediately postdose. Respiration was slightly deepened only. Approximately one and one-half hours postdose the animal appeared normal.
- 9.38 mg/kg Level: The predose heart rate of 96/minute reached 204/minute immediately postdose. By two minutes postdose, retching with mucoid emesis, rapid and pronounced respiratory contractions, and pink mucous membranes were observed. Five minutes postdose, and the animal appeared sedated but normal.
- 18.75 mg/kg Level: Depressed respiration, diaphragmatic contractions, reddened mucous membranes and a change from a predose heart rate of 54/minute to 190/minute were observed immediately postdose. Retching, mucoid emesis, and fully dilated pupils at three minutes and slight quivering at 18 minutes were also observed. By 24 hours, the animal appeared normal.
- 37.5 mg/kg Level: Approximately 30 seconds postdose the animal went down as if under anesthesia and was salivating slightly; by two minutes the toe-pinch reflex was absent and did not recover until 17 minutes. The predose heart rate of 108/minute increased to 240/minute at two minutes postdose. Retching (no emesis), deep and slightly irregular respiration, dilated pupils, and slight cyanosis were also observed at this time. By seven minutes postdose, respiration was normal and cyanosis was disappearing. By 24 hours, the animal appeared normal.

75 and 150 mg/kg Levels: Respiratory arrest, cyanosis, salivation and retching or cutaneous twitching, and increased heart rates preceded death at three minutes postdose in both animals.

Gross Pathology

18.75 mg/kg Level: The heart muscle appeared hard (Dog No. 15357).

37.5 mg/kg Level: A cyst was observed at the base of the pituitary (Dog No. 15405).

No gross alterations were observed among any of the other test animals which were sacrificed following the seven-day observation period.

Microscopic Pathology

Representative sections of liver and kidney were evaluated microscopically from Dogs No. 15400 (3.2 mg/kg), No. 15399 (4.69 mg/kg), No. 15376 (9.38 mg/kg), No. 15357 (18.75 mg/kg), and No. 15405 (37.5 mg/kg).

Incidental findings included hepatic mononuclear cell infiltration and chronic interstitial nephritis.

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No significant pathological alterations were detected which could be attributed to the test material.

Submitted by

Frederick E. Reno
FREDERICK E. RENO, Ph.D.
Project Manager, Drugs and
Industrial Chemicals Department
Toxicology-Biosciences Laboratory

Pathology by

John F. Ferrell
JOHN F. FERRELL, D.V.M.
Consultant Pathologist

Report Preparation: Horwatt
Supervision: Upman

gbb

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

Table No. 1 - Individual body weights and compound administration for male purebred beagles which received a single intravenous injection of WR 149,024 AD (AX 67287)

DOSE LEVEL - MG/KG														
3.2		4.69		9.38		DOG NO.		37.5		75.0		150.0		
15400		15399		15376		15357		15405		15265		15252		
TIME INTERVAL	WT.	CPD.	WT.	CPD.	WT.	CPD.	WT.	CPD.	WT.	CPD.	WT.	CPD.	WT.	CPD.
	kg.	mg.	kg.	mg.	kg.	mg.	kg.	mg.	kg.	mg.	kg.	mg.	kg.	mg.
Initial	9.4	30	11.8	55	9.2	87	11.3	210	10.6	395	14.5	1080	13.7	2050
Terminal*	9.1		11.6		9.1		11.2		10.2		**		**	
Net Change, kg.	-0.3		-0.2		-0.2		-0.1		-0.4					

* Terminal weights are fasted weights

** Death occurred three minutes postdose

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HISTOPATHOLOGICAL EVALUATION OF MALE PUREBRED BEAGLES
SACRIFICED AT TERMINATION

GROSS

MICROSCOPIC

GROUP NO. 1 - 3.2 MG/KG
Male Dog No. 15400

Liver:

No alterations observed. Minimal focal mononuclear cell infiltration.

The following organ was not altered grossly or microscopically: kidney.

GROUP NO. 2 - 4.69 MG/KG
Male Dog No. 15399

Kidney:

No alterations observed. Minimal focal chronic interstitial nephritis.

The following organ was not altered grossly or microscopically: liver.

GROUP NO. 3 - 9.38 MG/KG
Male Dog No. 15376

The following organs were not altered grossly or microscopically: liver and kidney.

GROUP NO. 4 - 18.75 MG/KG
Male Dog No. 15357

The following organs were not altered grossly or microscopically: liver and kidney.

GROUP NO. 5 - 37.5 MG/KG
Male Dog No. 15405

Liver:

No alterations observed. Minimal focal mononuclear cell infiltration.

The following organ was not altered grossly or microscopically: kidney.

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DETAILED HISTOPATHOLOGY INCIDENCE TABLE

ORGANS	ANIMAL NUMBER	MALES				
		DOSE LEVEL - MG/KG				
		3.2	4.69	9.38	18.75	37.5
		15400	15399	15376	15357	15405
LIVER						
Mononuclear Infiltration		1	X	X	X	1
KIDNEY						
Interstitial Nephritis		X	1	X	X	X

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HAZLETON LABORATORIES

SPONSOR: Walter Reed Army Institute of Research **DATE:** September 7, 1971

MATERIAL: WR 149,024 AD (AX 67287) **LOT NO:** 308/422

SUBJECT: REPORT NO. 40
Acute Intravenous Toxicity Study - Monkeys
Project No. 193-415

SUMMARY

WR 149,024 AD was evaluated for acute intravenous toxicity in male rhesus monkeys at six dosage levels ranging from 9.38 to 150.0 mg/kg of body weight. Observations for toxic and/or pharmacologic effect were recorded for seven days postdose, at which time the surviving animals were sacrificed. Representative tissues were preserved from all dead or sacrificed monkeys, and sections of liver and kidneys were examined microscopically from each animal.

Dosage levels of 150 and 75 mg/kg produced immediate death in the single animal treated at each level. The animal given 56.25 mg/kg developed shallow or temporary cessation of respiratory activity, but recovered. Two animals treated with 37.5 mg/kg showed rapid heart rates and respiration, but also recovered. No noticeable pharmacologic effects were observed at 18.75 or 9.38 mg/kg.

Microscopic examination of sections of liver and kidney revealed no consistent dosage-related alterations.

Therefore, the maximum nonlethal dose level tested was 56.25 mg/kg.



HAZLETON LABORATORIES

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OBJECTIVE

The purpose of this study was to evaluate the toxicity of WR 149, 024 AD (AX 67287) following a single intravenous dose to adult male monkeys.

MATERIAL

Identification WR 149,024 AD (AX 67287); Lot No. 308/422.

Description White powder.

Receipt Date May 12, 1971.

Purity Assumed 100% active ingredient.

METHODS

Experimental Animals

Breed: Young rhesus monkeys.

Number: Eight males.

Body Weight: At initiation from 1.8 to 3.5 kg.

Housing: Individually in metal cages.

Diet: Purina Monkey Chow twice daily, fresh fruit daily, and water ad libitum.

Groups and Dosage Levels

<u>Group No.</u>	<u>No. of Animals</u>	<u>Dosage Level</u> mg/kg
1	1	9.38
2	2	18.75
3	2	37.50
4	1	56.25
5	1	75.00
6	1	150.00

Compound Administration and Preparation

The test material was mixed with isotonic saline at a concentration of 300 mg/ml and injected once at the specified dose levels into the saphenous vein of the hindlimb at a rate of 0.1 ml. per 10 seconds.

Observations and Records

Daily: Appearance, behavior, appetite and elimination, and pharmacotoxic signs.

Initially and Terminally: Body weight.

Terminal Studies

Terminal Sacrifice: By exsanguination under anesthesia after seven days.

Gross Necropsies: On all sacrificed monkeys.

Tissues Preservation:

In 10% Neutral Buffered Formalin - Brain, pituitary, thoracic spinal cord, eye, thyroids, lung, heart, liver (two lobes), gallbladder,

spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, prostate, testes, skin, rib junction, bone marrow, nerve with muscle, and unusual lesions.

Microscopic Examination

The following tissues were examined from all animals: liver (one section from two lobes) and kidneys (three sections).

RESULTS

Appearance, Behavior, Body Weight Changes, and Signs of Compound Effect

Individual body weights and amounts of compound administered are presented in Table No. 1.

No apparent effects were observed in animals dosed at 9.38 and 18.75 mg/kg.

At two minutes postdose, Monkeys No. 825H and No. 823H (37.5 mg/kg levels) showed rapid heart rates, rapid or deep breathing, and were down in their cages. Recovery occurred four or six minutes postdose.

Labored and shallow respiration and faint, slow heart rate preceded a temporary cessation of respiration at two minutes postdose in Monkey No. 824H (56.25 mg/kg level). Recovery occurred at 11 minutes postdose.

Respiratory paralysis immediately postdose preceded death in Monkeys No. 821H and No. 820H (75 mg/kg and 150 mg/kg, respectively).

Gross Pathology

The stomach mucosa of Monkey No. 823H (37.5 mg/kg level) appeared reddened.

An encapsulated area attached to the left kidney of Monkey No. 828H was taken for microscopic analysis. The cut surface revealed a brown exudate and several small worms.

Signs of parasitic infestation (Monkey No. 828H) and adhesions of lungs to pleura (Monkey No. 827H) are commonly-occurring signs in monkeys and are considered incidental to the administration of the test compound.

Microscopic Pathology

No consistent, dosage-related alterations were observed in the sections examined which could be attributed to the test compound. Occasional collections of cells in the form of focal mononuclear infiltration or pericholangitis were seen in most sections of liver. Subacute pericholangitis was observed in Monkey No. 925H. However, the liver parenchyma was within normal limits, and the liver sections from the other animal at the same dose level (Monkey No. 823H) were considered not remarkable.

Minimal to mild interstitial nephritis was present in kidney sections from all animals and was not considered to be related to the test procedure. Mild edema and pyelitis were present in one animal treated at 37.5 mg/kg. However, this change was not seen in the other animal at the same dosage nor in the highest level animal.

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A section of stomach from Monkey No. 823H appeared to be within normal limits.

In conclusion, no consistent pathological alterations were detected in the sections examined which could be attributed to the test compound.

Submitted by

Frederick E. Reno
FREDERICK E. RENO, Ph.D.
Project Manager, Drugs and
Industrial Chemicals Department
Toxicology-Biosciences Laboratory

Pathology by

John F. Ferrell
JOHN F. FERRELL, D.V.M.
Consultant Pathologist

Report Preparation: Horwatt

Supervision: R. Thompson

gbb

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

Table No. 1 - Body weights and compound consumption for male rhesus monkeys

TIME INTERVAL weeks	MONKEY NO.															
	828H		826H		827H		825H		823H		824H		821H		820H	
	WT. kg.	CPD. mg.	WT. kg.	CPD. mg.	WT. kg.	CPD. mg.	WT. kg.	CPD. mg.	WT. kg.	CPD. mg.	WT. kg.	CPD. mg.	WT. kg.	CPD. mg.	WT. kg.	CPD. mg.
Initial	3.5	17.8	3.1	58.1	3.2	60.0	2.4	91.0	2.6	97.5	2.9	163.1	1.8	135.0	2.6	390.0
Terminal**	3.8		3.0		3.0		2.5		2.7		3.0		*		*	
Net Change, kg.	-0.3		-0.1		-0.2		+0.1		+0.1		+0.1		-		-	

* Not available

** Terminal weights are fasted weights

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HISTOPATHOLOGICAL EVALUATION OF MONKEYS

GROSS	MICROSCOPIC
Animal No. 828H 9.38 mg/kg	
Liver:	
No abnormalities observed.	Minimal focal mononuclear cell infiltration.
Kidney:	
Encapsulated area attached to left kidney. Cut surface revealed brownish exudate and several small worms.	There was an occasional minimal focus of chronic interstitial nephritis within the kidney parenchyma.
Parasitic nodules were seen throughout the mesentary.	There was a prominent granulomatous reaction containing nematode parasites on the capsular surface of the kidney.

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GROSS

MICROSCOPIC

Animal No. 826H
18.75 mg/kg

Liver:

No abnormalities observed. Minimal focal mononuclear cell
infiltration.

Kidney:

No abnormalities observed. Slight chronic interstitial
nephritis.

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GROSS

MICROSCOPIC

Animal No. 827H
18.75 mg/kg

Liver:

No abnormalities observed.

Minimal focal mononuclear cell
infiltration.

Kidney:

No abnormalities observed.

Minimal focal chronic interstitial
nephritis.

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GROSS

MICROSCOPIC

Animal No. 823H
37.5 mg/kg

Liver:

No abnormalities observed. Not remarkable.

Kidney:

No abnormalities observed. Minimal chronic interstitial
nephritis.

There was also a mild mononuclear
cell infiltration and looseness
of the tissue due apparently to
edema in the area of the pelvis.

Stomach:

Mucosa appeared slightly The tissue appeared to be within
reddened. normal limits.

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GROSS

MICROSCOPIC

Animal No. 825H
37.5 mg/kg

Liver:

No abnormalities observed.	Mild pericholangitis characterized by accumulations of neutrophils and mononuclear inflammatory cells in the areas surrounding the bile ducts.

Kidney:

No abnormalities observed.	Minimal focal chronic interstitial nephritis.

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GROSS

MICROSCOPIC

Animal No. 824H
56.25 mg/kg

Liver:

No abnormalities observed.

Minimal nonsuppurative peri-
cholangitis.

Kidney:

No abnormalities observed.

Slight focal chronic interstitial
nephritis.

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KEY FOR INCIDENCE TABLE

P = Present

NS = No Section

X = Not Remarkable

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderately Severe/High

5 = Severe/High

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DETAILED HISTOPATHOLOGY INCIDENCE TABLE

	Animal No.	Dose Level-mg/kg			
		9.38	18.75	37.5	56.25
		828H	826H 827H	823H 825H	824H
SEX		M	M M	M M	M
LIVER				X	
Mononuclear cell infiltration		1	1 1		
Pericholangitis				2	1
KIDNEY					
Parasitic granuloma		P			
Interstitial nephritis		1	2 1	1 1	2
Edema				2	
Pyelitis				2	
STOMACH				X	

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SPONSOR: Walter Reed Army Institute of Research

DATE: September 27, 1971

MATERIAL: WR 149,024 AD (AX 67287)

LOT NO: 308/422

SUBJECT: REPORT NO. 42
Subacute Intravenous Toxicity - Dogs
Project No. 193-416

SUMMARY

WR 149,024 AD (AX 67287) was tested for subacute (two weeks) intravenous toxicity in dogs by injections into the cephalic vein of the forelimb once daily, seven days a week, for two weeks, at dosage levels of 5, 10, and 20 mg/kg.

Postdose tachycardia, slight at the low level and increasing to moderate at the high level with recovery by two minutes postdose, and emesis were observed among all treated animals. Mydriasis, panting, and ataxia were also observed at the high level.

Analysis of clinical data and ophthalmoscopic examinations revealed no compound-induced alterations. Gross necropsy and inspection of organ/body weight data revealed no conclusive evidence of compound effect.

Microscopic examination of selected tissues revealed an increase in the amount of parafollicular tissue in the thyroids of the intermediate and high level females. This was not observed in the low level females or in any of the males. All other tissues examined failed to show an indication of compound-related effects.

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OBJECTIVE

The purpose of this study was to evaluate the toxicity of WR 149,024 AD (AX 67287) following intravenous injection daily seven days a week for two weeks.

MATERIAL

Identification WR 149,024 AD (AX 67287); Lot No. 308/422.

Description White powder.

Receipt Date May 12, 1971.

Purity Assumed 100% active ingredient.

METHODS

Experimental Animals

Breed: Young adult purebred beagles.

Number: Twelve males and 12 females.

Body Weight (At Initiation): From 8.0 to 14.4 kg. for males and 6.4 to 11.0 kg. for females.

Housing: Individually in elevated metal cages.

Diet: Ground Wayne Dog Meal.

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<u>Group No.</u>	<u>No. of Animals</u>		<u>Dosage Levels</u> mg/kg of body weight
	male	female	
1 (Control)	3	3	0
2	3	3	5
3	3	3	10
4	3	3	20

Compound Administration and Preparation

The compound was mixed with isotonic saline as a 5% solution and injected once daily, seven days a week, for two weeks, into the cephalic vein of the forelimb.

Observations and Records

Daily: Appearance, behavior, appetite, elimination, and pharmacotoxic signs.

Weekly: Body weight.

Clinical Signs

Performed: Initially and at one and two weeks.

Hematology: Hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte count, and clotting time.

Clinical Biochemistry: Fasting blood sugar, blood urea nitrogen, total serum protein, total serum bilirubin, serum albumin, serum sodium, serum potassium, serum chloride, carbon dioxide, serum calcium, serum glutamic-pyruvic transaminase, serum alkaline phosphatase, serum glutamic-oxaloacetic transaminase, and serum electrophoresis.

Urine Analysis: Specific gravity, pH, glucose, ketones, total protein, bilirubin, and microscopic examination of sediment.

Ophthalmoscopic Examination

Performed on all dogs initially and at termination.

Terminal Studies

Terminal Sacrifice: By exsanguination under Surital anesthesia.

Gross Necropsies: On all sacrificed dogs.

Tissue Preservation: In 10% neutral buffered formalin - Brain, pituitary, thoracic spinal cord, eye thyroids, lung, heart, liver, gallbladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, ureters, urethra, prostate, ovary, skin, rib junction, bone marrow, nerve with muscle, and any unusual lesions.

Organ Weights: Thyroids, heart, liver, spleen, kidneys, adrenals, and testis with epididymis.

Histopathological Examination

From Control and High Level Animals: Thyroids, heart, liver, gallbladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testis, ovary, and bone marrow.

From Low and Intermediate Level Animals: Liver, kidney, thyroids, and unusual lesions.

RESULTS

Appearance, Behavior, and Signs of Compound Effect

Individual weekly body weights are presented in Table No. 1.

Postdose tachycardia, slight among the low dose animals and increasing to moderate at the high dose, was observed among the treated animals. At the high dose, this was accompanied by panting, slight ataxia, reddening of the visible mucous membranes, scleral injection, and moderate mydriasis. Treated animals quickly returned to normal, however, within 15 to 20 seconds at the low dose and within two minutes at the high dose level.

Emesis following dosing was observed at least once during the study in all treated animals, with the incidence increasing to nearly daily at the high level. This was accompanied by salivation among two or three animals at the intermediate and high level.

Control animals appeared normal throughout the study.

Body weight losses of 7% to 8% of the initial weight were observed for high level animals. The remaining animals either gained or maintained ($\pm 5\%$) of body weight.

Clinical Studies

The results of the clinical studies on individual animals are presented in Tables No. 2 (hematology), No. 3 (blood chemistry), and No. 4 (urine analysis).

Clinical data revealed no consistent trends that could be attributable to the administration of the compound. A slight decrease in red blood cell values were observed in one or two animals of each sex at one and two weeks. Incidental variations were seen in one or two animals in control or test groups, and by themselves did not constitute trends.

