REPORT N° CD 98/6288T

FOUR-WEEK INTRAVENOUS DOSE RANGE-FINDING STUDY IN RATS.

TEST SUBSTANCE: IQB-9302. HCl

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Head Toxicology Department:	J. Zapatero Biologist
Study Director:	L. Canut Biologist
Histopathologist:	J. Alumà Medical Doctor and Surgeon
Formulation:	C. Santasusagna Biologist
Sponsor :	LABORATORIOS INIBSA, S.A. c/Loreto, 8 08029-BARCELONA Spain Tel.: 34 93 321 54 08 Fax : 34 93 843 96 95
Sponsor's Monitoring Scientist:	A. Galiano
Testing facilities:	CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. Centro Industrial Santiga c/Argenters, 6 08130-SANTA PERPÈTUA DE MOGODA (Barcelona) - Spain Tel. : 34 93 719 03 61 Fax : 34 93 718 96 67
Typed by: N. Pérombelon	
Date Report Issued:	

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No. pages in Report : 129

This Study was carried out according to the Good Laboratory Practice regulations published by the OECD (OECD Principles of Good Laboratory Practice, C (81) 30 (Final), Paris, 12th May, 1981. Annex 2), and adopted by the EEC (now EU) according to Directive 87/18/EEC of 18th December 1986 and in Spain by Real Decreto 822/1993, of 28th May.

No circumstances which could affect the reliability of the data obtained in the Study were recorded.

Head Toxicology Dpt. :

J. Zapatero — 1 March 1999 — Date

Study Director :

L. Canut — 1 March 1999 — Date

Histopathologist:

J. Aluma — 1 MARCH 1999 — Date

Formulation:

C. Santasusagna — 1 MARCH 1999 — Date

The results presented in this Report refer only to the sample(s) received and tested, as indicated in the corresponding section.

QUALITY ASSURANCE UNIT (QAU)

Inspection of Study no. **CD-98/6288T**

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The inspection dates are as follows :

DATE	*PHASE*	*QAU INSPECTION NUMBER*	*REPORTS TO MANAGEMENT*
30.SEP.98	*PROTOCOL*	15383	01.OCT.98
02.NOV.98	*FORMULATION*	15530	03.NOV.98
05.NOV.98	*WEIGHING, i.v. ADMINISTRATION AND CLINICAL SIGNS*	15543	06.NOV.98
20.NOV.98	*AUTOPSIES AND WEIGHING OF ORGANS*	15655	03.DEC.98
23.FEB.99	*FINAL REPORT*	16014	26.FEB.99

GLORIA SEGARRA — 1-March.1999

A. Flores — Date

Quality Assurance Unit

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REPORT NO. CD-98/6288T

FOUR-WEEK INTRAVENOUS DOSE-RANGE-FINDING STUDY IN RATS.

TEST SUBSTANCE: IQB-9302.HCl

SUMMARY

The test substance IQB-9302.HCl was administered intravenously, by bolus, to Crl:CD® (SD) BR Sprague-Dawley rats, for 4 consecutive weeks at the doses of 1, 2 and 4 mg/kg/day.

Each treatment group, including the Control group, consisted of five males and five females.

The Control group animals were treated with physiological saline under the same conditions as the rest of the treatment groups.

No mortality was registered among the animals belonging to the Control group nor in the animals treated with the test substance at the dose of 1 mg/kg/day.

Three animals treated at the dose of 2 mg/kg/day and nine animals treated at the dose of 4 mg/kg/day died during the treatment period.

The main clinical signs observed in the animals administered at the doses of 2 and 4 mg/kg/day were basically, ataxia, clonic convulsions, dyspnoea, decreased muscle tone, salivation, pallor and prostration. Similarly, some of the animals presented rigidity of the tail and the hindquarters.

In all cases, the clinical signs started immediately after administration and, in the case of the animals that survived the treatment, disappeared in the course of the six minutes post-administration.

The increase in bodyweight of the males treated with the test substance at the doses of 1, 2 and 4 mg/kg/day and the females treated at the doses of 1 and 2 mg/kg/day was similar to that of the Control group.

The bodyweight increase of the females treated with the test substance at the dose of 4 mg/kg/day was, from the 15th day of treatment, greater than that of the Control group.

The food intake in males treated with IQB-9302.HCl at the three doses administered and in females at the doses of 1 and 2 mg/kg/day was similar to that of the Control group but the intake of the females at 4 mg/kg/day was higher than that to the Control animals.

No organ weight alterations related to the treatment given were recorded at the different doses administered.

No macroscopic alterations were registered in the necropsies performed.

The microscopic examination of the hepatic samples revealed an increase in hepatocytary mitosis in two and six of the animals treated with IQB-9302 HCl at the doses of 2 and 4 mg/kg/day, respectively. No hepatic alterations were observed in the samples from the animals treated at the dose of 1 mg/kg/day.

The microscopic examination of the kidneys samples did not reveal any alterations in the samples from the animals treated at the three doses of IQB-9302.HCl.

CONCLUSIONS

In accordance with the results of this Study, the high dose to be used in the main Study should be between 2 and 2.5 mg/kg.

REPORT NO. CD-98/6288T

FOUR-WEEK INTRAVENOUS DOSE-RANGE-FINDING STUDY IN RATS.

TEST SUBSTANCE: IQB-9302.HCl

INTRODUCTION

The aim of this Study is to evaluate the toxicity of the test substance IQB-9302.HCl, a local anaesthetic, when administered intravenously to rats during a period of four weeks, so as to determine the adequate dose levels for a four-week toxicity Study.

This route has been chosen because it is the proposed route for administration to humans.

2. EXPERIMENTAL PROCEDURE

2.1. Animals

2.1.1. Supply

A total of 50 rats (25 males and 25 females) of the Crl:CD® (SD) BR Sprague-Dawley strain with an approximate age of 28 days and from CHARLES RIVER were supplied by CRIFFA, S.A. (c/Paraires, 1-7, Nave 5, Polígono Industrial Santiga, 08130-STA. PERPÈTUA DE MOGODA, Barcelona, Spain) on 21st October 1998.

