



**ADMINISTRATION ORAL VIA
AT REPEATED DOSES (14 DAYS)
IN RAT.**

Laboratory : GRUPO INTERLAB, S.L.

Assayed substance : Pharmaceutical Product (FR-91)

s/ Reference : HI-2915-0R (2 Units)

n/ Reference : 1484

Origin : CHACON FARMACEUTICA

Entrance date : January,4th,1996.

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I.- OBJECTIVE OF THE STUDY.

The objective of this assay is to show the effects produced by the assayed substance FR-91 on rat, after its administration for 14 days oral via.

Once administrated the assayed substance during the established period of time, we proceed to the sacrifice of the animals, performing the extraction of blood for the hematologic determinations and necropsy.

II.- MATERIAL AND METHOD.

SELECTED SPECIE.

For this assay, Wistar albin rats are used, young (less than 8 weeks of age at the beginning of the assay) and healthy. The females are nullipara and not pregnant. They are laboratory animals bred in France, having passed under all the sanitary control satisfactorily and supplied for this assay by our habitual supplier IFFA CREDO.

a) Lodging and maintenance.

Once the animals have arrived to our installation, they are carefully examined and lodged in cages with macrolon trays and cover of stainless steel grille, grouped together from five to five at random, and separated by sex, being identified individually.

They are kept a minimum period of 5 days of acclimatization to our laboratory conditions. During this time, they are kept under observation in order to detect the possible appearance of any pathology or change in behaviour.

Once the period of acclimatization is ended, they assay groups are assigned and they are properly identified for the beginning of the experiment.

The animalary conditions are controlled during the execution of the assay, keeping the following values:

- Temperature at 20°C (+/- 3°C)
- Humidity relative rate between 30 and 70%
- Photoperiod of 12/12 hours light /obscurity



The animals are provided of water and food "ad libitum" during all the acclimatization period. During the experimental phase, the feeding trays are taken away during the night, remaining fasting until 1 hour after the administration of the assayed substance in order to facilitate the sounding and the assimilation of the assayed substance.

The administrated diet is keeping up food for rodents in pellets (Rodent Toxicology Diet), supplied by BK Universal

b) Experimental Groups and Administration Vias.

The assay is performed with 2 lots of animals, grouped the following way.:

CONTROL Water - 5 males and 5 females
ORAL ADMINISTRATION FR-91 1484 - 5 males and 5 females

The administration dose has been determined by the Technical Direction of Chacón Farmacéutica, the following way:

GROUP S/REF.	DOSE N/REF.	ADMINISTRATION
CONTROL	1 mL/day WATER	Oral
FR - 91 (2 units)	1 mL/day 1484	Oral

2) PREPARATION OF THE SAMPLE.

The sample, of liquid nature, has been prepared in the origin laboratory, for its adequate oral administration, following what was agreed with the Technical Direction, being not necessary the utilization of a vehicle, nor any previous treatment.

The stability analysis and pureness of the product are the client's responsibility.

The conservation of the sample during all the experimental period is under refrigeration (4°C) and protected from light, following instructions of Chacón Farmacéutica.



3) OPERATIVE MODE.

a) Programation of the Assay.

- Period of acclimatization 5 days (minimum)
- Period of administration 2 weeks - 5 days a week
- Sacrifice, blood extraction, necropsy and taking of samples for the histopathologic examination

b) Administration of the assayed substance.

Ended the period of acclimatization, the animals are kept fasting during the night, administrating them the assayed substance at first hour of the day through gastric sounding.

One hour after the administration, the food trays with keeping up diet for rodents are put at disposition of the animals, allowing them the consumption "ad libitum" for 8 hours. Water is not rationed during all the assay.

For the administration oral via, metallic gastric sounds are used.

Blood samples of all the animals in the treated group, and, five animals in the control group (3 males and 2 females) are taken for the hematologic determination of the white series (Differential Recount of Leucocytes expressed in percentage), the days 1 (before the first administration) 3, 7 and 10. The day 14 (control group) and the day 16 (treated group), all animals are taken blood for the hematologic determinations (differential recount and total account of leucocytes) The blood samples are taken by punction in the ear.

Once the experimentation period is finished, the animals are sacrificed, being first anesthetized by intraperitoneal injection of sodic pentotal, obtaining the sample by cardiac punction. The experiment finishes the day 14 for the control group and the days 16 and 17 for the males and the females of the experimental group respectively.