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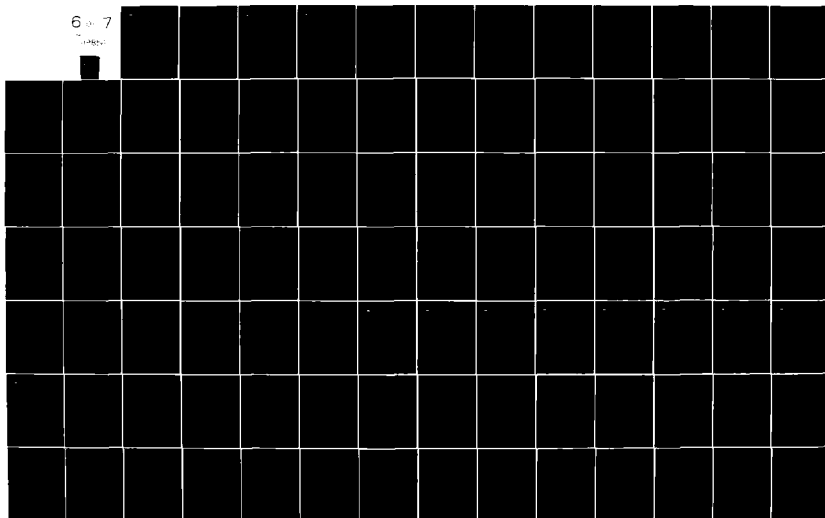
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Ophthalmoscopic Examination

Eye examinations were performed on all dogs initially and at the termination of the study using Mydriacyl as a mydriatic, a binocular magnifier, and a binocular indirect ophthalmoscope.

No compound-related ocular lesions were evident. Incidental changes which were present in two control dogs initially were also seen at terminal examination and are listed below.

Male Dog No. 15398: Prominent vitreous strand, both eyes; hypertrophy of Harders' gland, right eye.

Female Dog No. 15319: No tapetum lucidum present, both eyes.

The eyes of the remaining 22 dogs on the study appeared grossly normal.

Major Necropsy Findings

No compound-related alterations were found at necropsy. Dark pink or purple medulla of the kidney was observed in one low level male, two intermediate level males, and one high level male. The mucosa of the bladder was reddened in one intermediate level female. A moderate amount of yellowish green mucoid fluid in the stomach and dark green bile in the gallbladder were noted for high level male Dog No. 15459. The cut surface of the kidney was purple in one control female.

Organ Weights

Individual organ weights, terminal body weights, and organ/body weight ratios are presented in Table No. 5.

A high adrenal/body weight ratio was noted for low level male Dog No. 15454, a high testes/body weight ratio was observed for intermediate level Dog No. 15448, and a high spleen/body weight ratio was observed for high level male Dog No. 15377 and female Dog No. 15435.

Microscopic Pathology

The daily intravenous injection of WR 149,024 AD (AX 67287) for 14 consecutive days to male and female beagle dogs produced a relative increase in the parafollicular tissue in the thyroids of females injected at the dosage rates of 10.0 and 20.0 mg/kg of body weight. The size of the thyroid follicles and the morphological characteristics of the follicular epithelium were not meaningfully different from the controls. In the female dogs receiving 20.0 mg/kg of body weight, the increase in parafollicular tissue was more striking than that seen in the females injected with 10.0 mg/kg. A focal hyperplasia of parafollicular tissue was seen in female Dogs No. 15471 and No. 15470 injected with 20.0 and 10.0 mg/kg of body weight, respectively. Careful grading of the amount of parafollicular tissue in the male dogs injected intravenously with WR 149,024 AD (AX 67287) did not reveal any meaningful differences from the control male dogs.

An equivocally greater amount of parafollicular tissue was present in the males injected with 20.0 mg/kg of WR 149,024 AD (AX 67287), but because of the extreme variation in the controls, it was not considered to be related to the injection of the test material. It should also be noted that the amount of parafollicular tissue seen in the female dogs injected with 10.0 and 20.0 mg/kg of body weight was sometimes no greater than that seen in the control and test

males. The increase in thyroid parafollicular tissue observed in the female dogs injected with 10.0 and 20.0 mg/kg of body weight was not consistent and presented a somewhat confusing pattern when these animals were compared in detail with the control females. One female control (Dog No. 15432) had essentially the same amount of parafollicular tissue as that seen in female Dogs No. 15430 and No. 15434 that were injected with 10.0 mg/kg of body weight of WR 149,024 AD (AX 67287). This observation confuses the interpretation of the thyroid findings even further. However, it was felt that the increase in parafollicular tissue was great enough to attribute this finding to the injection of WR 149,024 AD (AX 67287).

Incidental microscopic alterations were seen in the spleen, liver, and kidneys from both the control and test dogs. In the spleen, a minimal to slight amount of pigment deposition was present in both the males and females. The incidence of this pigment deposition was slightly greater in the females, but the test females were not meaningfully different from the controls. Lesions of an incidental nature seen in both the test and control dogs consisted of minimal to slight bile duct proliferation, and the presence of a few bile plugs in some animals.

Minimal mineral deposition was seen in the medulla of the kidneys from the majority of the animals in both the control and test groups. Scattered incidences of chronic lymphocytic interstitial nephritis were seen in some of the males.

Moderate to severe focal chronic epididymitis was present in one control male Dog No. 15451. This microscopic alteration was characterized by a focal accumulation of spermatozoa surrounded by granulomatous inflammation.

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In conclusion, it can be stated that the intravenous injection of WR 149,024 AD (AX 67287) at the rate of 10.0 and 20.0 mg/kg of body weight per day for a period of 14 days to female beagle dogs resulted in the production of an increase in the amount of parafollicular tissue in the thyroid gland. No other compound-related histopathological alterations were noted in any of the tissues examined from these animals. Microscopic examination of the livers and kidneys from male and female beagle dogs receiving 5.0 and 10.0 mg/kg of body weight per day for a period of 14 days did not reveal any compound-related microscopic alterations.

Submitted by

Frederick E. Reno
FREDERICK E. RENO, Ph.D
Project Manager, Drugs and
Industrial Chemicals Department
Toxicology-Biosciences Laboratory

Pathology by

John F. Ferrell
JOHN F. FERRELL, D.V.M.
Consultant Pathologist

Report Preparation: Horwatt

Supervision: Upman

dc;gbb

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

EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

T = trace ($\pm$)

0 = negative

1 = slight (+)

2 = moderate (++)

3 = marked (+++)

4 = severe (++++)

Table No. 1 - Body weights of beagles receiving WR 149,024 AD (AX 67287)

TIME INTERVAL weeks	GROUP NO. 1 - SALINE CONTROL							
	DOG NO. 15358 M	DOG NO. 15398 M	DOG NO. 15451 M	DOG NO. 15319 F	DOG NO. 15432 F	DOG NO. 15436 F	WEIGHT	WEIGHT
	kg.	kg.	kg.	kg.	kg.	kg.		kg.
Initial	14.4	10.4	11.3	12.7	10.5	10.1		
1	15.0	10.5	11.5	12.5	10.6	10.0		
2	14.9	10.7	11.5	12.8	10.5	10.1		
Net Change, kg.	+0.5	+0.3	+0.2	+0.1	0	0		

Table No. 1 - Continued

TIME INTERVAL weeks	GROUP NO. 2 - 5 MG/KG OF BODY WEIGHT LEVEL							
	DOG NO. 15359 M WEIGHT kg.	DOG NO. 15426 M WEIGHT kg.	DOG NO. 15424 M WEIGHT kg.	DOG NO. 15322 F WEIGHT kg.	DOG NO. 15433 F WEIGHT kg.	DOG NO. 15437 F WEIGHT kg.		
Initial	8.8	12.7	13.2	7.0	11.0	9.3		
1	9.0	12.0	12.5	6.6	11.4	8.9		
2	8.8	12.1	12.5	6.8	11.3	9.2		
Net Change, kg.	0	-0.6	-0.7	-0.2	+0.3	-0.1		

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Table No. 1 - Continued

TIME INTERVAL weeks	GROUP NO. 3 - 10 MG/KG OF BODY WEIGHT LEVEL							
	DOG NO. 15360 M	DOG NO. 15448 M	DOG NO. 15458 M	DOG NO. 15430 F	DOG NO. 15434 F	DOG NO. 15470 F		
	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.		
Initial	10.7	8.0	11.5	8.5	10.4	8.4		
1	10.0	7.9	10.8	7.7	9.8	8.0		
2	11.0	7.7	11.1	7.8	9.9	8.1		
Net Change, kg.	+0.3	-0.3	-0.4	-0.7	-0.5	-0.3		

Table No. 1 - Continued

TIME INTERVAL weeks	GROUP NO. 4 - 20 MG/KG OF BODY WEIGHT LEVEL							
	DOG NO. 15377 M	DOG NO. 15449 M	DOG NO. 15459 M	DOG NO. 15431 F	DOG NO. 15435 F	DOG NO. 15471 F		
	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.		
Initial	12.1	8.3	8.5	8.0	6.4	9.4		
1	12.0	7.6	7.8	7.8	6.5	8.5		
2	11.8	8.3	8.0	7.3	6.2	8.7		
Net Change, kg.	-0.3	0	-0.5	-0.7	-0.2	-0.7		

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
PUREBRED BEAGLES RECEIVING WK149,024 AD (AX67287) FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	SEX	HCT %	HGB GM%	RBC MILLS	WBC THS	DIFFERENTIAL						
							METAS	BANDS	SEG	LYMPH	MONO	EOSIN	BASO
1	15358	M	52.0	18.7	5.04	8.8	0	0	47	38	4	11	0
1	15398	M	53.0	18.7	6.92	8.8	0	1	47	43	3	6	0
1	15451	M	47.0	17.2	5.32	19.4	0	0	78	18	3	1	0
GROUP MEAN			50.7	18.2	5.96	12.3							
2	15359	M	51.0	18.2	6.28	11.1	0	1	63	28	6	2	0
2	15426	M	51.5	18.7	7.03	5.6	0	0	55	34	3	4	0
2	15454	M	51.0	18.2	6.31	11.2	0	0	62	29	4	5	0
GROUP MEAN			51.2	18.4	6.54	9.3							
3	15360	M	53.0	18.9	5.91	10.5	0	0	59	37	0	4	0
3	15448	M	52.0	18.7	6.28	16.4	0	0	78	18	4	0	0
3	15458	M	50.5	17.9	5.87	6.5	0	0	53	30	5	12	0
GROUP MEAN			51.8	18.5	6.02	11.1							
4	15377	M	50.5	18.9	6.34	11.0	0	0	56	33	4	5	0
4	15449	M	57.0	19.5	7.26	9.1	0	1	74	23	2	0	0
4	15459	M	50.0	17.7	6.48	7.6	0	0	70	26	2	2	0
GROUP MEAN			52.5	18.7	6.69	9.2							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
PUKEBED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	HCT %	HGB GM%	RBC MILLS	WBC THS	DIFFERENTIAL						
							MET %	BAND %	SEG %	LYMPH %	MONO %	EUSIN %	BASO %
1	15358	M	52.0	18.7	6.72	8.2	0	0	51	46	1	2	0
1	15398	M	53.0	18.9	6.51	9.4	0	0	60	35	0	5	0
1	15451	M	50.0	17.7	6.18	9.5	0	0	72	26	0	2	0
GROUP MEAN			51.7	18.4	6.47	9.0							
2	15359	M	50.0	17.9	6.83	12.9	0	0	80	19	0	1	0
2	15426	M	53.5	18.7	6.64	5.5	0	0	57	42	0	1	0
2	15454	M	51.0	18.4	5.90	7.6	0	0	69	28	0	3	0
GROUP MEAN			51.5	18.3	6.46	8.7							
3	15360	M	51.0	17.7	6.17	8.8	0	0	56	44	0	0	0
3	15448	M	55.0	18.7	6.68	6.2	0	0	72	27	0	1	0
3	15458	M	51.0	18.6	6.18	6.0	0	0	67	32	0	1	0
GROUP MEAN			52.3	18.3	6.34	7.0							
4	15377	M	48.0	17.2	5.82	9.1	0	0	61	38	0	1	0
4	15449	M	58.0	19.9	6.45	5.5	0	0	73	25	2	0	0
4	15459	M	52.0	18.2	5.95	3.5	0	0	62	38	0	0	0
GROUP MEAN			52.7	18.4	6.07	6.0							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WRI49,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	E X	HCT %	HGB GM%	RBC MILLS	WBC THS	DIFFERENTIAL						
							MET %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	BASO %
1	15358	M	50.0	17.9	6.83	8.2	0	1	56	38	1	4	0
1	15398	M	52.0	18.2	7.22	10.3	0	0	56	37	0	7	0
1	15451	M	49.5	17.7	6.72	11.4	0	0	65	31	1	3	0
GROUP MEAN			50.5	17.9	6.92	10.0							
2	15359	M	48.0	16.7	6.60	10.3	0	0	61	35	4	0	0
2	15426	M	48.0	16.7	6.76	5.2	0	0	45	41	3	11	0
2	15454	M	51.0	17.7	6.60	7.8	0	0	57	38	2	3	0
GROUP MEAN			49.0	17.0	6.65	7.8							
3	15360	M	46.5	15.9	6.28	13.3	0	0	83	12	5	0	0
3	15448	M	53.0	18.2	7.28	7.2	0	0	60	39	0	1	0
3	15458	M	49.0	17.2	6.58	5.5	0	0	61	21	5	13	0
GROUP MEAN			49.5	17.1	6.71	8.7							
4	15377	M	49.0	17.2	6.25	9.5	0	0	54	42	2	2	0
4	15449	M	57.0	19.7	7.65	6.2	0	0	74	26	0	0	0
4	15459	M	46.0	15.9	6.14	3.8	0	1	67	30	2	0	0
GROUP MEAN			50.7	17.6	6.68	6.5							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS

GROUP NUMBER	ANIMAL NUMBER	SEX	HCT %	HGB GM%	RBC MILLS	WBC THS	DIFFERENTIAL							BASO %
							MET %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %		
1	15319	F	46.0	16.7	5.94	9.0	0	0	63	33	4	0	0	
	15432	F	47.0	16.5	6.06	10.7	0	1	59	33	2	5	0	
	15436	F	46.5	16.5	5.82	9.2	0	0	51	40	2	7	0	
GROUP MEAN			46.5	16.6	5.94	9.6								
2	15322	F	47.0	16.5	5.52	10.3	0	0	39	45	4	12	0	
	15433	F	46.0	16.5	6.42	11.3	0	0	52	34	6	8	0	
	15437	F	47.0	16.9	6.20	8.4	0	0	45	41	0	5	0	
GROUP MEAN			46.7	16.6	6.05	10.0								
3	15430	F	48.0	17.7	5.61	12.2	0	0	57	29	7	7	0	
	15434	F	46.0	16.5	5.44	7.7	0	0	60	25	1	14	0	
	15470	F	45.0	15.9	5.60	11.7	0	0	61	35	2	2	0	
GROUP MEAN			46.3	16.7	5.55	10.5								
4	15431	F	48.0	17.2	6.27	10.7	0	1	60	24	6	9	0	
	15435	F	47.0	17.2	6.00	8.9	0	0	51	43	2	4	0	
	15471	F	51.0	18.2	6.34	15.1	0	0	69	28	1	2	0	
GROUP MEAN			48.7	17.5	6.20	11.6								

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WRI49,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	HCT %	HGB GM%	RBC MILLS	WBC THS	DIFFERENTIAL							BASO %
							METABAND	SEG	LYMPH	MUNO	EOSIN			
							%	%	%	%	%	%	%	
1	15319	F	44.0	15.9	5.38	8.2	0	62	38	0	0	0	0	
1	15432	F	43.0	15.9	5.01	9.6	0	61	33	1	5	0	0	
1	15436	F	42.0	15.2	4.96	7.1	0	65	33	0	2	0	0	
GROUP MEAN			43.0	15.7	5.12	8.3								
2	15322	F	44.0	15.9	5.47	9.3	0	59	40	0	1	0	0	
2	15433	F	47.0	16.9	5.89	11.0	0	55	41	0	4	0	0	
2	15437	F	39.0	14.6	5.10	9.4	0	63	35	0	2	0	0	
GROUP MEAN			43.3	15.8	5.49	9.9								
3	15430	F	47.0	16.5	5.38	9.9	0	69	28	1	2	0	0	
3	15434	F	50.0	17.7	5.97	6.0	0	65	33	0	2	0	0	
3	15470	F	43.0	15.4	5.30	7.4	0	57	42	0	1	0	0	
GROUP MEAN			46.7	16.5	5.55	7.8								
4	15431	F	43.0	15.4	4.76	7.9	0	60	35	0	5	0	0	
4	15435	F	48.0	17.2	5.99	5.7	0	44	56	0	0	0	0	
4	15471	F	48.0	17.4	5.77	5.0	0	68	32	0	0	0	0	
GROUP MEAN			46.3	16.7	5.51	6.2								

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WRI49,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	E X	S	HCT %	HGB GM%	RBC MILLS	WBC THS	DIFFERENTIAL						BASO %
								MET %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	
1	15319	F		41.0	15.2	5.83	8.3	0	0	61	32	4	3	0
1	15432	F		41.0	14.6	5.47	9.5	0	0	68	29	2	1	0
1	15436	F		42.0	14.8	5.71	7.6	0	0	51	30	2	14	3
GROUP MEAN				41.3	14.9	5.67	8.5							
2	15322	F		49.0	16.3	6.41	8.4	0	0	51	43	1	5	0
2	15433	F		46.0	16.3	6.19	10.9	0	0	44	36	2	15	3
2	15437	F		40.0	13.4	5.47	9.8	0	0	41	43	2	14	0
GROUP MEAN				45.0	15.3	6.02	9.7							
3	15430	F		46.0	16.3	6.18	15.0	0	0	70	23	3	4	0
3	15434	F		50.0	17.7	6.44	6.5	0	0	56	36	2	6	0
3	15470	F		42.0	14.6	5.46	8.1	0	0	37	48	1	14	0
GROUP MEAN				46.0	16.2	6.03	9.9							
4	15431	F		40.0	15.9	5.53	11.0							
4	15435	F		49.0	16.7	6.06	8.9	0	0	67	27	3	3	0
4	15471	F		45.0	15.9	5.70	5.6	0	0	58	38	1	3	0
GROUP MEAN				44.7	16.2	5.76	8.5							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WRI49,024 AD (AX67287) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	COAGULATION MIN	SEC
1	15358	M	4	11
1	15398	M	4	35
1	15451	M	5	28
GROUP MEAN			4	45
2	15359	M	5	11
2	15426	M	4	46
2	15454	M	4	50
GROUP MEAN			4	56
3	15360	M	5	40
3	15448	M	4	31
3	15458	M	3	58
GROUP MEAN			4	43
4	15377	M	5	10
4	15449	M	5	07
4	15459	M	4	40
GROUP MEAN			4	59

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WRI49,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	COAGULATION MIN	SEC
1	15358	M	3	35
1	15398	M	3	52
1	15451	M	4	31
GROUP MEAN			3	59
2	15359	M	3	47
2	15426	M	4	10
2	15454	M	3	58
GROUP MEAN			3	58
3	15360	M	4	34
3	15448	M	3	38
3	15458	M	4	02
GROUP MEAN			4	05
4	15377	M	4	00
4	15449	M	2	09
4	15459	M	4	49
GROUP MEAN			3	39