On their arrival a sample of animals was chosen at random and weighed to ensure compliance with the age requested. The mean weights of males and females were 82 g and 84 g respectively.

The animals were housed in Makrolon cages (55 x 32.7 x 19 cm), with sawdust litter, in such a way that each cage contained a maximum of 5 animals of the same sex.

All animals underwent a period of 12 days of observation and acclimatization between the date of arrival and the start of treatment. During the course of this period, the animals were inspected by a veterinary surgeon to ensure that they fulfilled the health requirements necessary for initiation of the Study.

During the acclimatization period, 40 animals (20 males and 20 females) were selected for the Study. They were distributed among the experimental groups using a random distribution method. This procedure allows approximate equalization of initial bodyweights whilst allowing random allocation to experimental groups.

2.1.2. Identification

The rats were individually identified by numbers tattooed on the ears.

The marking of the animals was performed when the animals were distributed among the study groups.

2.1.3. Housing

The rats were housed in Makrolon cages (55 x 32.7 x 19 cm), placed on racks. The cages had sawdust on the floor (Ultrasorb, Panlab, S.L. Mejía Lequerica, 34, Barcelona, Spain) as litter. From the week before initiation of the treatment, each cage contained a maximum of 5 rats of the same sex and treatment group.

Each cage was identified by a card, colour coded according to the dose level. This card stated the cage number, number and sex of the animals it contained, Study number, test substance code, administration route, dose level and Study Director's name, date of the arrival of the animals and initiation of treatment.

The temperature and relative humidity were continuously monitored. The temperature was between 19ºC and 25ºC. The relative humidity was generally maintained at 40-70%. Humidity indices lower than 40% and higher than 70% were avoided for prolonged periods.

Lighting was controlled to supply 12 hours of light (7:00 to 19:00 hours) and 12 hours of dark for each 24-hour period.

The cages corresponding to each experimental group were distributed on racks in such a manner that external factors, such as environmental conditions, were balanced as far as possible.

2.2. Diet

All the rats had free access to a pelleted rat diet UAR A04C (Usine d'Alimentation Rationnelle, 91360-Villemoisson sur Orge, France) batch no. 80507.

The diet was analyzed by the manufacturer to check its composition and to detect possible contaminants.

Appendix I shows the diet analysis certificate.

2.3. Water

The water, supplied by the Compañía de Aguas de Sabadell, S.A. was offered *ad libitum* in bottles. The water was periodically analyzed to detect the presence of possible contaminants.

Appendix II shows the water analysis certificate.

2.4. Test substance

2.4.1. Identification

The substance IQB-9302.HCl, a local anaesthetic, was tested. This product was supplied by the Sponsor.

On 9th October 1998, Centro de Investigación y Desarrollo Aplicado, S.A.L. received approximately 8 g of IQB-9302.HCl lot 9454.001 in the form of a white powder supplied in a topaz crystal vial. It was stored at room temperature.

Appendix III contains the analysis certificate of the IQB-9302.HCl.

At the end of the Study a sample of the product was taken, which will be stored in the archives of Centro de Investigación y Desarrollo Aplicado, S.A.L. for 5 years from the date of issue of the Final Report or until its expiry date. The remainder will be returned to the Sponsor.

2.4.2. Formulation of the test substance

The test substance was prepared daily and dissolved in physiological saline.

2.4.3. Formulation analysis

Prior to the beginning of the treatment period and in the course of the first and third weeks of administration samples of the formulations to be administered were sent to the Sponsor for the quantification of their IQB-9302.HCl content. The samples were sent at room temperature.

The results of the formulation analyses are shown in Appendix IV.

2.4.4. Administration route

The test substance, IQB-9302.HCl, was administered intravenously, by bolus, in the tail vein, using a 23G (0.6 x 25 mm) sterile disposable needle.

The injection rate was 0.1 mL/second approximately.

This route has been chosen because it is the proposed route for administration to humans.

The rats belonging to the Control group were treated with the vehicle (physiological saline), at the same administration volume as the rest of the treatment groups.

2.4.5. Administration volume

The administration volume was 4 mL/kg.

The quantity of test substance administered to each animal was calculated from its bodyweight on the day of treatment.

2.4.6. Dose levels and group sizes

The 40 rats selected for the Study were distributed into four groups each consisting of 5 males and 5 females using a random distribution method.

Group	Treatment	Dose (mg/kg/day)	Animal no.		Colour code
			Males	Females	
1	CONTROL (vehicle)	-	1-5	21-25	White
2	IQB-9302.HCl	1	6-10	26-30	Blue
3	IQB-9302.HCl	2	11-15	31-35	Green
4	IQB-9302.HCl	4	16-20	36-40	Red

2.4.7. Frequency and duration of treatment

The tested substance was administered once a day, seven days a week during 4 weeks.

3. OBSERVATIONS

3.1. Clinical signs

All the rats were observed at least twice daily with the purpose of recording any symptoms of ill-health or behavioural changes. These observations were also performed on week-ends. The observations included but were not limited to changes in skin and fur, in the eyes and mucous membranes, in the respiratory, circulatory, central nervous and autonomous systems, somatomotor activity and behaviour.

3.2. Bodyweight

The bodyweight of each rat was recorded one week before the start of treatment, daily during the course of the same and on the day of sacrifice. The mean weights for the different groups and sexes were calculated from the individual weights.

3.3. Food intake

Prior to the beginning of treatment, and afterwards once a week, the food intake of each cage was recorded and the mean weekly intake per rat was calculated.

4. TERMINAL STUDIES

4.1. Macroscopic examination

After four weeks of treatment, all the rats were sacrificed by CO_2 inhalation.