The blood samples obtained at the end of the assay are processed in order to get the determination of the Total and Differential Recount of Leucocytes. The tissues taken for the histopathologic analysis are included in formol solution and sent to the laboratory of clinical analysis HEMOS, for their processing.



III RESULTS

Along the assay, the following data are collected

- CLINICAL SIGNS

The animals have been observed daily, and no alteration, clinical signs or changes in behaviour have been detected.

- MORTALITY

There have been no deaths of any experiment animal along the assay.

- CORPORAL WEIGHTS

The corporal weights are registered at the beginning of the assay and with weekly periodicity until the last day of the assay. The values are expressed in a table in Annexe I.

- ORGAN WEIGHTS

The results are expressed in table of Annexe II.
Control Group - five animals : 3 males (1,2,3) and two females (4,5)

- LEUCOCYTES: DIFFERENTIAL RECOUNTS

The differential recounts of leucocytes of the animals through blood extension and tinction has been made (Leucocyary formula). The results are expressed in table of Annexe III.



- LEUCOCYTES : TOTAL RECOUNTS.

At the end of the experimentation period, we proceed to the extraction of blood for the recount of leucocytes. It is performed by cardiac puncture, having the animals previously been anesthetized through intraperitoneal injection of sodic pentotal in watery solution. The results are shown in table of Annexe IV.

- NECROPSY.

At the end of the assay the necropsy of the animals used in the experiment is performed; five in the Control Group and all animals in the Treated Group. The results are gathered in table of Annexe V. The observed alterations are reduced to hemorrhagic and congestive lesions, located in the abdominal cavity. Since the appearance of such lesions is produced in all the cases in areas near the site of injection of the anesthetic used for the sacrifice, and since they are present in both, the control group and the experimental group, they could be attributed to the local tissular reaction produced by the irritating effect of the sodic pentotal.

IV DISCUSSION AND CONCLUSION.

The substance FR-91 has stimulated the total production of leucocytes detected by the statistical analysis up to a significant increase and the lymphocytes in the differential recount referred to the Control Group.

We declare that the assay has been performed following the described protocol.

Madrid, April 12th, 1996.

Handwritten signature of M. Jose Benitez de Huelva.

M^o JOSE BENITEZ DE HUELVA
Technical Supervisor

Handwritten signature of Paloma Azpeitia.

PALOMA AZPEITIA
Laboratory Director



ANEXO I

PESOS CORPORALES



TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Agua
FECHA INICIAL: 06/03/96

N/REF.: CONTROL
S/REF.: --
FECHA FINAL: 22/03/96

ANIMAL	SEXO	PESOS CORPORALES (g)		
		PESO 06/03/96	PESO 13/03/96	PESO 19/03/96
1	♂	196	242	274
2	♂	187	231	269
3	♂	195	237	270
4	♀	173	199	207
5	♀	173	195	212





TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Preparado farmacéutico
FECHA INICIAL: 06/03/96

N/REF.: 1484
S/REF.: HI-2915-OR (2 Unidades)
FECHA FINAL: 22/03/96

ANIMAL	SEXO	PESOS CORPORALES (g)		
		PESO 06/03/96	PESO 13/03/96	PESO 19/03/96
10	♂	207	255	298
11	♂	200	251	285
12	♂	184	225	260
13	♂	183	224	262
14	♂	201	244	283
15	♀	176	195	204
16	♀	168	191	205
17	♀	168	192	200
18	♀	167	188	200
19	♀	175	198	211





ANEXO II

PESO DE ORGANOS



TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
 PRODUCTO: Agua
 FECHA INICIAL: 06/03/96

N/REF.: CONTROL
 S/REF.: ---
 FECHA FINAL: 22/03/96

		NUMERO DE ANIMAL				
		1 ♂	2 ♂	3 ♂	4 ♀	5 ♀
P E S O D E O R G A N O S (g)	TIMO	0.51	0.53	0.41	0.59	0.52
	CORAZON	0.86	0.80	0.72	0.67	0.60
	BAZO	0.61	0.87	0.54	0.47	0.63
	HIGADO	10.87	10.84	9.73	7.19	6.95
	PULMONES	1.07	1.17	1.03	1.06	0.97
	RIÑON DCHO.	0.93	0.85	0.79	0.66	0.63
	RIÑON IZQ.	0.87	0.82	0.81	0.65	0.57
	C.SUPRAR. DCHA.	0.04	0.02	0.03	0.04	0.04
	C.SUPRAR. IZQ.	0.04	0.02	0.03	0.04	0.04
	TESTICULO/OVARIO DERECHO	1.34	1.43	1.25	0.05	0.05
	TESTICULO/OVARIO IZQUIERDO	1.39	1.46	1.27	0.04	0.05
	UTERO	---	---	---	0.49	0.89
	ENCEFALO	1.82	1.91	1.59	1.84	1.80
PESO TOTAL		274	269	270	207	212





TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
 PRODUCTO: Preparado Farmacéutico
 FECHA INICIAL: 06/03/96

N/REF.: 1484
 S/REF.: HI-2915-OR (2 Unidades)
 FECHA FINAL: 22/03/96

		NUMERO DE ANIMAL				
		10 ♂	11 ♂	12 ♂	13 ♂	14 ♂
P E S O D E O R G A N O S (g)	ORGANOS					
	TIMO	0.65	0.56	0.49	0.64	0.74
	CORAZON	0.94	0.83	0.75	0.76	0.84
	BAZO	0.61	0.72	0.55	0.66	0.66
	HIGADO	10.90	10.87	8.54	8.60	8.98
	PULMONES	1.27	1.28	1.08	1.08	1.20
	RIÑON DCHO.	0.97	0.87	0.80	0.89	0.86
	RIÑON IZQ.	0.88	0.88	0.86	0.85	0.83
	C.SUPRAR. DCHA.	0.03	0.03	0.03	0.02	0.03
	C.SUPRAR. IZQ.	0.04	0.03	0.03	0.03	0.03
	TESTICULO/OVARIO DERECHO	1.60	1.45	1.32	1.43	1.44
	TESTICULO/OVARIO IZQUIERDO	1.60	1.45	1.45	1.52	1.46
	UTERO	---	---	---	---	---
ENCEFALO	1.99	1.86	1.95	2.01	2.00	
PESO TOTAL		303	287	266	265	288





TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
 PRODUCTO: Preparado Farmaceutico
 FECHA INICIAL: 06/03/96

N/REF.: 1484
 S/REF.: HI-2915-OR (2 Unidades)
 FECHA FINAL: 22/03/96

		NUMERO DE ANIMAL				
		15 ♀	16 ♀	17 ♀	18 ♀	19 ♀
P E S O D E O R G A N O S (g)	ORGANOS					
	TIMO	0.48	0.43	0.55	0.46	0.49
	CORAZON	0.62	0.60	0.63	0.61	0.66
	BAZO	0.50	0.50	0.57	0.49	0.53
	HIGADO	7.98	6.65	6.96	7.35	6.73
	PULMONES	0.92	0.85	1.00	0.97	1.09
	RIÑON DCHO.	0.58	0.58	0.60	0.57	0.67
	RIÑON IZQ.	0.57	0.55	0.58	0.58	0.69
	C.SUPRAR. DCHA.	0.03	0.03	0.03	0.03	0.03
	C.SUPRAR. IZQ.	0.03	0.03	0.03	0.03	0.03
	TESTICULO/OVARIO DERECHO	0.05	0.05	0.05	0.05	0.07
	TESTICULO/OVARIO IZQUIERDO	0.06	0.05	0.05	0.05	0.07
	UTERO	0.40	0.58	0.74	0.64	0.73
ENCEFALO	1.81	1.90	1.83	1.93	2.01	
PESO TOTAL		207	208	211	212	222



ANEXO III

LEUCOCITOS: RECuentOS DIFERENCIALES



TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Agua
FECHA INICIAL: 06/03/96

N/REFERENCIA: CONTROL
S/REF.: ---
FECHA FINAL: 22/03/96

DIA 1

ANIMAL	SEXO	FORMULA LEUCOCITARIA (%)					FECHA: 06/03/96
		NEUTRÓFILOS	EOSINÓFILOS	BASÓFILOS	LINFOCITOS	MONOCITOS	
1	♂	16	1	0	79	4	
2	♂	18	3	0	75	4	
3	♂	32	1	0	62	5	
4	♀	17	1	0	78	4	
5	♀	11	1	0	84	4	





TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Agua
FECHA INICIAL: 06/03/96

N/REFERENCIA: CONTROL
S/REF.: ---
FECHA FINAL: 22/03/96

DIA 3

ANIMAL	SEXO	FORMULA LEUCOCITARIA (%)				FECHA: 08/03/96
		NEUTRÓFILOS	EOSINÓFILOS	BASÓFILOS	LINFOCITOS	MONOCITOS
1	♂	11	0	0	85	4
2	♂	13	1	0	82	4
3	♂	16	0	0	80	4
4	♀	7	0	0	89	4
5	♀	15	1	0	83	1



TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Agua
FECHA INICIAL: 06/03/96

N/REFERENCIA: CONTROL
S/REF.: ---
FECHA FINAL: 22/03/96

DIA 7

ANIMAL	SEXO	FORMULA LEUCOCITARIA (%)				FECHA: 12/03/96
		NEUTRÓFILOS	EOSINÓFILOS	BASÓFILOS	LINFOCITOS	MONOCITOS
1	♂	7	1	0	91	1
2	♂	13	1	0	86	0
3	♂	12	1	0	86	1
4	♀	24	0	0	75	1
5	♀	11	1	0	87	1



TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Agua
FECHA INICIAL: 06/03/96

N/REFERENCIA: CONTROL
S/REF.: ---
FECHA FINAL: 22/03/96

DIA 10

ANIMAL	SEXO	FORMULA LEUCOCITARIA (%)				FECHA: 15/03/96
		NEUTRÓFILOS	EOSINÓFILOS	BASÓFILOS	LINFOCITOS	MONOCITOS
1	♂	13	0	0	84	3
2	♂	30	3	0	63	4
3	♂	16	1	0	82	1
4	♀	19	0	0	81	0
5	♀	25	2	0	69	4



TOXICIDAD A DOSIS REPETIDAS (14 dias) VIA ORAL

EMPRESA : CHACON FARMACEUTICA
PRODUCTO : Agua
FECHA INICIAL : 06/03/96

N/REFERENCIA: 1484
S/REF: HI-2915-(2 Unidades)-OR
FECHA FINAL: 22/03/96

DIA 14

ANIMAL	SEXO	FORMULA LEUCOCITARIA (%)				FECHA: 19/03/96
		NEUTROFILOS	EOSINOFILOS	BASOFILOS	LINFOCITOS	MONOCITOS
1	♂	14	0	0	84	2
2	♂	9	3	0	88	0
3	♂	17	1	0	78	4
4	♀	17	0	0	81	2
5	♀	7	0	0	91	2
6	♂	10	0	0	88	2
7	♂	8	2	0	87	3
8	♀	15	1	0	84	0
9	♀	16	1	0	81	2
10	♀	16	0	0	83	1





TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Preparado farmacéutico
FECHA INICIAL: 06/03/96

N/REFERENCIA: 1484
S/REF.: HI-2915-(2 Unidades)-OR
FECHA FINAL: 22/03/96

DIA 1

ANIMAL	SEXO	FORMULA LEUCOCITARIA (%)				FECHA: 06/03/96
		NEUTRÓFILOS	EOSINÓFILOS	BASÓFILOS	LINFOCITOS	MONOCITOS
10	♂	27	0	0	71	2
11	♂	4	0	0	96	0
12	♂	13	0	0	85	2
13	♂	10	0	0	87	3
14	♂	14	0	0	84	2
15	♀	12	1	0	85	2
16	♀	15	0	0	84	1
17	♀	13	1	0	85	1
18	♀	20	0	0	79	1
19	♀	14	1	0	82	3





TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Preparado farmacéutico
FECHA INICIAL: 06/03/96

N/REFERENCIA: 1484
S/REF.: HI-2915-(2 Unidades)-OR
FECHA FINAL: 22/03/96

DIA 3

ANIMAL	SEXO	FORMULA LEUCOCITARIA (%)			FECHA: 08/03/96	
		NEUTRÓFILOS	EOSINÓFILOS	BASÓFILOS	LINFOCITOS	MONOCITOS
10	♂	12	0	0	86	2
11	♂	9	1	0	90	0
12	♂	9	1	0	88	2
13	♂	6	1	0	90	3
14	♂	13	2	0	84	1
15	♀	6	1	0	88	5
16	♀	6	1	0	90	3
17	♀	19	5	0	75	3
18	♀	14	2	0	83	1
19	♀	8	2	0	86	4





TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Preparado farmacéutico
FECHA INICIAL: 06/03/96