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	COAGULATION MIN	SEC
1	15358	M	4	11
1	15398	M	4	35
1	15451	M	5	28
GROUP MEAN				
			4	45
2	15359	M	5	11
2	15426	M	4	46
2	15454	M	4	50
GROUP MEAN				
			4	56
3	15360	M	5	40
3	15448	M	4	31
3	15458	M	3	58
GROUP MEAN				
			4	43
4	15377	M	5	10
4	15449	M	5	07
4	15459	M	4	40
GROUP MEAN				
			4	59

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	SEX	COAGULATION	
			MIN	SEC
1	15319	F	4	53
1	15432	F	3	56
1	15436	F	4	38
GROUP MEAN			4	29
2	15322	F	4	42
2	15433	F	5	21
2	15437	F	4	29
GROUP MEAN			4	51
3	15430	F	4	52
3	15434	F	5	15
3	15470	F	4	44
GROUP MEAN			4	57
4	15431	F	4	27
4	15435	F	4	42
4	15471	F	4	23
GROUP MEAN			4	31

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREHRED BEAGLES RECEIVING WK149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	COAGULATION MIN	SEC
1	15319	F	4	11
1	15432	F	3	54
1	15436	F	3	45
GROUP MEAN			3	57
2	15322	F	3	46
2	15433	F	3	55
2	15437	F	3	51
GROUP MEAN			3	51
3	15430	F	4	28
3	15434	F	4	25
3	15470	F	4	26
GROUP MEAN			4	20
4	15431	F	3	43
4	15435	F	3	15
4	15471	F	3	56
GROUP MEAN			3	38

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	COAGULATION MIN	SEC
1	15319	F	4	15
1	15432	F	3	56
1	15436	F	4	38
GROUP MEAN			4	16
2	15322	F	4	42
2	15433	F	5	21
2	15437	F	4	29
GROUP MEAN			4	51
3	15430	F	4	52
3	15434	F	5	15
3	15470	F	4	44
GROUP MEAN			4	57
4	15431	F	4	27
4	15435	F	4	42
4	15471	F	4	43
GROUP MEAN			4	37

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WRI49,024 AD (AX67287) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	15358	M	85.0	14.0	27.0	5.1	0.35	44.0
1	15398	M	96.0	14.0	25.0	2.6	0.33	41.0
1	15451	M	69.0	12.0	19.0	6.0	0.21	33.0
GROUP MEAN			83.3	13.3	23.7	4.6	0.30	39.3
2	15359	M	76.0	16.0	24.0	5.8	0.29	37.0
2	15426	M	87.0	8.0	32.0	4.5	0.29	25.0
2	15454	M	88.0	10.5	24.0	13.0	0.29	33.0
GROUP MEAN			83.7	11.5	26.7	7.8	0.29	31.7
3	15360	M	70.0	14.0	22.0	8.5	0.30	39.0
3	15448	M	85.0	8.0	29.0	4.5	0.29	43.0
3	15458	M	99.0	11.0	38.0	8.0	0.30	42.0
GROUP MEAN			84.7	11.0	29.7	7.0	0.30	41.3
4	15377	M	62.0	22.0	22.0	4.9	0.30	39.0
4	15449	M	93.0	14.0	22.0	9.0	0.31	37.0
4	15459	M	95.0	11.0	32.0	9.0	0.30	42.0
GROUP MEAN			83.3	15.7	25.3	7.6	0.30	39.3

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	GLUCOSE MG%	BUN MG%	SGPT R-F	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	15358 M	96.0	11.0	38.0	8.6	0.31	43.0
1	15398 M	90.0	16.0	35.0	5.9	0.31	44.0
1	15451 M	92.0	11.0	32.0	6.8	0.21	42.0
GROUP MEAN		92.7	12.7	35.0	7.1	0.28	43.0
2	15359 M	85.0	24.0	28.0	6.8	0.20	42.0
2	15426 M	96.0	11.0	35.0	6.1	0.26	37.0
2	15454 M	96.0	8.5	32.0	10.2	0.21	41.0
GROUP MEAN		92.3	14.5	31.7	7.7	0.22	40.0
3	15360 M	86.0	19.0	31.0	9.8	0.20	41.0
3	15448 M	124.0	11.0	39.0	6.0	0.20	48.0
3	15458 M	115.0	15.0	38.0	10.0	0.19	45.0
GROUP MEAN		108.3	15.0	36.0	8.6	0.20	44.7
4	15377 M	95.0	18.0	41.0	6.9	0.30	53.0
4	15449 M	120.0	15.0	31.0	10.0	0.20	42.0
4	15459 M	105.0	15.0	29.0	9.0	0.20	44.0
GROUP MEAN		106.7	16.0	33.7	8.6	0.23	46.3

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	15358	M	94.0	11.0	36.0	7.2	0.36	37.0
1	15398	M	99.0	12.0	35.0	5.9	0.29	35.0
1	15451	M	91.0	9.5	32.0	6.0	0.29	27.0
GROUP MEAN			94.7	10.8	34.3	6.4	0.31	33.0
2	15359	M	96.0	21.0	32.0	6.2	0.25	35.0
2	15426	M	100.0	12.0	38.0	6.2	0.30	32.0
2	15454	M	90.0	9.0	35.0	8.6	0.25	30.0
GROUP MEAN			95.3	14.0	35.0	7.0	0.27	32.3
3	15360	M	85.0	41.0	32.0	9.8	0.22	28.0
3	15448	M	111.0	10.0	36.0	6.9	0.22	41.0
3	15458	M	105.0	14.0	39.0	8.2	0.20	33.0
GROUP MEAN			100.3	21.7	35.7	8.3	0.21	34.0
4	15377	M	92.0	18.0	39.0	5.8	0.29	42.0
4	15449	M	114.0	15.0	29.0	9.0	0.29	31.0
4	15459	M	106.0	12.0	32.0	6.9	0.20	33.0
GROUP MEAN			104.0	15.0	33.3	7.2	0.26	35.3

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING MK149,024 AD (AX67287) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	15319	F	82.0	14.5	31.0	2.8	0.29	43.0
1	15432	F	71.0	11.0	29.0	6.0	0.30	49.0
1	15436	F	99.0	17.0	25.0	2.8	0.29	40.0
GROUP MEAN			84.0	14.2	28.3	3.9	0.29	44.0
2	15322	F	70.0	14.5	24.0	4.0	0.29	40.0
2	15433	F	93.0	15.5	27.0	2.8	0.30	38.0
2	15437	F	82.0	14.0	25.0	4.0	0.29	43.0
GROUP MEAN			81.7	14.7	25.3	3.6	0.29	40.3
3	15430	F	90.0	10.0	28.0	11.1	0.29	49.0
3	15434	F	95.0	7.0	25.0	4.4	0.30	43.0
3	15470	F	76.0	18.0	25.0	3.3	0.21	47.0
GROUP MEAN			87.0	11.7	26.0	6.3	0.27	46.3
4	15431	F	74.0	13.0	29.0	12.2	0.22	46.0
4	15435	F	88.0	13.0	24.0	3.1	0.20	42.0
4	15471	F	82.0	12.0	27.0	8.2	0.49	43.0
GROUP MEAN			81.3	12.7	26.7	7.8	0.30	43.7

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WRI49,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	15319	F	92.0	11.5	28.0	5.0	0.21	40.0
1	15432	F	84.0	16.0	35.0	9.1	0.21	49.0
1	15436	F	101.0	18.0	31.0	5.0	0.21	43.0
GROUP MEAN			92.3	15.2	31.3	6.4	0.21	44.0
2	15322	F	85.0	17.0	28.0	5.9	0.21	48.0
2	15433	F	106.0	17.0	31.0	5.9	0.21	43.0
2	15437	F	105.0	12.0	29.0	7.8	0.30	42.0
GROUP MEAN			98.7	15.3	29.3	6.5	0.24	44.3
3	15430	F	105.0	11.0	29.0	11.0	0.20	46.0
3	15434	F	106.0	12.0	38.0	6.1	0.20	44.0
3	15470	F	99.0	21.0	32.0	7.5	0.20	52.0
GROUP MEAN			103.3	14.7	33.0	8.2	0.20	47.3
4	15431	F	102.0	14.0	32.0	14.9	0.19	51.0
4	15435	F	124.0	14.0	28.0	7.0	0.20	48.0
4	15471	F	100.0	13.0	27.0	7.2	0.30	47.0
GROUP MEAN			108.7	13.7	29.0	9.7	0.23	48.7

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	15319	F	92.0	13.0	29.0	5.2	0.29	31.0
1	15432	F	85.0	15.0	36.0	8.9	0.30	39.0
1	15436	F	102.0	15.5	34.0	5.2	0.22	33.0
GROUP MEAN			93.0	14.5	33.0	6.4	0.27	34.3
2	15322	F	89.0	24.5	35.0	5.4	0.21	37.0
2	15433	F	106.0	15.0	28.0	5.0	0.21	33.0
2	15437	F	100.0	13.0	29.0	6.9	0.25	29.0
GROUP MEAN			98.3	17.5	30.7	5.8	0.22	33.0
3	15430	F	91.0	17.0	28.0	10.0	0.20	33.0
3	15434	F	106.0	13.0	35.0	5.9	0.30	36.0
3	15470	F	105.0	18.0	31.0	7.1	0.24	40.0
GROUP MEAN			100.7	16.0	31.3	7.7	0.25	36.3
4	15431	F	110.0	13.0	32.0	12.1	0.20	39.0
4	15435	F	86.0	15.5	28.0	7.6	0.21	37.0
4	15471	F	109.0	12.0	28.0	6.0	0.30	31.0
GROUP MEAN			101.7	13.5	29.3	8.6	0.24	35.7

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
PUKEBKED BEAGLES RECEIVING WRI49,024 AD (AX47287) FOR TWO WEEKS
INITIAL

GROUP NUMBER	S ANIMAL NUMBER	E X	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO2 MEQ/L
1	15358	M	145.0	4.45	112.0	10.6	25.8
1	15398	M	145.0	4.55	112.0	10.6	25.2
1	15451	M	145.0	4.75	108.5	10.5	26.1
GROUP MEAN			145.0	4.58	110.8	10.6	25.7
2	15359	M	146.0	4.50	112.0	10.5	26.1
2	15426	M	145.0	5.45	110.0	10.7	28.0
2	15454	M	144.0	5.00	106.0	11.0	26.1
GROUP MEAN			145.0	4.95	109.3	10.7	26.7
3	15360	M	146.0	4.10	112.0	10.6	25.2
3	15448	M	147.0	5.70	110.0	10.8	26.9
3	15458	M	144.0	5.30	110.0	10.3	26.8
GROUP MEAN			145.7	5.03	110.7	10.6	26.3
4	15377	M	148.0	4.40	113.0	11.3	26.0
4	15449	M	144.0	6.00	105.0	11.3	27.6
4	15459	M	143.0	5.10	107.0	10.1	26.5
GROUP MEAN			145.0	5.17	108.3	10.9	26.7

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	S ANIMAL NUMBER	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO ₂ MEQ/L
1	15358 M	148.0	4.95	103.5	11.2	25.3
1	15398 M	148.0	4.50	114.0	10.9	24.2
1	15451 M	145.0	4.60	112.0	10.6	24.5
GROUP MEAN		147.0	4.68	109.8	10.9	24.7
2	15359 M	146.0	4.10	114.0	10.5	24.9
2	15426 M	144.0	5.00	113.0	10.6	25.0
2	15454 M	145.0	5.05	113.5	10.5	24.9
GROUP MEAN		145.0	4.72	113.5	10.5	24.9
3	15360 M	147.0	4.30	113.0	10.2	25.1
3	15448 M	147.0	5.10	113.0	10.6	23.8
3	15458 M	147.0	4.80	114.0	10.3	23.9
GROUP MEAN		147.0	4.73	113.3	10.4	24.3
4	15377 M	148.0	3.80	114.0	10.8	24.5
4	15449 M	148.0	4.90	111.0	11.2	25.0
4	15459 M	148.0	4.50	114.0	10.5	26.6
GROUP MEAN		148.0	4.40	113.0	10.6	25.4

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO2 MEQ/L
1	15358	M	146.0	4.80	112.0	11.0	26.1
1	15398	M	146.0	5.00	111.0	10.8	26.2
1	15451	M	146.0	4.45	111.0	10.6	25.2
GROUP MEAN			146.0	4.75	111.3	10.8	25.8
2	15359	M	145.0	4.40	112.0	10.6	24.9
2	15426	M	147.0	4.90	112.0	10.8	25.8
2	15454	M	147.0	5.00	114.0	10.8	24.8
GROUP MEAN			146.3	4.77	112.7	10.7	25.2
3	15360	M	150.0	4.10	117.0	10.9	24.1
3	15448	M	145.0	5.30	111.0	10.6	24.1
3	15458	M	146.0	4.80	114.0	10.4	23.8
GROUP MEAN			147.0	4.73	114.0	10.6	24.0
4	15377	M	149.0	4.20	115.0	11.1	24.9
4	15449	M	148.0	5.00	111.0	11.5	26.0
4	15459	M	148.0	4.40	115.0	10.1	27.0
GROUP MEAN			148.3	4.53	113.7	10.9	26.0

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WK149,024 AD (AX67287) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO2 MEQ/L
1	15319	F	143.0	4.80	109.0	10.5	24.6
1	15432	F	143.0	4.60	109.0	10.8	24.9
1	15436	F	146.0	5.30	110.0	11.2	23.0
GROUP MEAN			144.0	4.90	109.3	10.8	24.2
2	15322	F	144.0	4.60	109.0	10.5	26.1
2	15433	F	143.0	4.80	108.0	11.0	26.0
2	15437	F	146.0	5.05	108.0	10.8	25.7
GROUP MEAN			144.3	4.82	108.3	10.8	25.9
3	15430	F	145.0	4.30	108.0	10.7	28.4
3	15434	F	147.0	5.00	109.0	11.0	25.0
3	15470	F	146.0	5.60	111.0	10.2	26.5
GROUP MEAN			146.0	4.97	109.3	10.6	26.6
4	15431	F	145.0	5.50	111.0	10.4	26.0
4	15435	F	148.0	5.25	111.0	10.0	25.2
4	15471	F	146.0	5.10	111.0	10.2	24.8
GROUP MEAN			146.3	5.28	111.0	10.2	25.3

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	S ANIMAL NUMBER	E X	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO2 MEQ/L
1	15319	F	144.0	4.90	111.0	10.6	24.2
1	15432	F	145.0	4.80	112.0	11.0	22.8
1	15436	F	144.0	4.65	115.0	10.6	21.8
GROUP MEAN			144.3	4.78	112.7	10.7	22.9
2	15322	F	148.0	4.40	113.5	10.4	25.8
2	15433	F	147.0	4.90	112.0	10.7	22.8
2	15437	F	145.0	4.55	110.0	10.6	22.6
GROUP MEAN			146.7	4.62	111.8	10.6	23.7
3	15430	F	149.0	4.30	115.0	10.1	25.9
3	15434	F	148.0	4.30	114.5	10.9	24.0
3	15470	F	148.0	5.30	113.5	10.6	25.8
GROUP MEAN			148.3	4.63	114.3	10.5	25.2
4	15431	F	149.0	3.65	115.0	10.4	25.6
4	15435	F	146.0	4.40	114.0	10.3	24.0
4	15471	F	147.0	4.40	114.0	11.0	24.8
GROUP MEAN			147.3	4.15	114.3	10.6	24.8

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO2 MEQ/L
1	15319	F	144.0	4.90	111.0	10.7	25.9
1	15432	F	144.0	4.80	111.5	10.6	24.5
1	15436	F	144.0	4.80	114.5	10.3	23.2
GROUP MEAN			144.0	4.83	112.3	10.5	24.5
2	15322	F	148.0	4.45	114.0	10.5	28.1
2	15433	F	146.0	5.20	113.0	10.8	23.5
2	15437	F	144.0	4.60	111.0	10.7	24.0
GROUP MEAN			146.0	4.75	112.7	10.7	25.2
3	15430	F	151.0	4.10	119.0	10.8	24.8
3	15434	F	151.0	4.60	117.0	10.8	23.5
3	15470	F	148.0	5.05	115.0	10.6	26.1
GROUP MEAN			150.0	4.58	117.0	10.7	24.8
4	15431	F	150.0	3.95	116.5	10.2	26.2
4	15435	F	149.0	4.70	113.0	10.4	25.1
4	15471	F	149.0	4.30	113.0	10.7	26.9
GROUP MEAN			149.3	4.32	114.2	10.4	26.1

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WRL49,024 AD (AX67287) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	TOTAL PROTEIN G%	ELECTROPHORESIS					TOTAL ALBUMIN G%
				ALBUMIN %	ALPHA1 %	ALPHA2 %	BETA %	GAMMA %	
1	15358 M		5.90	60.5	4.0	8.5	25.0	4.0	3.10
1	15398 M		6.00	53.0	6.0	11.0	22.5	7.5	2.71
1	15451 M		5.99	47.0	5.0	15.0	26.5	6.5	2.60
GROUP MEAN			5.96	53.5	5.0	11.5	24.0	6.0	2.80
2	15359 M		5.91	54.5	4.5	11.0	24.0	6.0	2.95
2	15426 M		5.60	52.0	7.0	11.0	24.0	6.0	2.69
2	15454 M		6.49	40.0	5.0	15.0	30.0	10.0	2.70
GROUP MEAN			6.00	48.8	5.5	12.3	26.0	7.3	2.78
3	15360 M		5.71	59.0	5.0	12.0	21.0	3.0	2.70
3	15448 M		6.20	53.0	6.0	12.5	23.5	5.0	2.60
3	15458 M		5.50	50.0	8.0	15.0	17.0	4.0	3.40
GROUP MEAN			5.80	56.0	6.3	13.2	20.5	4.0	2.90
4	15377 M		6.00	52.0	7.0	11.0	23.0	7.0	3.35
4	15449 M		6.50	49.0	5.0	11.0	29.0	6.0	3.79
4	15459 M		5.91	56.0	8.0	13.0	21.0	2.0	2.90
GROUP MEAN			6.14	52.3	6.7	11.7	24.3	5.0	3.35

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E	TOTAL PROTEIN G%	ELECTROPHORESIS					TOTAL ALBUMIN G%
				ALBUMIN %	ALPHA1 %	ALPHA2 %	BETA %	GAMMA %	
1	15358	M	6.30	52.0	4.0	8.5	26.0	9.0	3.09
1	15398	M	6.29	51.0	4.5	9.5	22.5	12.5	2.90
1	15451	M	5.81	51.0	3.0	14.0	24.0	8.0	2.89
GROUP MEAN			6.13	51.3	3.8	10.7	24.2	9.8	2.96
2	15359	M	6.00	51.0	4.0	9.0	29.0	7.0	2.78
2	15426	M	5.65	51.0	4.5	14.5	21.0	9.0	2.78
2	15454	M	5.81	50.0	4.0	14.0	24.0	8.0	2.65
GROUP MEAN			5.82	50.7	4.2	12.5	24.7	8.0	2.74
3	15360	M	5.40	49.0	6.0	12.0	25.0	8.0	2.49
3	15443	M	6.10	48.0	4.0	13.0	24.0	11.0	2.90
3	15458	M	5.60	50.0	6.0	18.0	21.0	5.0	3.40
GROUP MEAN			5.70	49.0	5.3	14.3	23.3	8.0	2.93
4	15377	M	5.60	51.0	5.0	17.0	20.0	7.0	3.48
4	15449	M	5.99	50.0	6.0	15.0	24.0	5.0	3.60
4	15459	M	5.85	54.0	5.0	14.0	23.0	4.0	2.99
GROUP MEAN			5.81	51.7	5.3	15.3	22.3	5.3	3.36