A complete autopsy was performed on all the animals. This included the examination of the external surface of the body, all the orifices, the cranial, thoracic and abdominal cavities and their contents *in situ* and after evisceration.

The autopsies were carried out on one day.

4.2. Organ weights

After the macroscopic examination the following organs were weighed after separating the superficial fat:

Adrenals	Pituitary
Brain	Prostate and seminal vesicles
Heart	Spleen
Kidneys	Testes and epididymes
Liver	Thymus
Lungs	Thyroids
Ovaries	Uterus

4.3. Taking of histological samples

Samples were taken of the following organs and tissues of all the animals and fixed in 10% neutral buffered formalin, with the exception of the eyes, which were preserved in Davidson's fixative:

Adrenal glands	Colon
Aorta	Eyes and optic nerves
Bone (sternum)	Femur (with joint)
Brain (bulbar, cerebellar and cortical sections)	Heart (with papillary muscle)
	Injection site (tail)
Caecum	Kidneys

Liver	Spinal cord (cervical, thoracic and lumbar)
Lungs and mainstem bronchi	Spleen
Lymphatic nodes (submandibular and mesenteric)	Stomach
Mammary gland	Testes and epididymides
Oesophagus	Thymus
Ovaries	Thyroids and parathyroids
Pancreas	Tissue masses or tumours (including regional lymph nodes)
Pituitary	Tongue
Prostate	Trachea
Salivary glands	Urinary bladder
Sciatic nerve	Uterus (corpus and cervix)
Seminal vesicles	Vagina
Skeletal muscle	And any other organ or tissue with macroscopic alterations.
Skin (abdominal)	
Small intestine (duodenum, jejunum and ileum)	

A bone marrow smear (femur) was taken, dried in air and fixed with anhydrous methanol.

4.4. Histopathological examination

Liver and kidney samples were embedded in paraffin and stained with haematoxylin and eosin (phloxine variant).

The microscopic examination was limited to :

- Observation of the liver and kidneys of all the animals treated with IBQ-9302.HCl at the high dose and the Control group animals and the liver and kidneys of the animal that died before the end of the treatment.

- All of the organs and tissues that presented macroscopic alterations.

5. STATISTICAL EVALUATION

The bodyweights and the organ weights were evaluated by the one-way analysis of the variance, and if this was found to be significant, the significant differences between the different groups were evaluated using the Duncan-Kramer method[1].

In the tables statistical significance is represented by an S. ($p<0.05$) at the bottom of the corresponding column. The letters A, B, C and D represent the mean values for the Control group and groups 2, 3 and 4 respectively.

The letters are placed in ascending order and may be interpreted statistically as follows :

- The difference between two means underlined by the same line is not statistically significant, according to the Duncan-Kramer test ($p<0.05$).

- The difference between two means not underlined by the same line is statistically significant, according to the Duncan-Kramer test ($p<0.05$).

In the tables the letters N.S. mean that for the corresponding parameters, the differences between mean values for the stated groups are not statistically significant.

6. ARCHIVES

All the data of this Study, including histological preparations and tissues, will be stored in the archives at Centro de Investigación y Desarrollo Aplicado, S.A.L. for at least 5 years. All the tissues preserved in formalin will be stored for a period of two years after the end of the Study.

[1] a) Duncan D.B. Multiple range and multiple F test.
Biometrics 11, 1-42 (1955).
b) Kramer C.Y. Extension of multiple range test to group means with unequal number of replication.
Biometrics 12, 307 (1956).

No material relating to this Study will be destroyed without the prior written consent of the Sponsor.

7. STUDY FACILITIES

This Study was conducted in the laboratories and animal housing of the Toxicology Department of Centro de Investigación y Desarrollo Aplicado, S.A.L., Centro Industrial Santiga, c/Argenters 6, 08130-SANTA PERPÈTUA DE MOGODA, Barcelona (Spain).

The histopathological examination of the histological preparations was performed at the Centro de Histopatología Veterinaria, c/Castellnou 21, 08017-BARCELONA (Spain).

8. STUDY DATES

The duration of the Study was the following:

Protocol signed : 9th October 1998

Protocol amendment no. 1 accepted : 29th October 1998

Date animals arrived : 21st October 1998

Beginning of treatment period : 2nd November 1998

End of treatment period : 30th November 1998

Report issued : See page I

9. EXPERIMENTAL PROTOCOL AND AMENDMENTS

Appendix V contains the experimental protocol.

Appendix VI presents the protocol amendment approved in the course of the Study.

10. STANDARD OPERATING PROCEDURES

All procedures of this Study were carried out according to the Centro de Investigación y Desarrollo Aplicado, S.A.L. Standard Operating Procedures.

11. DIRECTIVES

The Study procedures described in this Report are in accordance with Directive 91/507/EEC relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products (Annex, Part 3 referring to Toxicological and Pharmacological testing) and Annex I of recommendation 83/571/EEC.

12. RESULTS

12.1. Mortality

The mortalities recorded in the course of the Study are shown in Table no. 1.

There were no mortalities among the Control group animals, nor among the animals treated with IQB-9302.HCl at the dose of 1 mg/kg/day.

Of the 10 animals administered at the dose of 2 mg/kg/day, three of them died in the course of treatment (on the 9th, 10th and 25th days of treatment).

Of the 10 animals administered at the dose of 4 mg/kg/day, nine of them died during the treatment period.

One male died on the 1st day of administration, two males and one female on the 2nd day, two males and two females on the 4th day and one female on the 27th day of administration.

In all cases, the deaths occurred in the course of the first 6 minutes after administration.

12.2. Clinical signs

The frequency of the clinical signs according to sex and treatment group is shown in Table no. 2.

One animal from the Control group and two animals administered with IQB-9302.HCl at the dose of 1 mg/kg/day presented occasionally decreased muscle tone.