N/REFERENCIA: 1484
S/REF.: HI-2915-(2 Unidades)-OR
FECHA FINAL: 22/03/96

DIA 7

ANIMAL	SEXO	FORMULA LEUCOCITARIA (%)					FECHA: 12/03/96
		NEUTRÓFILOS	EOSINÓFILOS	BASÓFILOS	LINFOCITOS	MONOCITOS	
10	♂	10	0	0	90	0	
11	♂	11	1	0	85	3	
12	♂	14	1	0	85	0	
13	♂	27	1	0	72	0	
14	♂	12	1	0	85	2	
15	♀	12	0	0	87	1	
16	♀	9	1	0	88	2	
17	♀	12	1	0	86	1	
18	♀	13	1	0	84	2	
19	♀	17	2	0	81	0	





TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Preparado farmacéutico
FECHA INICIAL: 06/03/96

N/REFERENCIA: 1484
S/REF.: HI-2915-(2 Unidades)-OR
FECHA FINAL: 22/03/96

DIA 10

ANIMAL	SEXO	FORMULA LEUCOCITARIA (%)				FECHA: 15/03/96
		NEUTRÓFILOS	EOSINÓFILOS	BASÓFILOS	LINFOCITOS	MONOCITOS
10	♂	22	3	0	74	1
11	♂	14	2	0	83	1
12	♂	25	3	0	71	1
13	♂	18	1	0	80	1
14	♂	14	2	0	84	0
15	♀	15	1	0	82	2
16	♀	11	0	0	89	0
17	♀	28	2	0	67	3
18	♀	18	2	0	79	1
19	♀	11	2	0	87	0



TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Preparado farmacéutico
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N/REFERENCIA: 1484
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FECHA FINAL: 22/03/96

DIA 16

ANIMAL	SEXO	FORMULA LEUCOCITARIA (%) FECHAS: 21 Y 22/03/96				
		NEUTRÓFILOS	EOSINÓFILOS	BASÓFILOS	LINFOCITOS	MONOCITOS
10	♂	12	0	0	85	3
11	♂	8	0	0	91	1
12	♂	15	1	0	83	1
13	♂	10	0	0	87	3
14	♂	8	0	0	89	3
15	♀	9	1	0	89	1
16	♀	9	2	0	88	1
17	♀	12	1	0	85	2
18	♀	5	1	0	93	1
19	♀	16	3	0	80	1





ANEXO IV

LEUCOCITOS: RECUENTOS TOTALES



TOXICIDAD A DOSIS REPETIDAS (14 dias) VIA ORAL

EMPRESA : CHACON FARMACEUTICA
PRODUCTO : Agua
FECHA INICIAL : 06/03/96

N/REFERENCIA: CONTROL
S/REF: ---
FECHA FINAL: 22/03/96

RECuento DE LEUCOCITOS/mm ³		FECHA: 19/03/96
ANIMAL	SEXO	LEUCOCITOS/mm ³
1	♂	1200
2	♂	3000
3	♂	1700
4	♀	3000
5	♀	3100
6	♂	2800
7	♂	3200
8	♀	1200
9	♀	1200
10	♀	1800





TOXICIDAD A DOSIS REPETIDAS (14 días) VIA ORAL

EMPRESA: CHACÓN FARMACÉUTICA
PRODUCTO: Preparado farmacéutico
FECHA INICIAL: 06/03/96

N/REFERENCIA: 1484
S/REF.: HI-2915-(2 Unidades)-OR
FECHA FINAL: 22/03/96

RECuento DE LEUCOCITOS/mm ³ FECHAS: 21 Y 22/03/96		
ANIMAL	SEXO	LEUCOCITOS/mm ³
1	♂	4200
2	♂	3050
3	♂	3250
4	♂	4100
5	♂	3850
6	♀	3275
7	♀	2750
8	♀	1675
9	♀	4425
10	♀	1400



ANEXO V

HALLAZGOS DE NECROPSIA



GRUPO: CONTROL	
Sexo: MACHO	Nº animal: 1
ESTOMAGO	Nada anormal
INTESTINO DELGADO	● Inflamación hemorrágica de la pared a nivel de yeyuno
CIEGO	● Inflamación hemorrágica de la pared
INTESTINO GRUESO	Nada anormal
PANCREAS	● Hiperemia en el tejido graso del epiplon alrededor del páncreas
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	● Ganglios linfáticos mesentéricos con bordes hemorrágicos
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal

GRUPO: CONTROL	
Sexo: MACHO	Nº animal: 2
ESTOMAGO	Nada anormal
INTESTINO DELGADO	● Leve enrojecimiento a nivel de ileon
CIEGO	Nada anormal
INTESTINO GRUESO	Nada anormal
PANCREAS	● Hiperemia en el tejido graso del epiplon alrededor del páncreas
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal

GRUPO: CONTROL	
Sexo: MACHO	Nº animal: 3
ESTOMAGO	Nada anormal
INTESTINO DELGADO	● Pequeño foco hemorrágico a nivel de yeyuno
CIEGO	● Pequeño foco hemorrágico en zona aneja al yeyuno
INTESTINO GRUESO	Nada anormal
PANCREAS	● Hiperemia en el tejido graso del epiplon alrededor del páncreas
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal





GRUPO: CONTROL	
Sexo: HEMBRA	Nº animal: 4
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	● Pequeño foco hemorrágico
INTESTINO GRUESO	Nada anormal
PANCREAS	● Hiperemia en el tejido graso del epiplon alrededor del páncreas
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal

GRUPO: CONTROL	
Sexo: HEMBRA	Nº animal: 5
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	● Pequeño foco hemorrágico
INTESTINO GRUESO	Nada anormal
PANCREAS	Nada anormal
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	● Colección de líquido transparente en trompas
OTROS TEJIDOS / ÓRGANOS	Nada anormal



GRUPO: 1484 VIA ORAL HI-2915-OR (2 Unidades)	
Sexo: MACHO	Nº animal: 10
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	Nada anormal
INTESTINO GRUESO	Nada anormal
PANCREAS	Nada anormal
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal

GRUPO: 1484 VIA ORAL HI-2915-OR (2 Unidades)	
Sexo: MACHO	Nº animal: 11
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	● Pequeño foco de inflamación hemorrágica en la pared
INTESTINO GRUESO	Nada anormal
PANCREAS	Nada anormal
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal

GRUPO: 1484 VIA ORAL HI-2915-OR (2 Unidades)	
Sexo: MACHO	Nº animal: 12
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	● Pequeño foco de inflamación hemorrágica en la pared
INTESTINO GRUESO	Nada anormal
PANCREAS	Nada anormal
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal



GRUPO: 1484 VIA ORAL HI-2915-OR (2 Unidades)	
Sexo: MACHO	Nº animal: 13
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	Nada anormal
INTESTINO GRUESO	Nada anormal
PANCREAS	Nada anormal
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal

GRUPO: 1484 VIA ORAL HI-2915-OR (2 Unidades)	
Sexo: MACHO	Nº animal: 14
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	Nada anormal
INTESTINO GRUESO	Nada anormal
PANCREAS	Nada anormal
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal





GRUPO: 1484 VIA ORAL HI-2915-OR (2 Unidades)	
Sexo: HEMBRA	Nº animal: 15
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	Nada anormal
INTESTINO GRUESO	Nada anormal
PANCREAS	Nada anormal
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal

GRUPO: 1484 VIA ORAL HI-2915-OR (2 Unidades)	
Sexo: HEMBRA	Nº animal: 16
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	Nada anormal
INTESTINO GRUESO	Nada anormal
PANCREAS	Nada anormal
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal

GRUPO: 1484 VIA ORAL HI-2915-OR (2 Unidades)	
Sexo: HEMBRA	Nº animal: 17
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	• Leve inflamación hemorrágica de la pared
INTESTINO GRUESO	Nada anormal
PANCREAS	Nada anormal
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	• Colección de líquido transparente en las trompas
OTROS TEJIDOS / ÓRGANOS	Nada anormal



GRUPO: 1484 VIA ORAL HI-2915-OR (2 Unidades)	
Sexo: HEMBRA	Nº animal: 18
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	Nada anormal
INTESTINO GRUESO	Nada anormal
PANCREAS	Nada anormal
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	Nada anormal
OTROS TEJIDOS / ÓRGANOS	Nada anormal

GRUPO: 1484 VIA ORAL HI-2915-OR (2 Unidades)	
Sexo: HEMBRA	Nº animal: 19
ESTOMAGO	Nada anormal
INTESTINO DELGADO	Nada anormal
CIEGO	● Muy leve inflamación hemorrágica en la pared
INTESTINO GRUESO	Nada anormal
PANCREAS	Nada anormal
GRASA ABDOMINAL	Nada anormal
GANGLIOS LINFÁTICOS	Nada anormal
REPRODUCTOR Y ANEJOS	● Colección de líquido transparente en las trompas
OTROS TEJIDOS / ÓRGANOS	Nada anormal