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	SEX	TOTAL PROTEIN G%	ELECTROPHORESIS				TOTAL ALBUMIN G%
				ALBUMIN %	ALPHA1 %	ALPHA2 %	BETA %	
1	15358	M	6.00	53.5	4.0	14.0	22.5	3.20
1	15398	M	5.91	49.0	4.0	11.0	25.5	2.81
1	15451	M	5.61	53.0	4.5	14.5	21.0	3.00
GROUP MEAN			5.84	51.8	4.2	13.2	23.0	3.00
2	15359	M	5.90	52.0	4.0	16.0	19.0	3.05
2	15426	M	5.60	57.0	5.0	11.5	18.0	3.19
2	15454	M	5.80	48.0	6.0	16.0	21.0	2.89
GROUP MEAN			5.77	52.3	5.0	14.5	19.3	3.04
3	15360	M	6.20	49.0	5.5	11.5	27.0	2.80
3	15448	M	5.91	52.0	4.5	10.5	26.5	2.83
3	15458	M	5.50	55.0	4.0	13.5	21.5	3.49
GROUP MEAN			5.87	52.0	4.7	11.8	25.0	3.04
4	15377	M	6.11	56.0	3.0	9.0	23.0	3.49
4	15449	M	6.29	54.0	5.0	11.0	25.0	3.80
4	15459	M	5.50	59.0	3.0	11.0	20.0	3.00
GROUP MEAN			5.97	56.3	3.7	10.3	22.7	3.43

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	SEX	TOTAL PROTEIN G%	ELECTROPHORESIS				TOTAL ALBUMIN G%
				ALBUMIN %	ALPHA1 %	ALPHA2 %	BETA %	
1	15319	F	5.71	58.0	7.0	11.0	18.0	3.40
1	15432	F	6.49	44.0	6.0	12.0	31.0	2.89
1	15436	F	5.65	44.0	7.0	13.0	29.0	2.60
GROUP MEAN			5.95	48.7	6.7	12.0	26.0	2.96
2	15322	F	5.70	45.0	7.0	13.0	26.0	2.74
2	15433	F	6.20	46.0	6.0	10.0	31.0	2.75
2	15437	F	6.00	43.0	7.0	13.0	29.0	3.50
GROUP MEAN			5.97	44.7	6.7	12.0	28.7	3.00
3	15430	F	6.00	52.0	6.0	10.5	25.5	2.90
3	15434	F	5.99	48.0	6.0	11.0	27.0	3.91
3	15470	F	5.09	52.0	6.0	12.0	24.0	2.50
GROUP MEAN			5.69	50.7	6.0	11.2	25.5	3.10
4	15431	F	5.70	53.5	5.5	12.0	22.0	3.51
4	15435	F	4.89	52.0	7.0	12.0	22.0	2.50
4	15471	F	5.90	43.0	6.0	19.0	26.0	2.55
GROUP MEAN			5.50	49.5	6.2	14.3	23.3	2.85

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	SEX	TOTAL PROTEIN G%	ELECTROPHORESIS					TOTAL ALBUMIN G%
				ALBUMIN %	ALPHA1 %	ALPHA2 %	BETA %	GAMMA %	
1	15419	F	5.69	50.5	6.5	13.0	22.0	8.0	3.39
1	15432	F	6.41	43.0	6.0	11.0	31.0	9.0	2.71
1	15436	F	5.59	53.0	6.5	11.5	22.0	7.0	2.61
GROUP MEAN			5.90	48.8	6.3	11.8	25.0	8.0	2.90
2	15322	F	5.40	52.0	5.0	14.5	23.0	5.5	2.80
2	15433	F	6.10	48.0	6.5	13.0	24.5	8.0	2.91
2	15437	F	6.11	49.0	7.0	10.0	27.5	0.5	3.42
GROUP MEAN			5.87	49.7	6.2	12.5	25.0	6.7	3.04
3	15430	F	5.99	47.5	5.5	12.0	25.0	10.0	2.91
3	15434	F	6.30	53.0	6.0	11.0	26.0	4.0	4.00
3	15470	F	6.21	47.0	8.0	9.0	30.0	6.0	3.29
GROUP MEAN			6.17	49.2	6.5	10.7	27.0	6.7	3.40
4	15431	F	5.90	48.0	6.0	14.0	24.0	8.0	3.50
4	15435	F	5.30	53.0	6.0	14.0	21.0	6.0	2.81
4	15471	F	6.15	48.5	6.5	17.0	23.5	4.5	3.02
GROUP MEAN			5.78	49.8	6.2	15.0	22.3	6.2	3.11

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	SEX	TOTAL PROTEIN G%	ELECTROPHORESIS					TOTAL ALBUMIN G%
				ALBUMIN %	ALPHA1 %	ALPHA2 %	BETA %	GAMMA %	
1	15319	F	5.70	51.0	6.5	14.5	22.5	5.5	3.41
1	15432	F	6.40	45.5	6.0	16.5	23.0	9.0	2.84
1	15436	F	5.31	56.0	4.0	12.5	20.5	7.0	2.62
GROUP MEAN			5.80	50.8	5.5	14.5	22.0	7.2	2.96
2	15322	F	5.50	46.0	6.5	12.5	26.5	6.5	2.71
2	15433	F	5.91	46.0	7.0	15.0	23.0	9.0	2.89
2	15437	F	6.10	46.0	8.0	11.0	27.0	8.0	3.49
GROUP MEAN			5.84	46.0	7.2	12.8	26.2	7.8	3.03
3	15430	F	6.40	50.0	5.0	10.5	26.5	8.0	3.05
3	15434	F	6.41	59.0	3.0	8.5	24.5	5.0	4.25
3	15470	F	6.00	57.0	6.0	8.5	23.5	5.0	3.10
GROUP MEAN			6.27	55.3	4.7	9.2	24.8	6.0	3.47
4	15431	F	5.95	51.5	5.5	12.0	22.0	7.0	3.91
4	15435	F	5.40	55.0	5.0	13.5	20.5	6.0	2.99
4	15471	F	6.00	54.0	7.0	12.0	22.0	5.0	3.11
GROUP MEAN			5.78	53.5	5.8	12.5	21.5	6.0	3.34

TABLE NO. 4 - URINE ANALYSIS
 PURBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS

GROUP NUMBER	ANIMAL NUMBER	S E X	P H	SP. GR.	SU- GAR	ACE- TONE	PRO- TEIN	BILI- KUBIN	-----MICROSCOPIC FINDINGS-----						
									RBC	WBC	EPITH	AMORPH	CRYS	BACT	SPERM
1	15358	M	6	1.053	T	0	T	T	3-5	0-3	3-5	MANY	FEW	FEW	
1	15348	M	6	1.053	0	0	I	T		2-6	3-4	FEW			
1	15451	M	7	1.055	T	0	I	T		0-1	0-2	MANY	MANY		
2	15359	M	6	1.036	T	0	C	T		0-2	0-2	FEW	FEW	MANY	
2	15426	M	9	1.020	0	0	T	I		0-2	0-2	FEW	MANY	FEW	
2	15454	M	7	1.016	0	0	0	0		0-2	3-5		MANY	FEW	
3	15350	M	5	1.055	T	0	T	T			3-6	MANY		FEW	
3	15448	M	3	1.035	T	0	T	T			0-3	MANY	FEW		
3	15458	M	7	1.021	0	0	T	0		1-3	3-4	LITTLE	FEW		
4	15377	M	6	1.06+	T	0	T	T		1-3	2-5	MANY		FEW	
4	15449	M	7	1.055	T	0	I	T			4-5	FEW	FEW		
4	15459	M	8	1.025	0	0	0	T			2-3	FEW	FEW		

TABLE NO. 4 - URINE ANALYSIS
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	SEX	P H	SP.GR.	SU- GAR	ACE- TONE	PRU- TEIN	BILI- RUBIN	RBC	-----MICROSCOPIC FINDINGS-----				
										WBC	EPITH	AMORPH	CRYS	BACT SPERM
1	1451	M								0-2	0-3	LITTLE	MANY	FEW
1	15358	M	7	1.025	0	0	T	T	0-1			LITTLE	MANY	FEW
1	15398	M	7	1.049	0	0	1	2		0-4		MUCH	MANY	FEW
1	15431	M	8	1.042	0	0	1	1						
2	15359	M	6	1.060	1	0	1	T		0-3	4-6		MANY	FEW
2	15426	M	7	1.040	0	0	T	T			2-4	LITTLE	MANY	FEW
2	15454	M	7	1.040	T	0	1	T		2-4		MUCH	MANY	FEW
3	15360	M	8	1.060	T	0	1	T		0-2	10-20	MUCH	MANY	MANY
3	15448	M	6	1.055	T	0	T	T		0-3	0-2		MANY	FEW
3	15458	M	5	1.050	T	0	1	T		0-5	0-3	LITTLE	MANY	FEW
4	15377	M	7	1.055	1	0	1	T		5-7	2-3	LITTLE	FEW	MANY
4	15449	M	7	1.025	0	0	T	0		0-3	0-3	LITTLE	FEW	FEW
4	15459	M	0	1.027	0	0	1	T		0-1	0-1	FEW	MANY	FEW

TABLE NO. 4 - URINE ANALYSIS
 PUREBRED BEAGLES RECEIVING WRI49,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	P H	SP. GR.	SU- GAR	ACE- TONE	PRO- TEIN	BILI- RUBIN	RBC	-----MICROSCOPIC FINDINGS-----				
										WBC	EPITH	AMORPH	CRYS	BACT SPERM
1	15358	M	7	1.035	0	0	T	T		0-1	1-2		MANY	FEW
1	15398	M	6	1.050	0	0	T	1		3-4	3-4	LITTLE	MANY	FEW
1	15451	M							1-2	6-8	3-5	MUCH	MANY	FEW
2	15359	M	7	1.048	T	0	T	T		2-3	1-2		MANY	FEW
2	15426	M	8	1.041	T	0	1	1			3-4	LITTLE	MANY	FEW
2	15454	M	6	1.042	1	0	1	1	1-2	10-15	3-4	LITTLE	MANY	FEW
3	15360	M	9	1.011	0	0	0	0				MUCH	MANY	FEW
3	15448	M	6	1.016	0	0	0	0		2-3	3-4	MUCH	MANY	MANY
3	15458	M	7	1.040	0	0	T	0			2-3		MANY	FEW
4	15377	M	6	1.020	0	0	T	0		0-1	3-4	LITTLE	FEW	FEW
4	15449	M	7	1.012	0	0	0	0			3-4	MUCH	MANY	FEW
4	15459	M	7	1.020	0	0	T	0	0-1	6-8	3-8		MANY	FEW

TABLE NO. 4 - URINE ANALYSIS
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	P H	SP. GR.	SU- GAR	ACE- TONE	PRD- TEIN	BILI- RUBIN	RBC	MICROSCOPIC FINDINGS			
										WBC	EPITH	AMORPH	CRYSTALS
1	15319	F	6	1.060	T	0	T	0		3-8	2-6		MANY FEW
1	15432	F	7	1.06+	1	0	T	0			0-1		MANY FEW
1	15436	F	7	1.046	T	0	T	0			0-1		FEW FEW
2	15322	F	6	1.036	T	0	0	0	3-4		0-2		FEW FEW
2	15433	F	7	1.06+	1	0	T	0			1-2		MANY MANY
2	15437	F	7	1.056	T	0	T	0			0-3		MANY FEW
3	15430	F	6	1.059	0	0	0	0		0-2	3-4	LITTLE	FEW FEW
3	15434	F	8	1.045	T	0	T	0		1-2			MANY MANY
3	15470	F	8	1.055	T	0	T	0		0-2	3-5		MANY FEW
4	15431	F	6	1.06+	T	0	T	0		0-1	0-3		MANY FEW
4	15435	F	7	1.050	T	0	0	0		0-2	0-1	LITTLE	MANY MANY
4	15471	F	7	1.042	T	0	T	0		1-4	4-6	LITTLE	MANY MANY

TABLE NO. 4 - URINE ANALYSIS
 PUKEBRED BEAGLES RECEIVING WK149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	P H	SP.	GR.	SU- GAR	ACE- TONE	PRO- TEIN	HILI- RUBIN	-----MICROSCOPIC FINDINGS-----				
										RBC	WBC	EPITH	AMORPH	CRYSTALS
1	15319	F	7	1.031	0	0	0	T	T		0-2	2-4		MANY
1	15432	F	7	1.041	0	0	0	T	T		4-6	5-7		MANY
1	15436	F	6	1.060	T	0	0	T	T		0-2	2-3		FEW
2	15322	F	6	1.041	T	0	0	T	T		1-3	1-3	MUCH	MANY
2	15433	F	8	1.046	T	0	0	T	0		0-2	4-6	LITTLE	FEW
2	15437	F	8	1.032	T	0	0	0	0		0-2	4-6	MUCH	FEW
3	15430	F	7	1.045	T	0	0	1	0		0-3	0-5	MUCH	MANY
3	15434	F	6	1.037	0	0	0	T	0		5-15	2-3	LITTLE	FEW
3	15470	F	7	1.050	0	0	0	1	0		3-4	2-3	LITTLE	FEW
4	15431	F	7	1.025	0	0	0	0	0		5-12	0-2		FEW
4	15435	F	7	1.019	0	0	0	0	0		3-6	0-2		MANY
4	15471	F	6	1.030	T	0	0	T	0		0-1	0-2	LITTLE	FEW

TABLE NO. 4 - URINE ANALYSIS
 PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	E X	P H	SU- GAR	ACE- TONE	PRO- TEIN	BILI- RUBIN	RBC	MICROSCOPIC FINDINGS			
									WBC	EPITH	AMORPH	CRYS BACT SPERM
1	15319	F	7	1.020	0	0	0		3-4	1-2		MANY MANY
1	15432	F	7	1.041	T	0	0		6-7		MUCH	MANY FEW
1	15436	F	7	1.06+	1	0	1	0				MANY FEW
2	15322	F	6	1.038	T	0	0		1-2			FEW FEW
2	15433	F	6	1.041	T	0	0					FEW FEW
2	15437	F	6	1.041	T	0	0			2-3		MANY FEW
3	15430	F	7	1.010	T	0	0					FEW MANY
3	15434	F	7	1.041	0	0	0	2-3	3-4	3-4		FEW FEW
3	15470	F	7	1.046	T	0	0		4-5			MANY FEW
4	15431	F	6	1.031	T	0	0	2-3	10-15	3-5		FEW MANY
4	15435	F	8	1.021	0	0	0			2-3	MUCH	FEW MANY
4	15471	F	7	1.010	0	0	0		3-4	2-3	MUCH	FEW FEW

Table No. 5 - TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, AND ORGAN/BODY WEIGHT RATIOS

SPECIES AND STRAIN - PUREBRED BEAGLES
MATERIAL - WK 149,024 AD
INTERVAL - TWO WEEKS
ROUTE OF ADMINISTRATION - INTRAVENOUS

MALES - CONTROL

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
15358	13.80	1.250	0.0091	116.700	0.8457	319.000	2.3116	42.700	0.3094
15398	10.20	0.950	0.0093	84.600	0.8294	240.000	2.3529	30.100	0.2951
15451	11.10	1.300	0.0117	104.600	0.9423	299.700	2.7000	25.500	0.2297
MEAN	11.70	1.167	0.0100	101.967	0.8725	286.233	2.4548	32.767	0.2781

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		TESTES	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
15358	13.80	66.900	0.4848	1.190	0.0086	26.300	0.1906
15398	10.20	43.500	0.4265	1.150	0.0113	17.900	0.1755
15451	11.10	67.500	0.6081	1.500	0.0135	27.400	0.2468
MEAN	11.70	59.300	0.5065	1.280	0.0111	23.867	0.2043

Table No. 5 - Continued

MALES - 5 MG/KG

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID WEIGHT G	THYROID RATIO PCT	HEART WEIGHT G	HEART RATIO PCT	LIVER WEIGHT G	LIVER RATIO PCT	SPLEEN WEIGHT G	SPLEEN RATIO PCT
15359	8.50	1.100	0.0129	71.300	0.8447	205.000	2.4118	21.300	0.2500
15426	11.50	1.200	0.0104	100.500	0.8739	235.000	2.0435	26.000	0.2261
15454	12.00	1.190	0.0099	114.200	0.9517	301.000	2.5083	24.400	0.2033
MEAN	10.57	1.163	0.0111	95.500	0.8901	247.000	2.3212	23.900	0.2267

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS WEIGHT G	KIDNEYS RATIO PCT	ADRENALS WEIGHT G	ADRENALS RATIO PCT	TESTES WEIGHT G	TESTES RATIO PCT
15359	8.50	36.200	0.4259	0.900	0.0106	15.500	0.2294
15426	11.50	57.500	0.4983	1.400	0.0122	22.900	0.1991
15454	12.00	58.500	0.4875	1.930	0.0161	29.500	0.2456
MEAN	10.67	50.667	0.4705	1.410	0.0129	23.967	0.2248

524

Table No. 5 - Continued

MALES - 10 MG/KG

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
15360	10.20	1.140	0.0112	96.400	0.9451	307.000	3.0098	34.200	0.3353
15448	7.50	1.200	0.0160	71.200	0.9493	195.000	2.6000	21.300	0.2840
15458	10.30	1.100	0.0107	90.100	0.8748	257.000	2.4951	18.400	0.1756
MEAN	9.33	1.147	0.0126	85.900	0.9231	253.000	2.7016	24.633	0.2600

525

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		TESTES	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
15360	10.20	67.200	0.6588	1.330	0.0130	23.200	0.2275
15448	7.50	52.600	0.7013	1.100	0.0147	22.700	0.3027
15458	10.30	43.800	0.4252	1.400	0.0136	20.100	0.1951
MEAN	9.33	54.533	0.5951	1.277	0.0138	22.000	0.2418

Table No. 5 - Continued

MALES - 20 MG/KG											526
ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN			
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT		
15377	11.50	1.000	0.0067	109.000	0.3696	283.000	2.4609	44.800	0.5876		
15449	7.50	1.080	0.0144	73.000	0.9733	210.000	2.8000	17.400	0.2320		
15459	7.50	1.080	0.0144	70.500	0.9400	191.000	2.5467	16.900	0.2253		
MEAN	8.83	1.053	0.0125	81.167	0.9276	228.000	2.6025	26.567	0.2823		
ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		TESTES					
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT		
15377	11.50	47.800	0.4157	1.500	0.0130	24.100	0.2096				
15449	7.50	46.300	0.6173	1.150	0.0153	13.400	0.1787				
15459	7.50	48.000	0.6400	1.150	0.0153	15.200	0.2027				
MEAN	8.83	47.367	0.5577	1.267	0.0146	17.567	0.1970				

Table No. 5 - Continued

FEMALES - CONTROL

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
15319	12.40	1.200	0.0097	78.700	0.6347	343.000	2.7601	20.000	0.1613
15432	9.60	0.650	0.0099	58.000	0.7083	243.000	2.5313	32.000	0.3333
15436	9.60	0.670	0.0070	56.100	0.8969	202.000	2.1042	32.000	0.3336
MEAN	10.53	0.940	0.0089	77.000	0.7460	262.667	2.4672	28.200	0.2731