All of the animals treated at the dose of 2 mg/kg/day presented ataxia accompanied by clonic convulsions and dyspnoea. Nine of the animals administered at this dose presented salivation, as well as tail rigidity and prostration. In addition, four of the animals presented decreased muscle tone and seven animals showed pallor of mucosas. These clinical signs were observed intermittently in the course of the Study, starting immediately after administration and then disappearing in the course of the 5 minutes post-administration.

All of the animals treated at the doses of 4 mg/kg/day presented clonic convulsions, dyspnoea, pallor, salivation and prostration. These alterations were accompanied by rigidity of the tail in four animals, rigidity of the hindquarters in two animals, ataxia in three animals and decreased muscle tone in three animals. In all cases, these clinical signs were observed intermittently during the Study, starting immediately after administration and in the case of the animals that survived, disappearing in the course of the 6 minutes post-administration.

12.3. Bodyweight

The bodyweight increase, according to sex and treatment group, is shown in Figures nos. 1 and 2 and Tables nos. 3 and 4.

The individual values for each animal are shown in Tables nos. 12 to 15.

The increase in bodyweight of the males treated with the test substance at the doses of 1, 2 and 4 mg/kg/day and the females treated at the doses of 1 and 2 mg/kg/day was similar to that of the Control group.

The increase in bodyweight of the females treated with the test substance at the dose of 4 mg/kg/day was, from the 15th day of treatment, greater than that of the

Control group. This increase is probably a consequence of the mortalities that occurred among the animals in this cage.

12.4. Food intake

Tables nos. 5 and 6 contain the weekly mean food intake of the males and females pertaining to the different treatment groups.

The food intake in males treated with the test substance at the three doses administered was similar to that observed in the Control group.

The food intake in females treated with IQB-9302.HCl at the doses of 1 and 2 mg/kg/day was similar to that of the Control group but the food intake of the females administered at 4 mg/kg/day was higher than that of the Control group.

13. TERMINAL STUDIES

13.1. Organ weights

The mean values of the absolute and relative organ weights according to sex and treatment group can be found in Tables nos. 7 to 10.

The individual values can be found in Tables nos. 16 to 31.

No alterations related to the treatment given were recorded.

13.2. Macroscopic alterations

No macroscopic alterations were recorded among the animals treated at the doses of 1, 2 and 4 mg/kg/day, nor in the animals from the Control group.

13.3. Microscopic observations

The frequencies of the microscopic observations by organ, sex and treatment group can be found in Table no. 11.

The microscopic examination of the hepatic samples revealed the presence of a hepatic alteration characterized by an increase in the number of hepatocytes undergoing mitosis. There were no alterations noted in the renal samples.

A) MICROSCOPIC FINDINGS RELATED TO THE TREATMENT

LIVER

Increase in the number of hepatocytes undergoing mitosis

IQB-9302.HCl (2 mg/kg/day): 14 M, 34 F

(4 mg/kg/day): 16 M, 17 M, 18 M, 19 M, 36 F, 39 F

B) MICROSCOPIC FINDINGS NOT RELATED TO THE TREATMENT

LIVER

Microgranuloma

Control: 4 M, 5 M, 22 F, 25 F

IQB-9302.HCl (1 mg/kg/day): 26 F

(4 mg/kg/day): 40 F

KIDNEYS

Lymphocytary infiltrate, interstitial, focal, subcapsular

IQB-9302.HCl (2 mg/kg/day): 14 M

Slight pyelitis, chronic

IQB-9302.HCl (4 mg/kg/day): 40 F

Cyst, cortical, simple, unilateral

Control: 2 M

13.4. Histopathological summary

The microscopic observation of the hepatic samples of the groups treated with the test substance IQB-9302.HCl at the doses of 2 and 4 mg/kg/day revealed an

alteration characterized by an increase in hepatocytary mitosis, sign of hepatocytary hyperplasia.

This alteration was observed in two animals (14 M, 34 F) and six animals (16 M, 17 M, 18 M, 19 M, 36 F, 39 F) treated with IQB-9302.HCl at the doses of 2 and 4 mg/kg/day, respectively.