ANNEX VI



ORAL

NEUTROPHILS

EOSINOPHILS

BASOPHILS

LYNFOCYTES

MONOCYTES

LEUCOCYTES

10	12	0	0	0	85	3	4200
11	8	0	0	0	91	1	3000
12	15	1	0	0	83	1	3000
13	10	0	0	0	87	3	3000
14	8	0	0	0	89	3	3000
15	9	1	0	0	89	1	3000
16	9	2	0	0	88	1	3000
17	12	1	0	0	85	2	3000
18	5	1	0	0	93	1	3000
19	16	3	0	0	80	1	1400

SUM
 MEAN
 STD
 NUM
 X2
 m*n
 m2*n

104,00	9,00	0,00	870,00	17,00	31975,00
10,40	0,90	0,00	87,00	1,70	3197,50
3,37	0,99	0,00	3,86	0,95	1029,12
10,00	10,00	10,00	10,00	10,00	10,00
1184,00	17,00	0,00	75824,00	37,00	111771875,00
104,00	9,00	0,00	870,00	17,00	31975,00
1081,60	8,10	0,00	75690,00	28,90	102240062,50

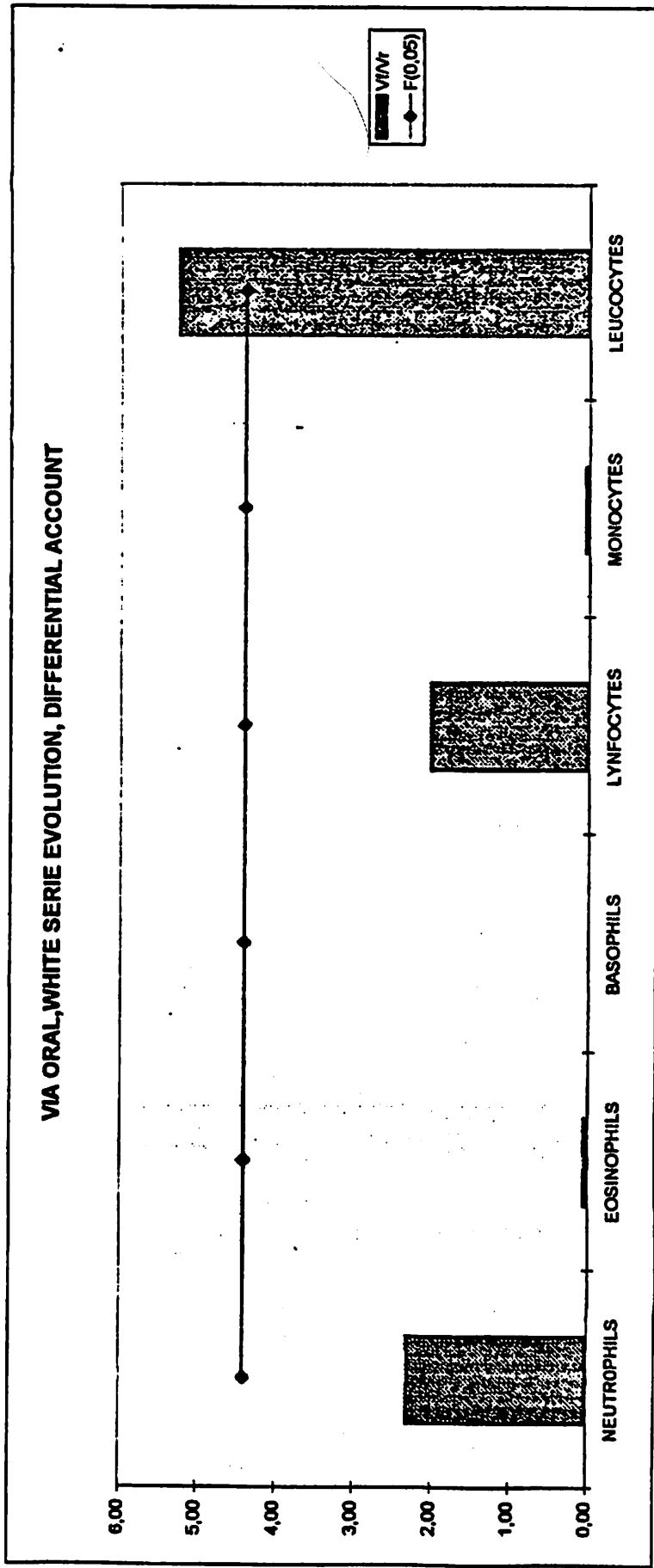


A-VARIANZA	NEUTROPHILS	EOSINOPHILS	BASOPHILS	LYNFOCYTES	MONOCYTES	LEUCOCYTES
N	20,00	20,00	20,00	20,00	20,00	20,00
M	11,65	0,85	0,00	85,75	1,75	2708,75
N°M2	2714,45	14,45	0,00	147061,25	61,25	146746531,25
m2*n	2745,70	14,50	0,00	147092,50	61,30	151524062,50
caX2	2989,00	33,00	0,00	147369,00	83,00	167911875,00
K	2,00	2,00	2,00	2,00	2,00	2,00
m2n-M2n	31,25	0,05	0,00	31,25	0,05	4777531,25
Vf	31,25	0,05	0,00	31,25	0,05	4777531,25
X2-m2n	243,30	18,50	0,00	276,50	21,70	16387812,50
Vr	13,52	1,03	0,00	15,36	1,21	910434,03
Vf/Vr	2,31	0,05	#1DIV/01	2,03	0,04	5,25
F=K-1	1,00					
F=N-K	18,00					
Velor F	0,05	4,41				
	0,01	8,28				



**EFFICIENCY IN RATES, ORAL TREATMENT
EVOLUTION OF THE WHITE SERIES
STATISTICS MEANING, VARIANCE ANALYSIS**

	NEUTROPHILS	EOSINOPHILS	BASOPHILS	LYNFOCYTES	MONOCYTES	LEUCOCYTES
V/Nr	2,31	0,05	#IDV/01	2,03	0,04	5,25
F(0,05)	4,41	4,41	4,41	4,41	4,41	4,41





**EFFICIENCY IN RATES, ORAL TREATMENT
EVOLUTION OF THE WHITE SERIES