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
15319	12.40	54.800	0.4403	1.300	0.0105
15432	9.60	41.200	0.4292	1.400	0.0146
15436	9.60	38.800	0.4042	1.450	0.0151
MEAN	10.53	44.867	0.4246	1.383	0.0134

527

Table No. 5 - Continued

FEMALES - 5 MG/KG

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
15324	6.50	0.700	0.0108	59.500	0.9154	141.000	2.1692	21.900	0.3354
15432	10.30	0.770	0.0071	88.200	0.8167	222.000	2.0556	30.100	0.2737
15437	8.70	0.620	0.0071	67.400	0.7747	238.000	2.7356	17.200	0.1977
MEAN	8.57	0.697	0.0083	71.700	0.8356	200.333	2.3201	23.033	0.2706

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
15322	6.20	27.600	0.4277	0.360	0.0132
15435	10.30	40.600	0.3759	1.060	0.0693
15437	8.70	40.700	0.4618	1.000	0.0115
MEAN	8.07	36.367	0.4238	0.973	0.0115

Table No. 5 - Continued

ANIMAL NO.	TERM. BODY WEIGHT KG	FEMALES - 10 MS/KG					
		THYROID	HEART	LIVER	SPLEEN		
		WEIGHT G	WEIGHT G	WEIGHT G	WEIGHT G	RATIO PCT	RATIO PCT
15430	7.50	0.800	65.900	187.000	16.500	2.4933	0.2200
15434	9.40	0.760	76.200	196.000	22.500	2.0851	0.2394
15470	7.60	0.800	67.500	219.000	20.200	2.8816	0.2658
MEAN	8.17	0.787	69.367	200.607	19.735	2.4867	0.2417
ANIMAL NO.	TERM. BODY WEIGHT KG						
		KIDNEYS	ADRENALS				
		WEIGHT G	WEIGHT G	RATIO PCT			
15430	7.50	41.000	1.280	0.9467	0.0171		
15434	9.40	42.000	1.150	0.4468	0.0122		
15470	7.60	43.400	1.200	0.5711	0.0153		
MEAN	8.17	42.133	1.210	0.5215	0.0150		

Table No. 5 - Continued

FEMALES - 20 MG/KG

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
15431	7.30	0.890	0.0122	73.100	1.0014	206.000	2.8219	17.600	0.2411
15435	6.00	0.490	0.0082	45.500	0.7583	145.000	2.4167	24.200	0.4033
15471	8.20	0.830	0.0101	71.300	0.8695	199.000	2.4268	22.700	0.2763
MEAN	7.17	0.737	0.0102	63.300	0.8764	183.333	2.5551	21.500	0.3071

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
15431	7.30	41.200	0.5644	1.000	0.0137
15435	6.00	29.000	0.4833	0.920	0.0153
15471	8.20	51.000	0.6220	1.390	0.0170
MEAN	7.17	40.400	0.5566	1.103	0.0153

KEY FOR INCIDENCE TABLE

P = Present

N = No Section

A = Autolysis

X = Not Remarkable

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderately Severe/High

5 = Severe/High

	Animal No.	Groups			
		1	2	3	4
Males	15358 15398 15451 15359 15426 15454 15448 15360 15458 15377 15449 15459				
KIDNEY					
Interstitial nephritis			1	2	X
Mineral deposit	1 1 1	1 1 1	1 2	1	
Tubular dilatation			2		
Papillary congestion					
Papillary epithelial hyperplasia			2		
Congestion			2	2	2
Epithelial vacuolation					
STOMACH	X X X				X
Glandular atrophy					
Dilatation of crypts					
Chronic gastritis					
PANCREAS	X X X				X
Peripancreatitis					
SMALL INTESTINE	X X X				X
LARGE INTESTINE	X X X				X
MESENTERIC LYMPH NODE	X X X				N
URINARY BLADDER	X X X				X
Cystitis					
Thickened epithelium					
Hydropic degeneration					
TESTIS	X X				X
Epididymitis	4				
OVARY					
Indeterminable activity					

[illegible]

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	Animal No.	Groups											
		1			2			3			4		
Females		15319	15432	15436	15322	15433	15437	15430	15434	15470	15431	15435	15471
ADRENAL													
Vacuolation/Z. Glomerulosa		2	1								1	2	1
Vacuolation/Z. Reticularis				3									
THYROID													
Parafollicular tissue		2	32-3		3	3	3	3	3	4	3-43-44-5		
Follicle size		2-32-32			2	2	2	1-22	2		2-32	3	
Epithelial height		1	1	1	1	21-2		1	11-2		11-21-2		
Follicular epithelial vacuolation		2	1	3	12-32			2	3	1	3	3	2
Mineralization of colloid		1			1	1		1	1	3	2		
Cystic parathyroid			P										
Parafollicular cell vacuolation		1	2		1	2	1	1	2	1	3	3	3
Focal parafollicular hyperplasia										P		P	
Lymphocytic thyroiditis					3								
HEART		X	X								X	X	X
Focal myocarditis				1									
SPLEEN													
Extramedullary hematopoiesis			1	1							1	1	
Increase lymphoid activity													
Pigmentation		1	3	1							3	2	
R.E. Hyperplasia											1		
Siderotic nodule													
Green pigment/Malpighian corpuscles											1		
GALL BLADDER			X	X							X	X	X
Lymphocytic cholecystitis		1											
Focal lymphoid infiltration							1						
LIVER		X							X	X			X
Bile duct proliferation			1			P					1		
Bile plugs											P	P	
Hepatocyte vacuolation													
Congestion													
Lymphocytic pericholangitis		1											

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	Animal No.	Groups			
		1	2	3	4
Males	15358				
	15398				
	15451				
	15359				
	15426				
	15454				
	15448				
	15360				
	15458				
	15377				
	15449				
	15459				
BONE MARROW		X X			X
Pigment					
Increase cellularity			2		
Decrease cellularity					2 2
PITUITARY					
Cystic pars distalis					P

	Animal No.	Groups			
		1	2	3	4
Females	15319 15432 15436 15322 15433 15437 15430 15434 15470 15431 15435 15471				
KIDNEY					
Interstitial nephritis					
Mineral deposit		1 1	1 1 1	1 1 1	1 1 1
Tubular dilatation	1				1
Papillary congestion					
Papillary epithelial hyperplasia					1 1 1
Congestion					
Epithelial vacuolation			2 2 2		
STOMACH	X				
Glandular atrophy					2 2
Dilatation of crypts					2
Chronic gastritis		2 3			
PANCREAS		X X			X X X
Peripancreatitis	P				
SMALL INTESTINE	X X X				X X X
LARGE INTESTINE	X X X				X X X
MESENTERIC LYMPH NODE	X X X				X X X
URINARY BLADDER	X X X				X X
Cystitis				4	
Thickened epithelium					1
Hydropic degeneration					2
TESTIS					
Epididymitis					
OVARY	X X X				X X
Indeterminable activity					P

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	Animal No.	Groups			
		1	2	3	4
Females	15319				
	15432				
	15436				
	15322				
	15433				
	15437				
	15430				
	15434				
	15470				
	15431				
	15435				
	15471				
BONE MARROW		X X X			X X
Pigment					2
Increase cellularity					
Decrease cellularity					
PITUITARY					
Cystic pars distalis					

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TRW

HAZLETON LABORATORIES

SPONSOR: Walter Reed Army Institute of Research **DATE:** September 27, 1971

MATERIAL: WR 149,024 AD (AX 67287) **LOT NO:** 308/422

SUBJECT: REPORT NO. 43
Subacute Intravenous Toxicity Study - Monkeys
Project No. 193-417

SUMMARY

WR 149,024 AD (AX 67287) was tested for subacute (two week) intravenous toxicity by injection into the saphenous vein of the hindlimb once daily, seven days a week, at dosage levels of 5, 10, and 20 mg/kg.

Aside from slight ataxia and decreased activity observed in five high level animals on one or two days only, all animals showed no indication of a compound-related effect with respect to the appearance and behavior of the animals.

Analysis of clinical laboratory data and ophthalmoscopic examinations revealed no compound-induced alterations. Gross necropsy and organ/body weight data was generally not remarkable.

Microscopic examination of tissue revealed no histopathological alterations attributable to the administration of the test material.

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OBJECTIVE

The purpose of this study was to evaluate the toxicity of WR 149,024 AD (AX 67287) following intravenous injection daily, seven days a week, for two weeks.

MATERIAL

Identification WR 149,024 AD (AX 67287); Lot No. 308/422.

Description White powder.

Receipt Date May 12, 1971.

Purity Assumed 100% active ingredient.

METHODS

Experimental Animals

Breed: Young rhesus monkeys.

Number: Twelve males and 12 females.

Body Weight (At Initiation): From 2.3 to 3.8 kg.

Housing: Individually in metal cages.

Diet: Purina Monkey Chow twice daily, fresh fruit daily, and water ad libitum.

Groups and Dosage Levels

<u>Group No.</u>	<u>No. of Animals</u>		<u>Dosage Levels</u> mg/kg of body weight
	<u>male</u>	<u>female</u>	
1 (Control)	3	3	0
2	3	3	5.0
3	3	3	10.0
4	3	3	20.0

Compound Administration and Preparation

The compound was mixed with isotonic saline at a concentration of 20 mg/ml and injected once daily, seven days a week, for two weeks into the saphenous vein of the hindlimb.

Observations and Records

Daily: Appearance, behavior, appetite, elimination, and pharmacotoxic signs.

Weekly: Body weight.

Clinical Studies

Performed: Initially and at one and two weeks.

Hematology: Hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte count, and clotting time.

Clinical Biochemistry: Fasting blood sugar, blood urea nitrogen, total serum protein, total serum bilirubin, serum albumin, serum potassium, serum chloride, carbon dioxide, serum calcium, serum glutamic-pyruvic transaminase, serum alkaline phosphatase, serum glutamic-oxaloacetic transaminase, and serum electrophoresis.

Urine Analysis: Specific gravity, pH, glucose, ketones, total protein, bilirubin, and microscopic examination of sediment.

Ophthalmologic Examination

Performed on monkeys initially and at termination.

Terminal Studies

Terminal Sacrifice: By exsanguination under anesthesia after 18 days.

Gross Necropsies: On all sacrificed monkeys.

Tissue Preservation:

In 10% Neutral Buffered Formalin - Brain, pituitary, thoracic spinal cord, eye, thyroids, lung, heart, liver (two lobes), gallbladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, prostate, testes, skin, rib junction, bone marrow, nerve with muscle, unusual lesions, and infection sites.

Organ Weights for Each Monkey - Thyroids, heart, liver, spleen, kidneys, adrenals, testes with epididymis, and ovaries.

Histopathological Examination

From Control and High Level Animals: Sections of brain, thoracic spinal cord, thyroids, heart, liver, gallbladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testes, ovary, and bone marrow.

From Low and Intermediate Level Animals: Liver, kidneys, and unusual lesions.

RESULTS

Appearance, Behavior, and Signs of Compound Effect

Individual weekly body weights are presented in Table No. 1.

Ataxia and decreased activity immediately after dosing was observed on one or two days in five high level animals. However, these animals appeared generally normal, otherwise, as did all animals at the intermediate and low level. Monkey No. 892 showed depression, salivation, and watery emesis immediately postdose on Day 12.

Incidental findings observed in several animals from each group including the control were anorexia, soft feces or diarrhea, piloerection, and rough haircoat. Body weight gains were similar between control and test animals.

Clinical Studies

The results of the clinical studies on individual animals are presented in Tables No. 2 (hematology), No. 3 (blood chemistry), and No. 4 (urine analysis).

Hematological data revealed no significant trends attributable to the consumption of the compound. Decreased white blood counts were observed in one Group No. 2 and one Group No. 3 level animal at two weeks.

Blood chemistry findings, likewise, indicated no signs of compound-induced alterations. Incidental findings included elevated blood urea nitrogen counts at two weeks in one control, one low, and one high level animal. High alkaline phosphatase values noted at one week in one control female, two low level females, one intermediate level male, and three high level males had returned to normal levels by Week 2.

Eye Examinations

Eye examinations were performed using Mydriacyl as a mydriatic, a binocular magnifier, a direct ophthalmoscope, and a binocular indirect ophthalmoscope while the animals were lightly anesthetized with Sernylan. No gross ocular changes were observed initially or at termination.

Gross Necropsy

No alterations were noted which were directly related to administration of the compound. Alterations noted in the control group included large intestines adherent to the abdominal wall (Monkey No. 908H) and a white elevated area in the stomach mucosa (Monkey No. 912H). Control Monkey No. 787H showed small thyroids, a swollen spleen, and cystic ovaries with the right ovary larger than the left.

Alterations observed in the low level group included an elevated area in the stomach mucosa measuring 2.5 cm. x 1.5 cm. in Monkey No. 925H, and a swollen spleen in Monkey No. 909H. In Monkey No. 913H, the left cerebral hemisphere had an oblique cavity located at the midline and extending ventrally into the parenchyma. The lesion was lined with a brownish, necrotic-looking material.

In the intermediate level group, Monkey No. 892H showed a granular-appearing spleen.

Adhesions from the lung to the pleura or signs of parasitic infestation were observed in all groups including the control and are routinely observed signs in laboratory primates.

Organ Weights

Individual terminal body weights, organ weights, and organ/body weight ratios are found in Table No. 5.

Incidental variations from normal ranges included a high ovary/body weight ratio in one control female (Monkey No. 787H), a high adrenal/body weight ratio in one intermediate female (Monkey No. 797H), and a high thyroid/body weight ratio in one high level female (Monkey No. 923H).

Microscopic Pathology

The daily intravenous injection of WR 149,024 AD (AX 67287) for a period of 14 consecutive days to male and female rhesus monkeys at the rate of 5.0, 10.0, and 20.0 mg/kg of body weight did not result in the production of any compound-related histopathological alterations in the tissues examined. Incidental lesions were seen in several of the organs examined, but the incidence and severity of these changes in the test animals were not meaningfully different from that of the controls.

The thyroid activity in the male control monkeys varied from slight to moderate. Similarly, the activity of the thyroid in the male monkeys receiving 20.0 mg/kg/day varied from slight to moderate. In the females, the activity of the thyroid was also slight to moderate in both the controls and in the animals receiving 20.0 mg/kg of body weight per day.

Scattered incidences of cortical and medullary mineralization were seen in the adrenals from both the control and test monkeys. The incidence of this microscopic finding was slightly greater in the female control and test animals than in the males.

Pericholangitis was a frequent finding in all groups, but in no case was it greater than slight in severity. Some variation in the degree of hepatocyte vacuolation was noted among individual animals in both the control and test groups. This microscopic observation was not consistent and was not seen any more frequently in the test animals than the controls.

Lesions associated with parasite infestation were seen in the mesenteric lymph nodes and on the serosal surfaces of the large and small intestines. Occasionally the parasite was present in the lesion, but more frequently it was absent. Pancreatitis was seen in Group No. 4 female Monkey No. 917H. This inflammatory lesion was characterized by an infiltration of mononuclear macrophages, lymphocytes, and some polymorphonuclear granulocytes into the parenchyma of the pancreas. The acinar cells of the affected lobules appeared to be undergoing a degeneration which was characterized by a loss of zymogen granules, cytoplasmic vacuolation, and slight nuclear vesiculation. The capsule of the pancreas in this area was severely thickened, and there was hyperplasia of fibrous connective tissue throughout the lobule.

In conclusion, it can be stated that the daily intravenous injection of WR 149,024 AD (AX 67287) for a period of 14 days to male and female rhesus monkeys at a dosage rate of up to 20.0 mg/kg does not cause any histopathological

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alterations in the tissues examined on this study. With the exception of scattered instances of parasitic disease and a few instances of chronic infections, the organs were generally within the limits of normal histological variation.

Submitted by

Frederick E. Reno

FREDERICK E. RENO, Ph.D.
Project Manager, Drugs and
Industrial Chemicals Department
Toxicology-Biosciences Laboratory

Pathology by

John F. Ferrell

JOHN F. FERRELL, D.V.M.
Consultant Pathologist

Report Preparation: Horwatt

Supervision: R. Thompson

dc;gbb

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

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EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

0 = negative

T = trace (±)

1 = slight (+)

2 = moderate (++)

3 = marked (+++)

4 = severe (++++)

V T L YEL = very turbid light yellow

T D YEL = turbid dark yellow

Table No. 1 - Individual body weights for rhesus monkeys
receiving WR 149,024 AD (AX 67287)

TIME INTERVAL weeks	GROUP NO. 1 - SALINE CONTROL							
	MONKEY NO. 900H M	MONKEY NO. 908H M	MONKEY NO. 912H M	MONKEY NO. 787H F	MONKEY NO. 804H F	MONKEY NO. 930H F	WEIGHT	kg.
	WEIGHT	WEIGHT	WEIGHT	WEIGHT	WEIGHT	WEIGHT		
	kg.	kg.	kg.	kg.	kg.	kg.		
Initial	2.4	3.0	3.8	3.1	2.7	2.5		
1	2.2	3.0	3.9	3.1	2.8	2.6		
2	2.5	2.9	4.0	3.1	2.9	2.6		
Terminal	2.6	2.7	4.1	3.2	2.9	2.6		
Net Change, kg.	+0.2	-0.3	+0.3	+0.1	+0.2	+0.1		

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Table No. 1 - Continued

TIME INTERVAL weeks	GROUP NO. 2 - 5.0 MG/KG OF BODY WEIGHT LEVEL							
	MONKEY NO. 889H M	WEIGHT kg.	MONKEY NO. 891H M	WEIGHT kg.	MONKEY NO. 909H M	WEIGHT kg.	MONKEY NO. 913H F	WEIGHT kg.
Initial		3.0	2.5	2.3		3.1	2.6	2.9
1		3.1	2.6	2.4		2.9	2.6	2.9
2		3.1	2.7	2.5		3.2	2.6	3.0
Terminal		3.2	2.6	2.4		3.1	2.6	3.0
Net Change, kg.		+0.2	+0.1	+0.1		0	0	+0.1

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Table No. 1 - Continued

TIME INTERVAL weeks	GROUP NO. 3 - 10.0 MG/KG OF BODY WEIGHT LEVEL							
	MONKEY NO. 881H M	MONKEY NO. 894H M	MONKEY NO. 897H M	MONKEY NO. 797H F	MONKEY NO. 802H F	MONKEY NO. 806H F		
	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.		
Initial	2.6	2.8	2.9	2.6	3.4	3.3		
1	2.7	2.9	3.1	2.6	3.5	3.3		
2	2.7	3.0	3.2	2.6	3.6	3.3		
Terminal	2.8	3.1	3.3	2.6	3.5	3.3		
Net Change, kg.	+0.2	+0.3	+0.4	0	+0.1	0		

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Table No. 1 - Continued

TIME INTERVAL weeks	GROUP NO. 4 - 20 MG/KG OF BODY WEIGHT LEVEL							
	MONKEY NO. 892H M	MONKEY NO. 895H M	MONKEY NO. 911H M	MONKEY NO. 807H F	MONKEY NO. 917H F	MONKEY NO. 923H F		
	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.		
Initial	2.5	2.7	3.1	2.9	2.9	3.1		
1	2.6	2.7	3.2	2.9	3.0	3.1		
2	2.3	2.8	3.3	3.0	3.0	3.2		
Terminal	2.2	2.8	3.3	3.1	3.0	3.2		
Net Change, kg.	-0.3	+0.1	+0.2	+0.2	+0.1	+0.1		