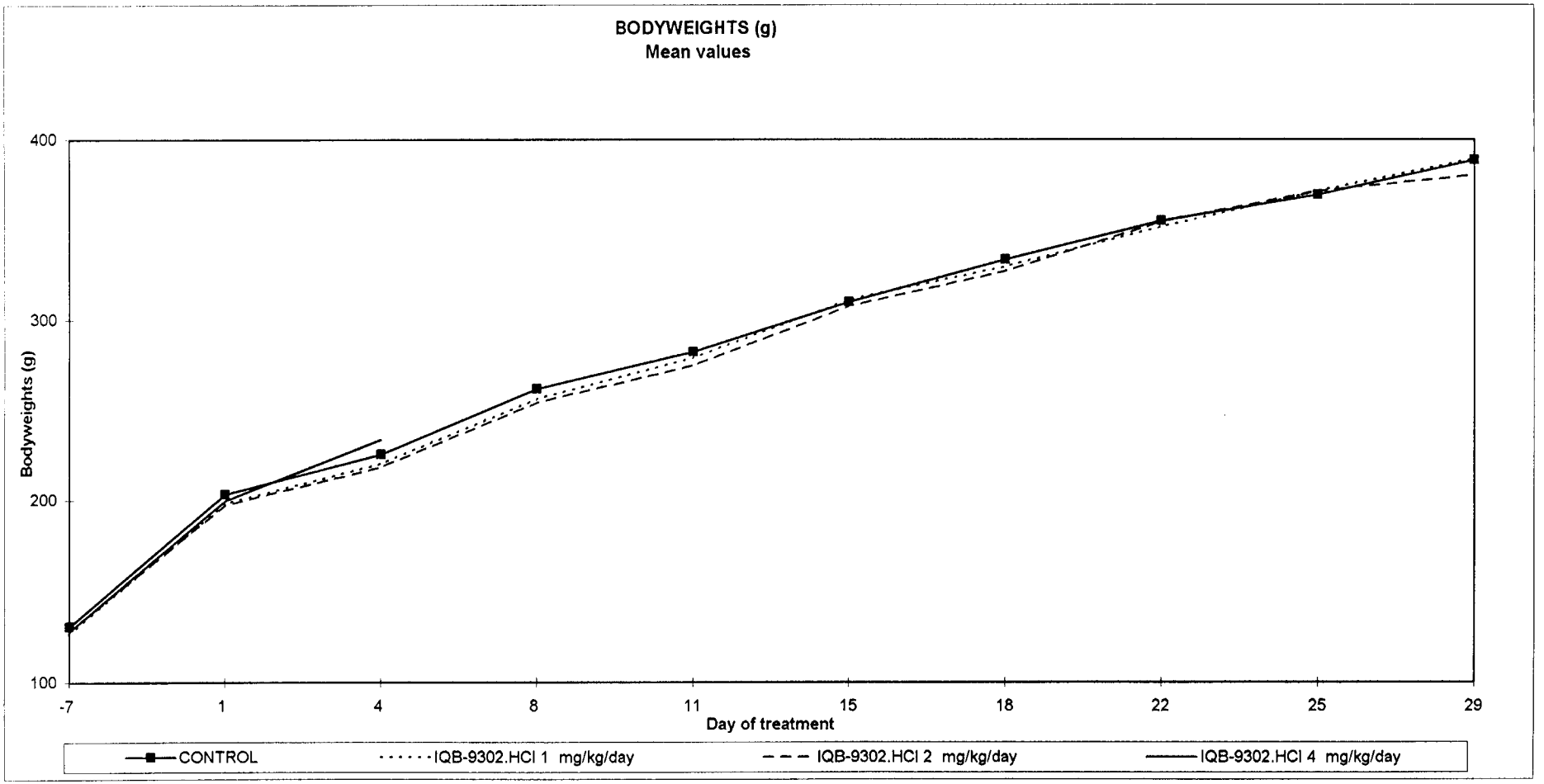
None of the animals treated with IQB-9302.HCl at the dose of 1 mg/kg/day presented this hepatic alteration.

No renal alterations related to the administration of the test substance IQB-9302.HCl at the doses of 1, 2 and 4 mg/kg/day were observed.

The rest of the microscopic findings are not related to the administration of the test substance and are common in this type of laboratory animal.

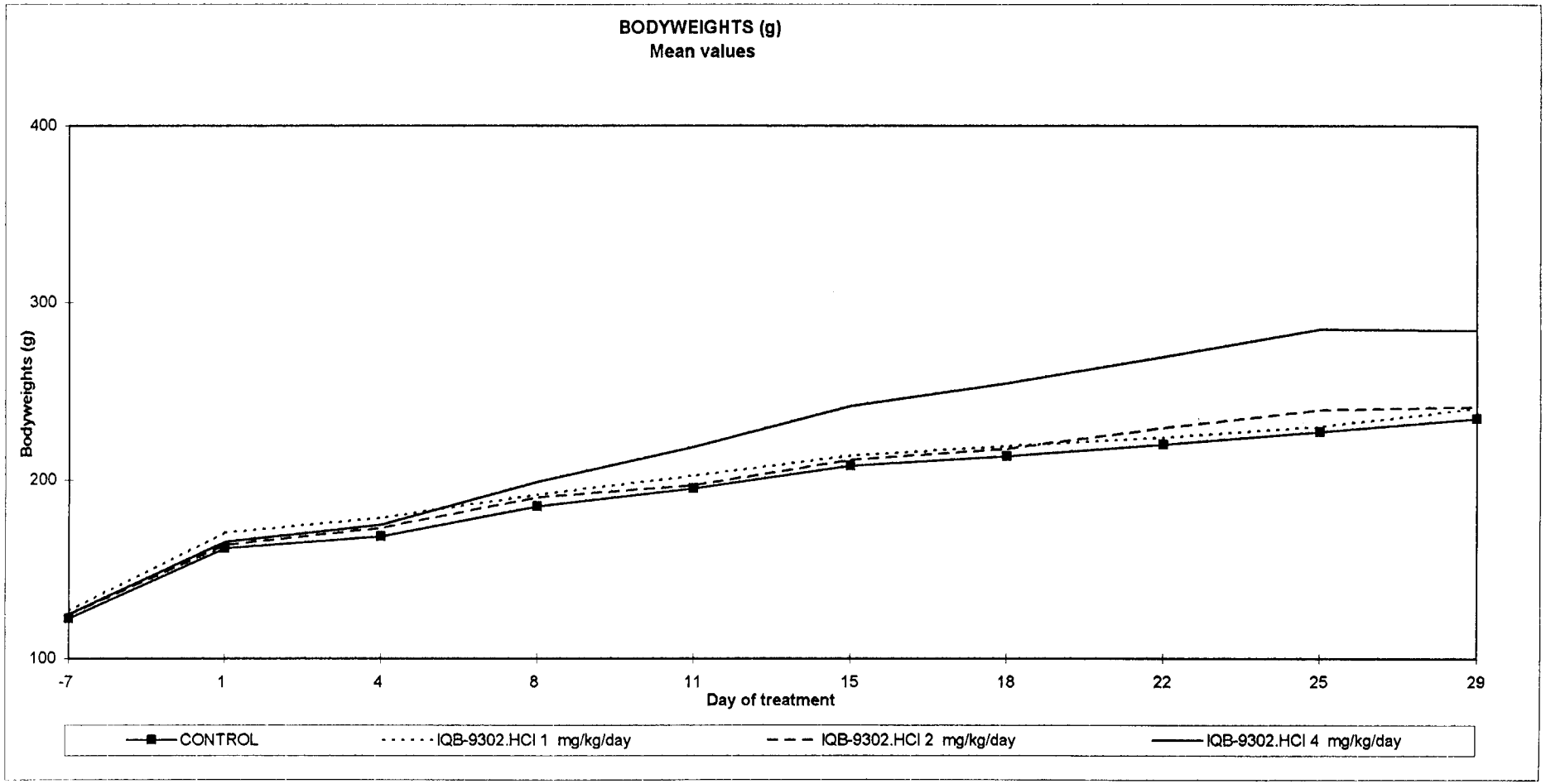
CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Figure no.: 1