STATISTICS MEANING, VARIANCE ANALYSIS**

CONTROL	NEUTROPHILS	EOSINOPHILS	BASOPHILS	LYMPHOCYTES	MONOCYTES	LEUCOCYTES
1	168	0	0	0	1008	24
2	270	90	0	0	2640	0
3	289	17	0	0	1326	68
4	510	0	0	0	2430	60
5	217	0	0	0	2821	62
6	280	0	0	0	2464	56
7	256	64	0	0	2784	96
8	180	12	0	0	1008	0
9	192	12	0	0	972	24
10	288	0	0	0	1494	18
SUM	2650,00	195,00	0,00	0,00	18947,00	408,00
MEAN	265,00	19,50	0,00	0,00	1894,70	40,80
STD	97,60	31,57	0,00	0,00	797,41	32,06
NUM	10,00	10,00	10,00	10,00	10,00	10,00
X2	787978,00	12773,00	41621717,00	41621717,00	25896,00	56140000,00
m*n	2650,00	195,00	0,00	0,00	18947,00	22200,00
m2*n	702250,00	3802,50	0,00	0,00	16646,40	49284000,00



A.VARIANZA	NEUTROPHILS	EOSINOPHILS	BASOPHILS	LYNFOCYTES	MONOCYTES	LEUCOCYTES
ORAL						
N	20,00	20,00	20,00	20,00	20,00	20,00
M	289,60	20,91	0,00	2348,86	49,38	2708,75
N*M2	1677363,20	8746,65	0,00	110343100,88	48757,81	146746531,25
m2*g	1689466,40	8786,56	0,00	114468372,41	50228,43	151524062,50
X2 N	1889812,63	21929,44	0,00	128379828,94	77332,88	167911875,00
K	2,00	2,00	2,00	2,00	2,00	2,00
m2n-M2n	12103,20	39,90	0,00	4125271,53	1470,61	4777531,25
Vf	12103,20	39,90	0,00	4125271,53	1470,61	4777531,25
X2-m2n	200346,23	13142,88	0,00	13911456,53	27104,45	16387812,50
Vr	11130,35	730,16	0,00	772858,70	1505,80	910434,03
Vf/Vr	1,09	0,05	#1DIV/01	5,34	0,98	5,25
F=K-1	1,00					
F=N-K	18,00					
Valor F	0,05	4,41				
	0,01	8,28				



**EFFICIENCY IN RATES, ORAL TREATMENT
EVOLUTION OF THE WHITE SERIES
STATISTICS MEANING, VARIANCE ANALYSIS**

	NEUTROPHILS	EOSINOPHILS	BASOPHILS	LYNFOCYTES	MONOCYTES	LEUCOCYTES
V1/r	1,09	0,05	#1DIV101	5,34	0,98	5,25
F(0.05)	4,41	4,41	4,41	4,41	4,41	4,41