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHESUS MONKEYS RECEIVING WK 149,024 AD (AX67287) FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	E X	HCT %	HGB GM%	RBC MILLS	WBC THS	META %	DIFFERENTIAL						BASO %
								BAND %	SEG %	LYMPH %	MONO %	EOSIN %		
1	900H	M	36.0	13.0	5.01	8.3	0	0	35	61	2	2	0	
1	908H	M	39.0	12.8	5.40	12.6	0	0	58	40	1	0	1	
1	912H	M	41.0	14.2	5.30	8.5	0	0	54	43	2	0	1	
GROUP MEAN			38.7	13.3	5.24	9.8								
2	889H	M	40.0	13.8	5.54	14.3	0	0	20	76	3	1	0	
2	891H	M	40.0	13.9	5.61	6.4	0	0	57	42	1	0	0	
2	909H	M	37.5	12.7	5.43	9.7	0	0	54	43	0	2	1	
GROUP MEAN			39.2	13.5	5.53	10.1								
3	881H	M	41.5	13.8	5.69	9.1	0	0	42	54	3	1	0	
3	894H	M	39.5	13.4	5.42	8.0	0	0	41	54	0	5	0	
3	897H	M	37.0	13.4	5.72	7.2	0	0	39	59	1	1	0	
GROUP MEAN			39.3	13.5	5.61	8.1								
4	892H	M	39.0	13.4	5.48	11.9	0	0	14	80	2	2	2	
4	895H	M	40.0	14.4	6.00	12.1	0	0	40	56	1	1	2	
4	911H	M	38.5	13.0	5.09	8.7	0	0	43	54	0	1	2	
GROUP MEAN			39.2	13.6	5.52	10.9								

GROUP NUMBER	ANIMAL NUMBER	E X	HCT %	HGB GM%	RBC MILLS	WBC THS	META %	DIFFERENTIAL						BASO %
								BAND %	SEG %	LYMPH %	MONO %	EOSIN %		
1	900H	M	37.0	12.3	4.92	8.6	0	0	51	46	1	2	0	
1	908H	M	39.0	11.8	4.96	13.6	0	0	58	42	0	0	0	
1	912H	M	37.5	11.8	4.35	6.6	0	0	35	64	0	1	0	
GROUP MEAN			37.8	12.0	4.74	9.6								
2	889H	M	39.5	12.3	5.01	9.7	0	0	24	76	0	0	0	
2	891H	M	38.0	12.8	5.05	6.2	0	0	57	42	1	0	0	
2	909H	M	35.0	11.8	5.20	6.2	0	0	37	61	1	1	0	
GROUP MEAN			37.5	12.3	5.09	7.4								
3	881H	M	38.0	11.9	4.83	13.1	0	0	55	41	3	1	0	
3	894H	M	36.0	11.9	4.91	5.8	0	0	55	43	0	2	0	
3	897H	M	35.0	11.6	4.70	5.9	0	0	53	45	0	2	0	
GROUP MEAN			36.3	11.8	4.81	8.3								
4	892H	M	39.0	12.7	5.20	15.5	0	0	69	29	2	0	0	
4	895H	M	41.0	13.4	5.54	8.8	0	0	36	62	1	1	0	
4	911H	M	37.0	11.9	4.57	11.3	0	0	62	38	0	0	0	
GROUP MEAN			39.0	12.7	5.10	11.9								

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHEBUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	E X	HCT %	HGB GM%	RBC MILLS	WBC THS	DIFFERENTIAL							BASO %
							META %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %		
1	900H	M	39.0	12.8	5.20	8.4	0	0	61	37	0	2	0	
1	908H	M	39.0	12.3	5.16	21.1	0	0	69	27	1	3	0	
1	912H	M	39.0	13.0	4.80	7.6	0	0	52	44	2	1	1	
GROUP MEAN			39.0	12.7	5.05	12.4								
2	889H	M	44.0	13.2	5.24	14.8	0	0	48	48	2	2	0	
2	891H	M	40.0	13.8	5.36	8.2	0	0	49	50	0	1	0	
2	909H	M	35.0	12.5	5.35	12.5	0	0	71	29	0	0	0	
GROUP MEAN			39.7	13.2	5.32	11.8								
3	881H	M	36.0	11.4	4.70	15.2	0	0	61	35	1	3	0	
3	894H	M	37.0	12.3	5.05	4.9	0	0	31	67	0	2	0	
3	897H	M	35.0	11.8	5.03	5.8	0	0	47	52	1	0	0	
GROUP MEAN			36.0	11.8	4.93	8.6								
4	892H	M	38.0	12.7	5.43	18.3	0	0	60	36	3	1	0	
4	895H	M	37.0	12.7	5.25	9.2	0	0	52	47	0	1	0	
4	911H	M	38.0	11.9	4.70	11.0	0	0	70	30	0	0	0	
GROUP MEAN			37.7	12.4	5.13	12.8								

GROUP NUMBER	ANIMAL NUMBER	E X	HCT %	HGB GM%	RBC MILLS	WBC THS	DIFFERENTIAL						
							MET %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	BASO %
1	787H	F	38.0	12.7	5.14	7.5	0	0	22	68	3	7	0
1	804H	F	40.0	13.0	5.25	13.6	0	0	21	69	4	6	0
1	930H	F	40.5	13.8	5.08	7.7	0	0	49	49	1	1	0
GROUP MEAN			39.5	13.2	5.16	9.6							
2	779H	F	37.5	12.5	5.03	13.8	0	0	39	58	2	1	0
2	913H	F	40.0	14.2	5.44	4.5	0	0	20	76	2	2	0
2	925H	F	42.0	13.6	5.82	17.1	0	0	55	36	0	9	0
GROUP MEAN			39.8	13.4	5.43	11.8							
3	797H	F	39.5	13.4	5.15	11.3	0	0	49	48	1	1	1
3	802H	F	36.0	12.7	4.89	11.8	0	0	23	72	5	0	0
3	806H	F	40.0	13.4	5.26	7.7	0	0	42	53	2	3	0
GROUP MEAN			38.5	13.2	5.10	10.3							
4	805H	F	41.0	13.9	5.46	8.2	0	0	43	50	4	3	0
4	917H	F	44.0	14.6	6.13	7.1	0	0	26	69	3	1	1
4	923H	F	40.0	13.2	5.19	16.0	0	0	34	60	3	2	1
GROUP MEAN			41.7	13.9	5.59	10.4							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
Rhesus Monkeys Receiving WR 149,024 AD (AX67287) For Two Weeks
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	E X	HCT %	HGB GM%	RBC MILLS	WBC THS	DIFFERENTIAL						
							MET	BAND	SEG	LYMPH	MONO	EOSIN	BASO
							%	%	%	%	%	%	%
1	787H	F	36.5	11.6	4.61	6.7	0	0	49	49	0	2	0
1	804H	F	36.5	11.9	4.75	11.2	0	0	39	57	1	3	0
1	930H	F	43.0	13.4	5.08	6.7	0	0	55	44	0	1	0
GROUP MEAN			38.7	12.3	4.81	8.2							
2	799H	F	34.0	11.1	4.44	11.3	0	0	69	28	2	1	0
2	913H	F	38.0	12.5	4.66	4.1	0	0	31	69	0	0	0
2	925H	F	40.0	12.5	5.25	12.8	0	0	66	34	0	0	0
GROUP MEAN			37.3	12.0	4.78	9.4							
3	797H	F	39.0	12.5	4.65	7.7	0	0	43	55	1	1	0
3	802H	F	37.5	11.9	4.54	10.7	0	0	35	65	0	0	0
3	806H	F	40.0	13.0	4.91	7.4	0	0	65	35	0	0	0
GROUP MEAN			38.8	12.5	4.70	8.6							
4	807H	F	36.0	12.1	4.65	15.1	0	0	64	36	0	0	0
4	917H	F	38.5	12.7	5.37	6.2	0	0	58	41	0	1	0
4	923H	F	37.0	11.8	4.74	8.2	0	0	38	60	1	1	0
GROUP ME			37.2	12.2	4.92	9.8							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
Rhesus Monkeys Receiving MR 149,024 AD (AX67287) For Two Weeks
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	SEX	HCT %	HGB GMS	RBC MILLS	WBC THS	META %	BAND %	SEG %	DIFFERENTIAL			
										LYMPH %	MONO %	EOSIN %	BASO %
1	787H	F	38.0	12.7	5.12	8.2	0	0	55	44	0	1	0
1	804H	F	39.0	13.4	5.44	11.7	0	0	59	38	0	2	1
1	930H	F	44.0	14.6	5.47	8.1	0	0	49	47	1	3	0
GROUP MEAN			40.3	13.6	5.34	9.3							
2	799H	F	39.0	12.8	5.08	18.2	0	0	74	24	0	2	0
2	913H	F	37.0	12.8	4.81	4.9	0	0	42	56	1	1	0
2	925H	F	38.0	12.8	5.38	15.3	0	0	61	35	1	1	2
GROUP MEAN			38.0	12.8	5.09	12.8							
3	797H	F	37.0	11.9	4.76	8.0	0	0	50	49	0	1	0
3	802H	F	38.0	12.3	4.83	7.6	0	0	50	47	1	2	0
3	806H	F	39.0	13.0	5.07	11.2	0	0	70	29	0	1	0
GROUP MEAN			38.0	12.4	4.89	8.9							
4	807H	F	36.0	12.1	4.93	11.0	0	0	60	40	0	0	0
4	917H	F	41.0	13.0	5.74	6.5	0	0	35	65	0	0	0
4	923H	F	36.0	11.6	4.75	13.0	0	0	67	31	0	2	0
GROUP MEAN			37.7	12.2	5.14	10.2							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
Rhesus Monkeys Receiving WR 149,024 AD (AX67287) for Two Weeks
Initial

GROUP NUMBER	ANIMAL NUMBER	S E X	COAGULATION MIN	SEC
1	900H	M	4	47
1	908H	M	3	58
1	912H	M	4	19
GROUP MEAN			4	21
2	889H	M	4	19
2	891H	M	4	47
2	909H	M	4	31
GROUP MEAN			4	32
3	881H	M	4	23
3	894H	M	4	56
3	897H	M	4	50
GROUP MEAN			4	43
4	892H	M	4	13
4	895H	M	4	08
4	911H	M	4	17
GROUP MEAN			4	13

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
Rhesus Monkeys Receiving WR 149,024 AD (AX67287) For Two Weeks
Week 1

GROUP NUMBER	ANIMAL NUMBER	S E X	COAGULATION MIN	SEC
1	900H	M	3	45
1	908H	M	3	40
1	912H	M	3	48
GROUP MEAN			3	44
2	889H	M	3	26
2	891H	M	3	15
2	909H	M	3	12
GROUP MEAN			3	18
3	881H	M	3	30
3	894H	M	3	42
3	897H	M	3	45
GROUP MEAN			3	39
4	892H	M	2	56
4	895H	M	3	06
4	911H	M	3	19
GROUP MEAN			3	07

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
Rhesus Monkeys Receiving WR 149,024 AD (AX67287) For Two Weeks
Week 2

GROUP NUMBER	S ANIMAL NUMBER	E X	COAGULATION MIN	SEC
1	900H	M	3	15
1	908H	M	3	29
1	912H	M	3	25
GROUP MEAN			3	23
2	889H	M	3	18
2	891H	M	3	22
2	909H	M	3	10
GROUP MEAN			3	17
3	881H	M	3	07
3	894H	M	3	39
3	897H	M	3	22
GROUP MEAN			3	23
4	892H	M	3	51
4	895H	M	3	05
4	911H	M	3	02
GROUP MEAN			3	19

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHEBUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	COAGULATION	
			MIN	SEC
1	787H	F	4	00
1	804H	F	5	08
1	930H	F	3	49
GROUP MEAN			4	19
2	779H	F	4	29
2	913H	F	4	42
2	925H	F	3	44
GROUP MEAN			4	18
3	797H	F	4	27
3	802H	F	4	46
3	806H	F	3	41
GROUP MEAN			4	18
4	805H	F	3	44
4	917H	F	4	30
4	923H	F	4	22
GROUP MEAN			4	12

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
Rhesus Monkeys Receiving WR 149,024 AD (AX67287) For Two Weeks
Week 1

GROUP NUMBER	ANIMAL NUMBER	S E X	COAGULATION MIN	SEC
1	767H	F	3	00
1	804H	F	3	10
1	930H	F	2	59
GROUP	MEAN		3	03
2	799H	F	3	14
2	913H	F	3	15
2	925H	F	3	20
GROUP	MEAN		3	16
3	797H	F	3	20
3	802H	F	3	28
3	806H	F	3	10
GROUP	MEAN		3	19
4	807H	F	3	45
4	917H	F	2	45
4	923H	F	3	39
GROUP	MEAN		3	23

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHEBUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	SEX	COAGULATION	
			MIN	SEC
1	787H	F	3	14
1	804H	F	3	19
1	930H	F	3	00
GROUP MEAN			3	11
2	799H	F	3	03
2	913H	F	3	25
2	925H	F	3	15
GROUP MEAN			3	14
3	797H	F	3	45
3	802H	F	2	50
3	806H	F	3	03
GROUP MEAN			3	13
4	807H	F	3	20
4	917H	F	3	35
4	923H	F	3	12
GROUP MEAN			3	22

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	900H	M	95.0	15.0	31.0	45.0	0.31	49.0
1	908H	M	92.0	11.0	29.0	25.0	0.30	52.0
1	912H	M	99.0	15.0	28.0	49.0	0.40	45.0
GROUP MEAN			95.3	13.7	29.3	39.7	0.34	48.7
2	889H	M	90.0	13.0	35.0	43.1	0.31	53.0
2	891H	M	92.0	17.0	36.0	39.0	0.40	55.0
2	909H	M	83.0	11.0	31.0	86.4	0.31	42.0
GROUP MEAN			88.3	13.7	34.0	56.2	0.34	50.0
3	881H	M	89.0	15.0	34.0	48.0	0.39	59.0
3	894H	M	106.0	11.5	31.0	81.6	0.38	56.0
3	897H	M	92.0	16.0	31.0	40.1	0.40	50.0
GROUP MEAN			95.7	14.2	32.0	56.6	0.39	55.0
4	892H	M	82.0	13.0	28.0	73.6	0.30	56.0
4	895H	M	94.0	17.0	38.0	81.6	0.49	57.0
4	911H	M	85.0	14.0	32.0	48.0	0.30	48.0
GROUP MEAN			87.0	14.7	32.7	67.7	0.36	53.7

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	900H	M	86.0	22.0	25.0	82.8	0.31	57.0
1	908H	M	110.0	15.0	31.0	33.2	0.29	46.0
1	912H	M	115.0	28.0	38.0	106.8	0.39	48.0
GROUP MEAN			103.7	21.7	31.3	74.3	0.33	50.3
2	889H	M	89.0	20.0	38.0	92.0	0.30	51.0
2	891H	M	90.0	27.0	39.0	39.0	0.28	50.0
2	909H	M	90.0	13.0	35.0	121.6	0.30	39.0
GROUP MEAN			89.7	20.0	37.3	84.2	0.29	46.7
3	881H	M	86.0	21.0	36.0	49.0	0.30	46.0
3	894H	M	84.0	16.5	35.0	150.0	0.21	44.0
3	897H	M	99.0	23.0	39.0	42.2	0.29	49.0
GROUP MEAN			89.7	20.2	36.7	80.4	0.27	46.3
4	892H	M	104.0	21.0	36.0	121.6	0.38	52.0
4	895H	M	126.0	20.0	41.0	153.2	0.34	53.0
4	911H	M	104.0	25.0	41.0	136.8	0.30	57.0
GROUP MEAN			111.3	22.0	39.3	137.2	0.34	54.0

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
Rhesus Monkeys Receiving MR 149,024 AD (AX67287) for Two Weeks
Week 2

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	900H	M	105.0	27.0	27.0	68.0	0.30	75.0
1	908H	M	86.0	19.0	27.0	39.0	0.51	74.0
1	912H	M	116.0	35.0	28.0	71.2	0.39	55.0
GROUP MEAN			102.3	27.0	27.3	59.4	0.40	68.0
2	889H	M	114.0	23.0	27.0	66.4	0.29	54.0
2	891H	M	124.0	28.0	27.0	52.0	0.39	65.0
2	909H	M	94.0	29.0	27.0	77.2	0.25	53.0
GROUP MEAN			110.7	26.7	27.0	65.2	0.31	57.3
3	881H	M	60.0	28.0	27.0	48.8	0.25	61.0
3	894H	M	84.0	23.0	25.0	71.2	0.20	55.0
3	897H	M	99.0	25.0	24.0	50.0	0.30	64.0
GROUP MEAN			81.0	25.3	25.3	56.7	0.25	60.0
4	892H	M	100.0	16.5	24.0	48.8	0.30	53.0
4	895H	M	110.0	26.0	28.0	104.8	0.29	60.0
4	911H	M	94.0	27.0	28.0	68.0	0.29	66.0
GROUP MEAN			101.3	23.2	26.7	73.9	0.29	59.7

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	787H	F	76.0	15.0	35.0	79.2	0.39	58.0
1	804H	F	79.0	15.0	36.0	65.6	0.30	58.0
1	930H	F	85.0	19.0	34.0	39.0	0.40	65.0
GROUP MEAN			80.0	16.3	35.0	61.3	0.36	60.3
2	799H	F	85.0	16.0	32.0	45.2	0.30	70.0
2	913H	F	75.0	13.0	38.0	49.9	0.40	56.0
2	925H	F	100.0	8.0	32.0	49.0	0.31	70.0
GROUP MEAN			86.7	12.3	34.0	48.0	0.34	65.3
3	797H	F	69.0	12.0	38.0	46.0	0.30	61.0
3	802H	F	80.0	14.0	32.0	68.0	0.40	62.0
3	806H	F	69.0	12.0	31.0	44.9	0.30	64.0
GROUP MEAN			72.7	12.7	33.7	53.0	0.33	62.3
4	805H	F	65.0	15.0	34.0	43.0	0.29	82.0
4	917H	F	64.0	11.0	32.0	46.8	0.31	76.0
4	923H	F	85.0	9.0	28.0	85.6	0.31	75.0
GROUP MEAN			71.3	11.7	31.3	58.5	0.30	77.7

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
Rhesus Monkeys Receiving MK 149,024 AD (AX67287) For Two Weeks
Week 1

GROUP NUMBER	ANIMAL NUMBER	E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	787H	F	94.0	15.0	39.0	130.4	0.31	49.0
1	804H	F	92.0	18.0	44.0	114.4	0.25	42.0
1	930H	F	109.0	28.0	42.0	103.6	0.30	45.0
GROUP MEAN			98.3	20.3	41.7	116.1	0.29	45.3
2	799H	F	95.0	27.0	39.0	90.8	0.30	55.0
2	913H	F	85.0	11.0	41.0	153.2	0.29	50.0
2	925H	F	135.0	11.0	36.0	132.0	0.28	45.0
GROUP MEAN			105.0	16.3	38.7	125.3	0.29	50.0
3	797H	F	85.0	16.0	41.0	101.6	0.30	54.0
3	802H	F	115.0	18.0	38.0	114.4	0.30	50.0
3	806H	F	100.0	14.0	36.0	108.0	0.30	44.0
GROUP MEAN			100.0	16.0	38.3	108.0	0.30	49.3
4	807H	F	90.0	19.0	38.0	62.0	0.30	51.0
4	917H	F	77.0	14.0	44.0	68.0	0.29	55.0
4	923H	F	130.0	14.0	35.0	142.0	0.21	49.0
GROUP MEAN			99.0	15.7	39.0	90.7	0.27	51.7