Study no.: CD-98/6288T
Sex: Male



CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Figure no.: 2

Study no.: CD-98/6288T
Sex: Female



MORTALITES RECORDED

Treatment mg/kg/day	Animal		No. of administrations given	Study week
	No.	Sex		
CONTROL -	-	-	-	-
IQB-9302.HCl 1	-	-	-	-
IQB-9302.HCl 2	14	M	25	4
	31	F	9	2
	34	F	10	2
IQB-9302.HCl 4	16	M	1	1
	17	M	2	1
	18	M	2	1
	19	M	4	1
	20	M	4	1
	36	F	4	1
	37	F	2	1
	39	F	4	1
	40	F	27	4

NUMBER OF ANIMALS WITH CLINICAL SIGNS IN THE COURSE OF TREATMENT

CLINICAL SIGNS	Treatment group	CONTROL		IQB-9302.HCl mg/kg/day 1		2		4	
	Sex	M	F	M	F	M	F	M	F
	Animal/group	5	5	5	5	5	5	5	5
Decreased muscle tone			1	2		3	1	1	2
Ataxia						5	5		3
Clonic convulsions						5	5	5	5
Decreased motor activity						1			
Dyspnoea						5	5	5	5
Salivation						5	4	5	5
Tail rigidity						5	4		4
Rigidity of hindquarters						1	1		2
Prostration						5	4	5	5
Pallor						4	3	5	5

CENTRO DE INVESTIGACIÓN Y
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Toxicology Department
Table no.: 3

BODYWEIGHTS (g)
Mean values

Study no.: CD-98/6288T
Sex: Male

	TREATMENT DOSE mg/kg/day		Treatment day -7	1	4	8	11	15	18	22	25	29
A:	CONTROL --	MEAN	130.8	203.6	225.6	261.8	282.6	310.2	333.8	355.2	369.8	388.8
		S.D.	6.02	8.71	10.81	10.73	12.44	13.41	11.69	11.73	11.01	11.17
		n	5	5	5	5	5	5	5	5	5	5
B:	IQB-9302.HCl 1	MEAN	126.6	198.6	220.6	256.2	279.2	311.4	329.8	352.0	371.6	389.6
		S.D.	6.02	8.20	6.80	7.98	7.56	8.62	12.21	11.53	10.50	7.92
		n	5	5	5	5	5	5	5	5	5	5
C:	IQB-9302.HCl 2	MEAN	127.8	197.6	218.6	254.2	274.8	307.8	327.2	354.8	371.8	380.5
		S.D.	7.66	12.14	10.04	13.42	18.35	19.55	23.68	26.19	28.46	8.35
		n	5	5	5	5	5	5	5	5	5	4
D:	IQB-9302.HCl 4	MEAN	128.2	200.0	234.0							
		S.D.	7.92	13.60	1.41							
		n	5	5	2							
One-way analysis of variance ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 4

BODYWEIGHTS (g)
Mean values

Study no.: CD-98/6288T
Sex: Female

	TREATMENT DOSE mg/kg/day		Treatment day -7	1	4	8	11	15	18	22	25	29
A:	CONTROL	MEAN	122.6	162.0	168.4	185.4	195.4	208.4	213.8	220.4	227.6	235.2
	--	S.D.	4.39	8.46	12.05	12.80	11.89	12.18	11.86	11.28	13.28	12.74
		n	5	5	5	5	5	5	5	5	5	5
B:	IQB-9302.HCl	MEAN	126.6	170.6	179.0	191.8	202.8	214.0	219.6	224.4	230.6	240.8
	1	S.D.	5.68	7.16	6.04	7.85	7.73	8.43	9.07	9.50	11.67	11.84
		n	5	5	5	5	5	5	5	5	5	5
C:	IQB-9302.HCl	MEAN	124.4	163.8	173.2	190.4	197.3	211.7	218.0	229.7	240.0	241.7
	2	S.D.	7.99	14.69	16.69	19.36	5.86	10.02	12.77	10.21	7.94	10.02
		n	5	5	5	5	3	3	3	3	3	3
D:	IQB-9302.HCl	MEAN	125.0	165.6	175.0	199.0	219.0	242.0	255.0	270.0	285.5	285.0
	4	S.D.	6.20	7.57	8.79	8.49	4.24	8.49	14.14	9.90	7.78	-
		n	5	5	4	2	2	2	2	2	2	1
One-way analysis of variance ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	S.	S.	S.	S.	N.S.
Duncan-Kramer test ($p<0.05$)								ACBD	ACBD	ABCD	ABCD	

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no. : 5

Study no. CD-98/6288T
Sex: Males

FOOD INTAKE
Mean values
(g/animal/day)

Study week	Control	IQB-9302.HCl					
		1		2		4	
		Mean	% with respect to Control	Mean	% with respect to Control	Mean	% with respect to Control
-1	25.1	24.4	97.2	23.3	92.8	24.2	96.4
1	26.8	25.5	95.1	25.7	95.9	27.0	100.7
2	28.3	27.1	95.8	26.8	94.7	-	-
3	28.3	27.1	95.8	27.5	97.2	-	-
4	28.0	27.4	97.9	27.1	96.8	-	-
Weekly means (1 to 4)	27.9	26.8	96.1	26.8	96.1	27.0	100.7

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 6

Study no. CD-98/6288T
Sex: Females

FOOD INTAKE
Mean values
(g/animal/day)