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
Rhesus Monkeys Receiving WR 149,024 AD (AX67287) for Two Weeks
Week 2

GROUP NUMBER	ANIMAL NUMBER	S E X	GLUCOSE MG%	BUN MG%	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG%	SGOT K. UNITS
1	787H	F	116.0	25.0	31.0	75.2	0.30	56.0
1	804H	F	96.0	23.0	28.0	88.8	0.25	49.0
1	930H	F	125.0	28.0	27.0	56.0	0.30	48.0
GROUP MEAN			112.3	25.3	28.7	73.3	0.28	51.0
2	799H	F	109.0	37.0	27.0	49.0	0.25	54.0
2	913H	F	100.0	22.0	29.0	66.4	0.33	61.0
2	925H	F	125.0	16.0	28.0	52.0	0.30	63.0
GROUP MEAN			111.3	25.0	28.0	55.8	0.29	59.3
3	797H	F	86.0	19.0	27.0	47.6	0.20	65.0
3	802H	F	89.0	20.0	24.0	60.0	0.31	63.0
3	806H	F	94.0	16.0	25.0	50.4	0.31	58.0
GROUP MEAN			89.7	18.3	25.3	52.7	0.27	62.0
4	807H	F	94.0	37.0	28.0	85.6	0.23	58.0
4	917H	F	92.0	25.0	35.0	53.2	0.20	67.0
4	923H	F	100.0	26.0	25.0	90.8	0.20	55.0
GROUP MEAN			95.3	29.3	29.3	76.5	0.21	60.0

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO2 MEQ/L
1	900H	M	149.0	4.70	108.0	10.8	23.0
1	908H	M	151.0	5.90	113.0	11.2	16.6
1	912H	M	153.0	5.45	117.0	11.3	15.0
GROUP MEAN			151.0	5.35	112.7	11.1	18.2
2	889H	M	150.0	5.55	117.0	11.4	14.9
2	891H	M	154.0	5.15	114.0	11.4	20.9
2	909H	M	149.0	5.00	111.0	11.0	21.0
GROUP MEAN			151.0	5.23	114.0	11.3	18.9
3	881H	M	152.0	4.70	115.0	10.3	21.8
3	894H	M	147.0	4.00	110.0	10.0	17.2
3	897H	M	155.0	4.70	112.0	11.2	22.2
GROUP MEAN			151.3	4.47	112.3	10.5	20.4
4	892H	M	150.0	4.50	116.0	10.8	18.2
4	895H	M	156.0	5.10	117.0	12.1	17.5
4	911H	M	151.0	4.80	110.0	10.5	23.0
GROUP MEAN			152.3	4.80	114.3	11.1	19.6

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO2 MEQ/L
1	900H	M	145.0	4.20	109.5	9.7	21.1
1	908H	M	148.0	4.20	109.0	9.8	18.8
1	912H	M	150.0	4.90	116.0	10.0	9.9
GROUP MEAN			147.7	4.43	111.5	9.8	16.6
2	889H	M	146.0	4.20	108.0	9.8	21.3
2	891H	M	147.0	4.40	109.0	9.9	21.9
2	909H	M	144.0	4.60	112.0	10.2	17.0
GROUP MEAN			145.7	4.40	109.7	10.0	20.1
3	881H	M	151.0	4.30	111.0	10.0	20.9
3	894H	M	146.0	3.55	110.0	8.8	20.2
3	897H	M	146.0	4.00	107.0	9.8	21.0
GROUP MEAN			147.7	3.95	109.3	9.5	20.7
4	892H	M	149.0	3.80	111.0	10.2	18.0
4	895H	M	149.0	4.60	114.0	10.0	11.0
4	911H	M	148.0	4.20	111.5	9.4	19.9
GROUP MEAN			148.7	4.20	112.2	9.9	16.3

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO2 MEQ/L
1	900H	M	152.0	4.50	111.0	10.0	25.1
1	908H	M	149.0	3.90	104.0	9.3	22.6
1	912H	M	160.0	5.00	116.0	10.4	20.8
GROUP MEAN			153.7	4.47	110.3	9.9	22.8
2	889H	M	156.0	4.30	115.0	9.4	14.9
2	891H	M	158.0	4.95	112.0	11.2	16.7
2	909H	M	149.0	3.60	115.0	10.6	21.5
GROUP MEAN			154.3	4.28	114.0	10.4	17.7
3	881H	M	150.0	4.10	112.5	9.6	25.1
3	894H	M	148.0	3.70	113.0	8.8	24.9
3	897H	M	145.0	4.60	112.0	9.6	17.9
GROUP MEAN			147.7	4.13	112.5	9.3	22.6
4	892H	M	147.0	4.00	100.5	11.4	24.0
4	895H	M	156.0	4.50	114.5	10.1	21.2
4	911H	M	151.0	4.20	109.0	9.5	24.1
GROUP MEAN			151.3	4.23	108.0	10.3	23.1

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO ₂ MEQ/L
1	787H	F	149.0	4.60	112.0	10.7	21.0
1	804H	F	150.0	5.10	113.0	10.5	18.1
1	930H	F	149.0	5.05	107.0	11.3	18.0
GROUP MEAN			149.3	4.92	110.7	10.8	19.0
2	799H	F	154.0	5.60	114.0	11.6	21.2
2	913H	F	157.0	5.10	116.0	11.6	21.1
2	925H	F	149.0	4.75	109.0	10.9	20.2
GROUP MEAN			153.3	5.15	113.0	11.4	20.8
3	797H	F	154.0	5.20	115.0	11.1	21.8
3	802H	F	150.0	4.80	113.0	10.6	20.5
3	806H	F	150.0	4.70	112.0	10.9	26.1
GROUP MEAN			151.3	4.90	113.3	10.9	22.8
4	805H	F	151.0	5.00	112.0	10.7	24.1
4	917H	F	151.0	4.40	114.0	10.8	21.0
4	923H	F	149.0	5.15	109.0	11.3	19.5
GROUP MEAN			150.3	4.85	111.7	10.9	21.5

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO2 MEQ/L
1	787H	F	147.0	4.20	113.0	10.0	16.1
1	804H	F	145.0	4.55	111.0	9.9	15.1
1	930H	F	146.0	4.30	114.0	9.5	13.1
GROUP MEAN			146.0	4.35	112.7	9.8	14.8
2	799H	F	149.0	4.40	111.0	10.1	22.8
2	913H	F	148.0	3.70	113.0	9.9	17.2
2	925H	F	147.0	3.90	108.0	9.8	16.5
GROUP MEAN			148.0	4.00	110.7	9.9	18.8
3	797H	F	147.0	4.35	107.0	10.5	19.9
3	802H	F	146.0	4.10	111.0	10.0	18.5
3	806H	F	146.0	3.80	109.0	10.0	19.0
GROUP MEAN			146.3	4.08	109.0	10.2	19.1
4	807H	F	147.0	4.90	111.0	10.3	18.1
4	917H	F	147.0	4.90	112.0	9.8	21.6
4	923H	F	149.0	4.00	111.0	10.0	16.6
GROUP MEAN			147.7	4.60	111.3	10.0	18.8

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
 RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	S ANIMAL NUMBER	E X	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG%	CO2 MEQ/L
1	787H	F	154.0	4.20	118.0	9.6	17.1
1	804H	F	154.0	4.50	113.0	9.6	23.0
1	930H	F	158.0	4.60	117.0	10.2	18.2
GROUP MEAN			155.3	4.43	116.0	9.8	19.4
2	799H	F	151.0	4.35	114.0	10.6	22.8
2	913H	F	148.0	4.30	114.0	9.7	15.9
2	925H	F	150.0	5.00	110.0	9.8	18.9
GROUP MEAN			149.7	4.55	112.7	10.0	19.2
3	797H	F	148.0	4.35	110.0	9.7	25.0
3	802H	F	147.0	4.20	111.0	9.7	22.9
3	806H	F	145.0	4.80	111.0	10.9	22.4
GROUP MEAN			146.7	4.45	110.7	10.1	23.4
4	807H	F	151.0	4.30	112.0	10.2	23.5
4	917H	F	153.0	4.15	115.0	10.3	22.0
4	923H	F	153.0	4.20	112.0	10.1	21.4
GROUP MEAN			152.3	4.22	113.0	10.2	22.3

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
Rhesus Monkeys Receiving WR 149,024 AD (AX67287) For Two Weeks

GROUP NUMBER	ANIMAL NUMBER	S E X	TOTAL PROTEIN G%	ELECTROPHORESIS					TOTAL ALBUMIN G%
				ALBUMIN %	ALPHA1 %	ALPHA2 %	BETA %	GAMMA %	
1	900H	M	7.11	60.0	5.0	9.0	15.0	11.0	3.30
1	908H	M	7.80	53.0	4.0	8.0	20.0	15.0	2.80
1	912H	M	7.50	50.0	4.0	6.0	22.0	18.0	2.90
GROUP MEAN			7.47	54.3	4.3	7.7	19.0	14.7	3.00
2	889H	M	7.80	53.0	7.0	8.0	19.0	13.0	2.89
2	891H	M	7.90	60.0	6.0	8.0	15.0	11.0	2.75
2	909H	M	6.89	68.0	4.0	4.0	16.0	8.0	3.10
GROUP MEAN			7.53	60.3	5.7	6.7	16.7	10.7	2.91
3	881H	M	7.99	52.0	3.0	7.5	26.0	11.5	3.11
3	894H	M	8.00	44.0	5.0	6.0	19.0	26.0	2.40
3	897H	M	7.25	58.0	3.0	8.0	20.0	11.0	3.60
GROUP MEAN			7.75	51.3	3.7	7.2	21.7	16.2	3.04
4	892H	M	7.20	55.0	4.0	8.0	19.0	14.0	3.05
4	895H	M	8.69	53.0	7.0	14.0	13.0	13.0	3.51
4	911H	M	7.10	54.0	4.0	6.0	20.0	16.0	2.55
GROUP MEAN			7.66	54.0	5.0	9.3	17.3	14.3	3.04

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
Rhesus Monkeys Receiving MR 149,024 AD (AX67287) for Two Weeks
Week 1

Group Number	Animal Number	Sex	Total Protein G%	Electrophoresis					Total Albumin G%
				Albumin %	Alpha1 %	Alpha2 %	Beta %	Gamma %	
1	900H	M	7.00	56.0	3.0	5.0	24.5	11.5	3.12
1	908H	M	8.00	42.0	5.0	7.0	38.0	8.0	2.51
1	912H	M	7.79	47.5	3.5	5.0	28.0	16.0	2.80
Group Mean			7.60	48.5	3.8	5.7	30.2	11.8	2.81
2	889H	M	7.40	49.0	4.0	6.0	25.0	16.0	2.52
2	891H	M	7.41	56.5	3.5	5.0	24.0	11.0	3.31
2	909H	M	7.11	56.0	3.0	5.0	24.0	12.0	3.19
Group Mean			7.31	53.8	3.5	5.3	24.3	13.0	3.01
3	881H	M	7.54	47.0	3.0	9.0	27.0	14.0	2.50
3	894H	M	7.79	47.0	3.0	6.5	26.0	17.5	2.30
3	897H	M	7.30	49.0	4.0	8.5	22.5	16.0	2.99
Group Mean			7.54	47.7	3.3	8.0	25.2	15.8	2.60
4	892H	M	7.00	51.5	4.5	7.0	21.0	16.0	2.90
4	895H	M	7.71	55.0	3.0	5.0	25.5	11.5	3.20
4	911H	M	6.91	50.0	2.0	6.0	28.0	14.0	2.49
Group Mean			7.21	52.2	3.2	6.0	24.8	13.8	2.86

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	SEX	TOTAL PROTEIN G%	ELECTROPHORESIS				TOTAL ALBUMIN G%	
				ALBUMIN %	ALPHA %	BETA %	GAMMA %		
1	900H	M	7.20	51.0	3.0	6.0	27.0	13.0	3.20
1	908H	M	7.35	38.5	3.5	12.0	31.0	15.0	1.85
1	912H	M	8.30	46.0	3.0	6.0	25.0	20.0	3.09
GROUP MEAN			7.62	45.2	3.2	8.0	27.7	16.0	2.71
2	889H	M	7.49	48.0	3.5	5.5	26.0	17.0	2.75
2	891H	M	7.83	50.0	2.0	6.5	28.5	13.0	3.72
2	909H	M	7.30	56.0	3.0	5.0	26.0	10.0	3.35
GROUP MEAN			7.54	51.3	2.8	5.7	26.8	13.3	3.27
3	881H	M	7.91	42.0	4.0	9.0	31.0	14.0	2.50
3	894H	M	7.60	43.0	3.0	9.0	23.0	22.0	2.31
3	897H	M	7.19	50.0	3.0	6.0	26.0	15.0	3.15
GROUP MEAN			7.57	45.0	3.3	8.0	26.7	17.0	2.65
4	892H	M	7.40	47.0	6.0	10.0	23.0	14.0	2.65
4	895H	M	8.11	53.0	3.0	8.0	26.0	10.0	3.21
4	911H	M	7.40	49.5	2.5	5.0	29.0	14.0	2.50
GROUP MEAN			7.64	49.8	3.8	7.7	26.0	12.7	2.79

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
INITIAL

GROUP NUMBER	ANIMAL NUMBER	S E X	TOTAL PROTEIN G%	ELECTROPHORESIS					TOTAL ALBUMIN G%
				ALBUMIN %	ALPHA1 %	ALPHA2 %	BETA %	GAMMA %	
1	787H	F	6.64	63.5	3.5	5.0	19.0	9.0	3.30
1	804H	F	7.51	50.0	7.0	8.0	24.0	11.0	2.71
1	930H	F	7.01	54.0	4.0	9.0	20.0	13.0	3.15
GROUP MEAN			7.05	55.8	4.8	7.3	21.0	11.0	3.05
2	799H	F	7.61	48.0	4.0	10.0	23.0	15.0	2.80
2	913H	F	7.59	58.0	3.5	5.0	19.5	14.0	3.60
2	925H	F	7.60	47.0	4.0	8.0	25.0	16.0	2.79
GROUP MEAN			7.60	51.0	3.8	7.7	22.5	15.0	3.06
3	797H	F	7.90	51.0	3.0	8.0	21.0	17.0	2.89
3	802H	F	6.80	60.5	6.0	9.5	17.0	12.0	3.01
3	806H	F	7.00	57.0	5.0	7.0	19.0	12.0	3.10
GROUP MEAN			7.23	56.2	4.7	8.2	19.0	13.7	3.00
4	805H	F	7.10	51.0	8.0	7.0	18.0	16.0	3.08
4	917H	F	7.19	55.0	6.0	8.0	20.0	11.0	3.18
4	923H	F	8.20	43.0	5.0	6.0	26.0	20.0	2.51
GROUP MEAN			7.50	49.7	6.3	7.0	21.3	15.7	2.92

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING MR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	TOTAL PROTEIN G%	ELECTROPHORESIS					TOTAL ALBUMIN G%
				ALBUMIN %	ALPHA1 %	ALPHA2 %	BETA %	GAMMA %	
1	787H	F	6.91	56.0	3.0	5.5	26.5	9.0	3.00
1	804H	F	7.60	44.0	4.0	6.0	32.5	13.5	2.50
1	930H	F	6.91	55.5	4.5	4.0	27.0	9.0	2.90
GROUP MEAN			7.14	51.8	3.8	5.2	28.7	10.5	2.80
2	799H	F	7.40	48.0	5.0	7.0	26.5	13.5	2.81
2	913H	F	7.00	52.5	4.5	5.0	23.0	14.0	3.30
2	925H	F	8.00	52.0	3.0	6.0	24.0	15.0	2.85
GROUP MEAN			7.47	50.8	4.2	6.0	24.5	14.2	2.99
3	797H	F	8.09	53.0	2.5	6.0	24.5	14.0	2.85
3	802H	F	7.00	56.0	3.5	5.0	22.5	13.0	3.00
3	806H	F	7.71	52.0	3.0	6.0	26.0	13.0	3.21
GROUP MEAN			7.60	53.7	3.0	5.7	24.3	13.3	3.02
4	807H	F	7.49	51.5	4.0	6.0	28.5	10.0	3.06
4	917H	F	6.89	49.5	4.0	7.5	26.0	13.0	2.90
4	923H	F	7.60	47.0	4.5	9.0	27.5	12.0	2.48
GROUP MEAN			7.33	49.3	4.2	7.5	27.3	11.7	2.81

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
Rhesus Monkeys Receiving MR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	TOTAL PROTEIN G%	ELECTROPHORESIS					TOTAL ALBUMIN G%
				ALBUMIN %	ALPHA1 %	ALPHA2 %	BETA %	GAMMA %	
1	787H	F	6.99	50.0	2.0	9.0	29.0	10.0	2.91
1	804H	F	7.80	44.0	3.0	7.0	34.0	12.0	2.70
1	930H	F	7.10	51.0	3.0	6.0	28.0	12.0	3.08
GROUP MEAN			7.30	48.3	2.7	7.3	30.3	11.3	2.90
2	799H	F	8.09	47.5	2.5	6.0	32.0	12.0	3.01
2	913H	F	7.10	57.0	4.0	7.0	20.0	12.0	3.29
2	925H	F	8.49	44.5	3.5	7.0	32.0	13.0	2.71
GROUP MEAN			7.89	49.7	3.3	6.7	28.0	12.3	3.00
3	797H	F	7.50	49.0	3.0	6.0	26.0	16.0	2.80
3	802H	F	6.69	58.5	3.5	6.0	22.5	9.5	3.01
3	806H	F	7.80	54.0	2.0	5.0	23.0	16.0	3.30
GROUP MEAN			7.33	53.8	2.8	5.7	23.8	13.8	3.04
4	807H	F	7.99	46.5	2.5	8.0	30.0	13.0	3.29
4	917H	F	7.39	48.0	3.0	8.0	26.0	15.0	3.01
4	923H	F	7.90	41.0	3.0	6.0	31.0	9.0	2.41
GROUP MEAN			7.76	45.2	2.8	7.3	29.0	12.3	2.90

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TABLE NO. 4 - URINE ANALYSIS
 RHESUS MONKEYS RECEIVING WK 149,024 AD (AX67287) FOR TWO WEEKS
 INITIAL

GROUP NUMBER	ANIMAL NUMBER	E X	S APPEAR.	P H	SP.GR.	SU- GAR	ACE- TONE	PRU- TEIN	BILI- RUBIN	MICROSCOPIC FINDINGS-----			
										RBC	WBC	EPITH	AMORPH CRYSTALS
1	900H	M	T YEL	5	1.032	0	0	0	0	0-2	0-1	3-4	FEW FEW
1	908H	M	T YEL	7	1.031	0	0	0	0	0-1	0-1		MANY FEW
1	912H	M	T YEL	6	1.022	0	0	0	0	0-1			MANY FEW
2	889H	M	T YEL	6	1.031	0	0	T	0	0-1			MANY FEW
2	891H	M	T YEL	6	1.045	0	0	0	0				FEW FEW
2	909H	M	T YEL	6	1.053	0	0	0	0		0-2	LITTLE	FEW FEW
3	881H	M	V T YEL	6	1.035	0	0	T	0		0-2	0-4	MUCH FEW MANY
3	894H	M	T YEL	8	1.040	0	0	0	0	0-2	0-1		LITTLE MANY FEW
3	897H	M	T YEL	6	1.049	0	0	T	0		0-2		LITTLE MANY FEW
4	892H	M	T YEL	5	1.030	0	0	0	0		0-1	0-2	MANY FEW
4	895H	M	T YEL	7	1.040	T	1	T	0		0-2	0-1	MANY FEW
4	911H	M	T YEL	6	1.040	0	0	0	0		0-2	0-2	MANY FEW

TABLE NO. 4 - URINE ANALYSIS
 RHESUS MONKEYS RECEIVING WK 149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 1

GROUP NUMBER	ANIMAL NUMBER	S E X	APPEAR.	P H	SP.GR.	SU- ACE- PRO-		BILI- RUBIN	RBC	-----MICROSCOPIC FINDINGS-----			
						GAR	TEIN			WBC	EPITH	AMORPH	CRYS BACT SPERM
1	900H	M	T YEL	8	1.033	0	0	0	0-1	0-1	0-1	LITTLE	FEW
1	908H	M	T YEL	9	1.031	0	0	0	0-1	0-1	0-3	MUCH	MANY
1	912H	M	T YEL	9	1.031	0	0	0	0-1	0-1	0-3	MUCH	MANY
2	889H	M	T YEL	8	1.030	0	0	0	0-2			LITTLE	FEW
2	891H	M	T YEL	8	1.036	0	0	0				LITTLE	FEW
2	909H	M	T YEL	9	1.032	0	0	0				LITTLE	FEW
3	881H	M	V T YEL	7	1.027	0	0	0		0-1		MUCH	MANY
3	894H	M	T YEL	8	1.031	0	0	0				MUCH	FEW
3	897H	M	T YEL	8	1.030	0	0	0				MUCH	MANY
4	892H	M	T YEL	6	1.025	0	0	0				MUCH	FEW
4	895H	M	T YEL	7	1.035	0	4	T		0-1		MUCH	FEW
4	911H	M	T YEL	9	1.040	0	0	0		0-2	0-2	LITTLE	MANY

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TABLE NO. 4 - URINE ANALYSIS
 RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	S E X	APPEAR.	P H	SP. GR.	SU- ACE- PRO- BILI-			RBC	-----MICROSCOPIC FINDINGS-----			
						GAR	TON	TEIN		WBC	EPITH	AMORPH	CRYS BACT SPERM
1	900H	M	T YEL	9	1.041	0	0	0	0				
1	908H	M	T YEL	6	1.027	0	2	1	0			MUCH	FEW FEW
1	912H	M	T YEL	8	1.032	0	T	0	0			FEW FEW	FEW FEW
												LITTLE	MANY
2	889H	M	T YEL	8	1.035	0	0	0	0				
2	891H	M	V T YEL	7	1.043	0	0	0	0	0-2		LITTLE	FEW FEW
2	909H	M	T YEL	8	1.040	0	0	0	0			MUCH	FEW FEW
												MUCH	FEW FEW
3	881H	M	V T YEL	8	1.035	0	0	0	0				
3	894H	M	T YEL	8	1.041	0	0	0	0	0-1	5-10	MUCH	FEW FEW
3	897H	M	V T YEL	8	1.032	0	0	0	0	0-2	0-4	LITTLE	FEW FEW
										0-1	0-2	MUCH	FEW FEW
4	892H	M	T L YEL	7	1.010	0	0	0	0				
4	895H	M	T YEL	9	1.028	0	0	0	0	0-1	0-1	LITTLE	FEW MANY
4	911H	M	V T YEL	9	1.043	0	0	0	0	0-3	5-6	MUCH	MANY FEW

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TABLE NO. 4 - URINE ANALYSIS
Rhesus Monkeys Receiving WR 149,024 AD (AX67287) for Two Weeks

GROUP NUMBER	ANIMAL NUMBER	S E X	P H	APPEAR.	SU- GAR	ACE- TONE	PRO- TEIN	BILI- RUBIN	RBC	MICROSCOPIC FINDINGS			
										WBC	EPITH	AMORPH	CRYSTALS
1	787H	F	6	T YEL	0	0	0	0	0-2	1-3			MANY FEW
1	804H	F	7	V T YEL	0	0	0	0	0-1	6-12	5-10	MUCH	FEW FEW
1	930H	F	7	T YEL	0	0	0	0	0-1	1-3	5-7	LITTLE	MANY FEW
2	799H	F	6	T YEL	0	0	1	0		4-8	3-7	MUCH	FEW
2	913H	F	7	VT L YEL	0	0	0	0				MUCH	
2	925H	F	5	T YEL	0	2	T	0		1-3	1-2	LITTLE	FEW FEW
3	797H	F	7	T YEL	0	0	0	0		0-2			MANY FEW
3	802H	F	8	T YEL	0	0	0	0		6-12	7-10		MANY MANY
3	806H	F	7	T YEL	0	0	T	0		2-3	8-10	LITTLE	FEW MANY
4	807H	F	7	T YEL	0	0	0	0		0-5	0-4	LITTLE	FEW FEW
4	917H	F	6	T YEL	0	0	0	0	15-20	3-5	0-2	MUCH	FEW FEW
4	923H	F	7	T YEL	0	0	0	0		0-2	0-2	MUCH	FEW FEW

TABLE NO. 4 - URINE ANALYSIS
RHEBUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	E X	S APPEAR.	P H	SP.GR.	SU- GAR	ACE- TONE	PRO- TEIN	BILI- RUBIN	RBC	-----MICROSCOPIC FINDINGS-----			
											WBC	EPITH	AMORPH	CRYSTALS
1	787H	F	T YEL	8	1.022	0	0	0	0	0-2	4-6	0-3	LITTLE	FEW
1	804H	F	T YEL	9	1.035	0	0	0	0				MUCH	FEW
1	930H	F	V T YEL	8	1.048	0	0	0	0				MUCH	FEW
2	799H	F	T D YEL	8	1.050	0	0	0	0		0-2	2-3	MUCH	MANY
2	913H	F	T L YEL	8	1.022	0	0	0	0		0-2	0-3	MUCH	FEW
2	925H	F	T YEL	9	1.030	0	0	0	0		6-9	4-6	MUCH	FEW
3	797H	F	T YEL	8	1.023	0	0	0	0			0-2	MUCH	MANY
3	802H	F	T YEL	9	1.030	0	0	0	0				MUCH	FEW
3	806H	F	T D YEL	9	1.050	0	0	T	0	4-6	2-3	3-5	MUCH	FEW
4	807H	F	T YEL	8	1.020	0	0	0	0		0-2	0-2		FEW
4	917H	F	T YEL	7	1.024	0	0	0	0		0-2	0-2		MANY
4	923H	F	T YEL	7	1.028	0	0	0	0		0-2			FEW

TABLE NO. 4 - URINE ANALYSIS
 RHESUS MONKEYS RECEIVING MR 149,024 AD (AX67287) FOR TWO WEEKS
 WEEK 2

GROUP NUMBER	ANIMAL NUMBER	E X	S APPEAR.	P H	SP.GR.	SU- GAR	ACE- TONE	PRO- TEIN	BILI- RUBIN	MICROSCOPIC FINDINGS				
										RBC	WBC	EPITH	AMORPH	CRYSTALS
1	787H	F	V T YEL	8	1.033	0	0	0	0	0-1		MUCH	FEW	FEW
1	804H	F	T YEL	7	1.043	0	0	0	0	3-5		MUCH	FEW	FEW
1	930H	F	T YEL	8	1.038	0	0	0	0	0-3		LITTLE	FEW	FEW
2	799H	F	T YEL	8	1.030	0	0	0	0	2-4	3-5	MUCH	FEW	FEW
2	913H	F	T YEL	7	1.030	0	0	0	0			MUCH	FEW	FEW
2	925H	F	T YEL	7	1.030	0	0	0	0	10-12	1-3	MUCH	FEW	FEW
3	797H	F	T YEL	8	1.032	0	0	0	0	5-10	0-2		FEW	FEW
3	802H	F	V T YEL	8	1.035	0	0	0	0	0-2	5-10	MUCH	FEW	FEW
3	806H	F	V T YEL	8	1.033	0	0	0	0	8-12	4-5	MUCH	MANY	
4	807H	F	T YEL	8	1.025	0	0	0	0	4-7			FEW	
4	917H	F	T YEL	6	1.030	0	0	0	0	2-3	0-1	LITTLE		
4	923H	F	V T YEL	9	1.037	0	0	0	0	5-10	0-5	LITTLE	MANY	

TABLE NO. 5 - TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, AND ORGAN/BODY WEIGHT RATIOS
 SPECIES AND STRAIN - RHESUS MONKEYS
 MATERIAL - WR 149,024 AD
 ROUTE OF ADMINISTRATION - INTRAVENOUS
 INTERVAL - TWO WEEKS

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID				HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
900H	2.60	0.380	0.0146	12.285	0.4725	77.840	2.9938	3.070	0.1181		
908H	2.70	0.610	0.0226	14.285	0.5291	89.565	3.3172	5.450	0.2019		
912H	4.10	0.605	0.0148	18.325	0.4470	83.010	2.0246	3.050	0.0744		
MEAN	3.13	0.532	0.0173	14.965	0.4828	83.472	2.7786	3.857	0.1314		

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		TESTES	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
900H	2.60	9.775	0.3760	0.550	0.0212	0.900	0.0346
908H	2.70	17.925	0.6639	0.705	0.0261	1.905	0.0706
912H	4.10	14.645	0.3572	0.530	0.0129	11.625	0.2835
MEAN	3.13	14.115	0.4657	0.595	0.0201	4.810	0.1296

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Table No. 5 - Continued

MALES - 5.0 MG/KG/DAY

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
889H	3.20	0.460	0.0144	12.495	0.3905	85.290	2.6653	4.170	0.1303
891H	2.60	0.535	0.0206	13.000	0.5000	58.635	2.2552	3.095	0.1190
909H	2.40	0.445	0.0185	12.025	0.5010	56.465	2.3527	4.885	0.2035
MEAN	2.73	0.480	0.0178	12.507	0.4638	66.797	2.4244	4.050	0.1510

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		TESTES	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
889H	3.20	11.340	0.3544	0.655	0.0205	1.500	0.0469
891H	2.60	11.935	0.4590	0.595	0.0229	0.0	0.0
909H	2.40	11.320	0.4717	0.655	0.0273	1.020	0.0425
MEAN	2.73	11.532	0.4284	0.635	0.0235	1.260	0.0447

NOTE - ZEROS FOR ORGAN WEIGHT AND RATIO INDICATE ORGAN WEIGHT NOT RECORDED.

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Table No. 5 - Continued

MALES - 10.0 MG/KG/DAY

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
881H	2.80	0.730	0.0261	13.790	0.4925	75.295	2.6891	3.105	0.1109
894H	3.10	0.495	0.0160	11.980	0.3865	71.640	2.3110	3.245	0.1047
897H	3.30	0.480	0.0145	14.325	0.4341	68.140	2.0648	4.190	0.1270
MEAN	3.07	0.568	0.0189	13.365	0.4377	71.692	2.3550	3.513	0.1142

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		TESTES	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
881H	2.80	10.755	0.3841	0.615	0.0220	1.195	0.0427
894H	3.10	12.240	0.3948	0.665	0.0215	1.185	0.0382
897H	3.30	10.895	0.3302	0.685	0.0208	1.520	0.0461
MEAN	3.07	11.297	0.3697	0.655	0.0214	1.300	0.0423

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Table No. 5 - Continued

MALES - 20.0 MG/KG/DAY

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID WEIGHT G	THYROID RATIO PCT	HEART WEIGHT G	HEART RATIO PCT	LIVER WEIGHT G	LIVER RATIO PCT	SPLEEN WEIGHT G	SPLEEN RATIO PCT
892H	2.20	0.345	0.0157	12.360	0.5618	62.005	2.8184	3.000	0.1364
895H	2.80	0.705	0.0252	15.185	0.5423	57.250	2.0446	5.985	0.2138
911H	3.30	0.380	0.0115	14.050	0.4258	73.100	2.2152	4.855	0.1471
MEAN	2.77	0.477	0.0175	13.865	0.5100	64.118	2.3594	4.613	0.1657

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS WEIGHT G	KIDNEYS RATIO PCT	ADRENALS WEIGHT G	ADRENALS RATIO PCT	TESTES WEIGHT G	TESTES RATIO PCT
892H	2.20	11.190	0.5086	0.465	0.0211	1.240	0.0564
895H	2.80	11.660	0.4164	0.445	0.0159	1.235	0.0441
911H	3.30	11.775	0.3568	0.455	0.0138	2.005	0.0608
MEAN	2.77	11.542	0.4273	0.455	0.0169	1.493	0.0537

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Table No. 5 - Continued

FEMALES - CONTROL

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID WEIGHT G	THYROID RATIO PCT	HEART WEIGHT G	HEART RATIO PCT	LIVER WEIGHT G	LIVER RATIO PCT	SPLEEN WEIGHT G	SPLEEN RATIO PCT
787H	3.20	0.305	0.0095	14.300	0.4469	76.940	2.4044	4.395	0.1373
804H	2.90	0.625	0.0216	16.635	0.5736	80.205	2.7657	4.610	0.1590
930H	2.60	0.380	0.0146	12.030	0.4627	61.200	2.3538	2.570	0.0988
MEAN	2.90	0.437	0.0152	14.322	0.4944	72.782	2.5080	3.858	0.1317

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ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS WEIGHT G	KIDNEYS RATIO PCT	ADRENALS WEIGHT G	ADRENALS RATIO PCT	OVARIES WEIGHT G	OVARIES RATIO PCT
787H	3.20	11.565	0.3614	0.485	0.0152	1.410	0.0441
804H	2.90	12.565	0.4333	0.505	0.0174	0.195	0.0067
930H	2.60	10.885	0.4187	0.545	0.0210	0.225	0.0087
MEAN	2.90	11.672	0.4044	0.512	0.0178	0.610	0.0198

Table No. 5 - Continued

FEMALES - 5.0 MG/KG/DAY

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
799H	3.10	0.465	0.0150	15.700	0.5065	79.855	2.5760	4.185	0.1350
913H	2.60	0.360	0.0138	12.840	0.4938	62.205	2.3925	2.810	0.1081
925H	3.00	0.715	0.0238	15.775	0.5258	73.140	2.4380	5.215	0.1738
MEAN	2.90	0.513	0.0176	14.772	0.5087	71.733	2.4688	4.070	0.1390

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		OVARIES	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
799H	3.10	12.550	0.4048	0.645	0.0208	0.160	0.0052
913H	2.60	10.780	0.4146	0.685	0.0263	0.105	0.0040
925H	3.00	12.380	0.4127	0.800	0.0267	0.290	0.0097
MEAN	2.90	11.903	0.4107	0.710	0.0246	0.185	0.0063

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Table No. 5 - Continued

FEMALES - 10.0 MG/KG/DAY

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
797H	2.60	0.400	0.0154	15.045	0.5787	74.020	2.8469	2.925	0.1125
802H	3.50	0.685	0.0196	15.895	0.4541	78.100	2.2314	4.195	0.1199
806H	3.30	0.445	0.0135	17.920	0.5430	71.580	2.1691	2.495	0.0756
MEAN	3.13	0.510	0.0161	16.287	0.5253	74.567	2.4158	3.205	0.1027

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		OVARIES	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
797H	2.60	11.765	0.4525	0.800	0.0308	0.160	0.0062
802H	3.50	13.900	0.3971	0.600	0.0171	0.320	0.0091
806H	3.30	16.120	0.4885	0.705	0.0214	0.250	0.0076
MEAN	3.13	13.928	0.4460	0.702	0.0231	0.243	0.0076

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Table No. 5 - Continued

FEMALES - 20.0 MG/KG/DAY

ANIMAL NO.	TERM. BODY WEIGHT KG	THYROID		HEART		LIVER		SPLEEN	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
807H	3.10	0.515	0.0166	16.050	0.5177	80.570	2.5990	3.535	0.1140
917H	3.00	0.495	0.0165	13.370	0.4457	74.120	2.4707	2.805	0.0935
923H	3.20	0.870	0.0272	15.395	0.4811	75.740	2.3669	5.060	0.1581
MEAN	3.10	0.627	0.0201	14.938	0.4815	76.810	2.4789	3.800	0.1219

ANIMAL NO.	TERM. BODY WEIGHT KG	KIDNEYS		ADRENALS		OVARIES	
		WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT	WEIGHT G	RATIO PCT
807H	3.10	11.670	0.3765	0.585	0.0189	0.235	0.0076
917H	3.00	11.775	0.3925	0.525	0.0175	0.180	0.0060
923H	3.20	13.530	0.4228	0.730	0.0228	0.145	0.0045
MEAN	3.10	12.325	0.3973	0.613	0.0197	0.187	0.0060

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KEY FOR INCIDENCE TABLE

P = Present

N = No Section

A = Autolysis

X = Not Remarkable

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderately Severe/High

5 = Severe/High

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DETAILED HISTOPATHOLOGY INCIDENCE TABLE

Males	Animal No.	Groups								
		1			2			3		
		900H	908H	912H	891H	909H	889H	881H	894H	897H
THYROID										
Level of activity		3	2	2						
ADRENAL										
Mineralization		1	X	X						
MESENTERIC LYMPH NODE										
Periadenitis		X		X						
Pigmentation			4							
Parasites										
Increase in neutrophils										
Adenitis										
HEART										
Focal endocarditis		X	X	X						
Focal myocarditis										
SPLEEN										
Pigmentation										
Extramedullary		1	2							
hematopoiesis		1	2							
Congestion										
Lymphoid hyperplasia			2							

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Females	Animal No.	Groups								
		1			2			3		
		804H	930H	787H	799H	913H	925H	797H	802H	806H
THYROID										
Level of activity		3	2	2						
ADRENAL		X								
Mineralization			1	3						
MESENTERIC LYMPH NODE			X	X						
Periadenitis										
Pigmentation										
Parasites										
Increase in neutrophils		3								
Adenitis										
HEART			X							
Focal endocarditis		1								
Focal myocarditis				3						
SPLEEN		X	X							
Pigmentation										
Extramedullary										
hematopoiesis										
Congestion										
Lymphoid hyperplasia				2						

[illegible]

[illegible]

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[illegible]

Females	Animal No.	Groups								
		1			2			3		
		804H	930H	787H	799H	913H	925H	797H	802H	806H
PANCREAS		X	X							
Focal lymphoid hyperplasia				2						
Pancreatitis										
URINARY BLADDER		X	X	X						
Cystitis										
TESTIS										
Prepubital										
OVARY		N	X							
Cysts				P						
BONE MARROW		X	X	X						
Increase cellularity										
Decrease cellularity										
LUNG										
Lungmite										
Pleural thickening					3					
BRAIN										
Focal fibrosis						P				

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