Study week	Control	IQB-9302.HCl					
		1		2		4	
		Mean	% with respect to Control	Mean	% with respect to Control	Mean	% with respect to Control
-1	17.4	19.2	110.3	17.9	102.9	18.0	103.4
1	17.2	16.5	95.9	16.6	96.5	19.8	115.1
2	18.5	17.9	96.8	18.6	100.5	24.9	134.6
3	17.6	17.5	99.4	18.5	105.1	25.4	144.3
4	17.4	17.9	102.9	17.9	102.9	26.2	150.6
Weekly means (1 to 4)	17.7	17.5	98.7	17.9	101.3	24.1	136.2

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 7

ABSOLUTE ORGAN WEIGHTS
Mean values

Study no.: CD-98/6288T
Sex: Male

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
A:	CONTROL --	MEAN	388.8	54.0	4.06	18.6	2.99	2.05	1.24	17.41	0.80	2.11	1.62	0.57	9.8
		S.D.	11.17	8.46	0.171	6.19	0.248	0.104	0.076	1.603	0.095	0.208	0.228	0.031	1.79
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
B:	IQB-9302.HCl 1	MEAN	389.6	62.4	4.36	22.4	3.07	2.07	1.39	18.13	0.97	1.96	1.80	0.74	12.0
		S.D.	7.92	7.13	0.360	2.19	0.229	0.070	0.137	2.127	0.125	0.307	0.224	0.088	1.22
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
C:	IQB-9302.HCl 2	MEAN	380.5	66.3	4.24	21.5	2.85	1.98	1.35	16.27	0.93	2.02	1.69	0.59	12.8
		S.D.	8.35	10.40	0.111	6.86	0.158	0.109	0.058	1.558	0.268	0.214	0.039	0.143	1.50
		n	4	4	4	4	4	4	4	4	4	4	4	4	4
D:	IQB-9302.HCl 4	MEAN													
		S.D.													
		n													
One-way analysis of variance (p<0.05)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.	S.
Duncan-Kramer test (p<0.05)														ACB	ABC

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 8

ABSOLUTE ORGAN WEIGHTS
Mean values

Study no.: CD-98/6288T
Sex: Female

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
A:	CONTROL --	MEAN	235.2	70.6	131.0	17.6	1.88	1.82	0.87	10.32	0.61	0.52	1.36	0.51	13.2
		S.D.	12.74	11.74	22.46	2.61	0.265	0.044	0.063	0.432	0.143	0.064	0.088	0.091	1.64
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
B:	IQB-9302.HCl 1	MEAN	240.8	75.4	129.0	20.8	1.95	1.87	0.90	10.48	0.78	0.61	1.36	0.56	13.8
		S.D.	11.84	7.83	24.30	4.60	0.163	0.110	0.040	0.656	0.062	0.143	0.057	0.094	0.84
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
C:	IQB-9302.HCl 2	MEAN	241.7	64.3	126.3	16.0	1.99	1.96	0.97	10.80	0.77	0.43	1.32	0.60	16.0
		S.D.	10.02	4.73	15.01	3.61	0.101	0.153	0.084	0.252	0.106	0.070	0.114	0.159	1.00
		n	3	3	3	3	3	3	3	3	3	3	3	3	3
D:	IQB-9302.HCl 4	MEAN	285.0	94.0	96.0	28.0	2.07	1.97	1.11	13.35	0.75	0.95	1.74	0.75	15.0
		S.D.	-	-	-	-	-	-	-	-	-	-	-	-	-
		n	1	1	1	1	1	1	1	1	1	1	1	1	1
One-way analysis of variance ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.
Duncan-Kramer test ($p<0.05$)															ABC

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 9

RELATIVE ORGAN WEIGHTS
Mean values

Study no.: CD-98/6288T
Sex: Male

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
A:	CONTROL --	MEAN	388.8	1.39	1.05	0.48	0.77	0.53	0.32	4.48	0.21	0.54	0.42	0.15	0.25
		S.D.	11.17	0.219	0.051	0.141	0.042	0.025	0.014	0.390	0.028	0.052	0.067	0.009	0.038
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
B:	IQB-9302.HCl 1	MEAN	389.6	1.60	1.12	0.57	0.79	0.53	0.36	4.65	0.25	0.50	0.46	0.19	0.31
		S.D.	7.92	0.208	0.092	0.051	0.047	0.015	0.041	0.516	0.028	0.085	0.050	0.025	0.029
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
C:	IQB-9302.HCl 2	MEAN	380.5	1.74	1.12	0.57	0.75	0.52	0.35	4.28	0.24	0.53	0.45	0.16	0.34
		S.D.	8.35	0.283	0.042	0.179	0.056	0.037	0.017	0.461	0.072	0.062	0.021	0.042	0.044
		n	4	4	4	4	4	4	4	4	4	4	4	4	4
D:	IQB-9302.HCl 4	MEAN													
		S.D.													
		n													
One-way analysis of variance (p<0.05)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.
Duncan-Kramer test (p<0.05)															ABC

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 10

RELATIVE ORGAN WEIGHTS
Mean values

Study no.: CD-98/6288T
Sex: Female

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
A:	CONTROL	MEAN	235.2	3.01	5.59	0.75	0.80	0.78	0.37	4.39	0.26	0.22	0.58	0.22	0.56
	--	S.D.	12.74	0.568	1.029	0.097	0.085	0.047	0.019	0.270	0.053	0.027	0.063	0.039	0.060
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
B:	IQB-9302.HCl	MEAN	240.8	3.14	5.33	0.86	0.81	0.77	0.38	4.36	0.33	0.25	0.57	0.23	0.57
	1	S.D.	11.84	0.434	0.795	0.187	0.104	0.011	0.024	0.328	0.030	0.065	0.015	0.024	0.050
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
C:	IQB-9302.HCl	MEAN	241.7	2.66	5.24	0.67	0.82	0.81	0.40	4.47	0.32	0.18	0.55	0.25	0.66
	2	S.D.	10.02	0.106	0.756	0.175	0.064	0.090	0.035	0.177	0.052	0.036	0.068	0.064	0.065
		n	3	3	3	3	3	3	3	3	3	3	3	3	3
D:	IQB-9302.HCl	MEAN	285.0	3.30	3.37	0.98	0.73	0.69	0.39	4.68	0.26	0.33	0.61	0.26	0.53
	4	S.D.	-	-	-	-	-	-	-	-	-	-	-	-	-
		n	1	1	1	1	1	1	1	1	1	1	1	1	1
One-way analysis of variance ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

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Toxicology Department
Table no. 11

Study no. CD-98/628

MICROSCOPIC OBSERVATIONS BY ORGAN/SEX/GROUP

(Number of affected animals)

Codes for treatment groups and doses:

Group 1: CONTROL

Group 2: IQB-9302.HCl 1 mg/kg/day

Group 3: IQB-9302.HCl 2 mg/kg/day

Group 4: IQB-9302.HCl 4 mg/kg/day

ORGANS/MICROSCOPIC OBSERVATIONS	Treatment group:	1		2		3		4	
	Sex:	M	F	M	F	M	F	M	F
	Animals/group:	5	5	5	5	5	5	5	5
LIVER	Animals exam:	5	5	5	5	5	5	5	5
Increase in number of hepatocytes undergoing mitosis						1	1	4	2
Microgranuloma		2	2		1				1
KIDNEYS	Animals exam:	5	5			1	2	5	5
Lymphocytary infiltrate, interstitial, focal, subcapsular						1			
Slight pyelitis, chronic									1
Cyst, cortical, simple, unilateral		1							

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DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 12

BODYWEIGHTS (g)
Individual results

Study no.: CD-98/6288T
Test substance: CONTROL
Dose: --

ANIMAL		Treatment day									
No.	Sex	-7	1	4	8	11	15	18	22	25	29
1	M	123	193	211	248	266	293	322	345	358	381
2	M	127	203	227	266	284	314	335	356	368	382
3	M	131	198	219	255	276	303	329	350	367	389
4	M	138	215	238	276	299	329	353	375	388	408
5	M	135	209	233	264	288	312	330	350	368	384
	MEAN	130.8	203.6	225.6	261.8	282.6	310.2	333.8	355.2	369.8	388.8
	S.D.	6.02	8.71	10.81	10.73	12.44	13.41	11.69	11.73	11.01	11.17
	n	5	5	5	5	5	5	5	5	5	5
21	F	118	154	156	172	185	200	206	213	220	228
22	F	123	165	174	192	196	211	214	222	227	233
23	F	119	152	155	171	182	192	199	206	210	219
24	F	129	169	181	196	209	219	229	235	242	249
25	F	124	170	176	196	205	220	221	226	239	247
	MEAN	122.6	162.0	168.4	185.4	195.4	208.4	213.8	220.4	227.6	235.2
	S.D.	4.39	8.46	12.05	12.80	11.89	12.18	11.86	11.28	13.28	12.74
	n	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 13

BODYWEIGHTS (g)
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 1 mg/kg/day

ANIMAL		Treatment day									
No.	Sex	-7	1	4	8	11	15	18	22	25	29
6	M	123	191	213	246	271	298	313	335	357	381
7	M	128	208	227	265	287	319	341	361	380	397
8	M	128	202	222	256	278	310	321	345	364	381
9	M	135	203	227	263	287	319	339	360	377	394
10	M	119	189	214	251	273	311	335	359	380	395
	MEAN	126.6	198.6	220.6	256.2	279.2	311.4	329.8	352.0	371.6	389.6
	S.D.	6.02	8.20	6.80	7.98	7.56	8.62	12.21	11.53	10.50	7.92
	n	5	5	5	5	5	5	5	5	5	5
26	F	127	170	185	196	207	221	225	228	238	243
27	F	136	176	179	189	201	207	214	214	219	227
28	F	121	167	172	181	196	207	209	217	227	240
29	F	124	161	174	191	196	210	218	225	222	235
30	F	125	179	185	202	214	225	232	238	247	259
	MEAN	126.6	170.6	179.0	191.8	202.8	214.0	219.6	224.4	230.6	240.8
	S.D.	5.68	7.16	6.04	7.85	7.73	8.43	9.07	9.50	11.67	11.84
	n	5	5	5	5	5	5	5	5	5	5

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Toxicology Department
Table no.: 14

BODYWEIGHTS (g)
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 2 mg/kg/day

ANIMAL		Treatment day									
No.	Sex	-7	1	4	8	11	15	18	22	25	29
11	M	133	197	218	246	270	298	317	344	356	376
12	M	119	182	208	242	254	291	308	346	359	391
13	M	120	190	214	247	269	298	317	336	355	372
14	M	132	211	235	274	304	340	368	401	422	-
15	M	135	208	218	262	277	312	326	347	367	383
	MEAN	127.8	197.6	218.6	254.2	274.8	307.8	327.2	354.8	371.8	380.5
	S.D.	7.66	12.14	10.04	13.42	18.35	19.55	23.68	26.19	28.46	8.35
	n	5	5	5	5	5	5	5	5	5	4
31	F	117	147	151	165	-	-	-	-	-	-
32	F	121	159	174	193	204	223	229	237	246	241
33	F	123	160	171	185	193	204	204	218	231	232
34	F	138	187	198	219	-	-	-	-	-	-
35	F	123	166	172	190	195	208	221	234	243	252
	MEAN	124.4	163.8	173.2	190.4	197.3	211.7	218.0	229.7	240.0	241.7
	S.D.	7.99	14.69	16.69	19.36	5.86	10.02	12.77	10.21	7.94	10.02
	n	5	5	5	5	3	3	3	3	3	3

-: Animal died before the end of treatment.

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DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 15

BODYWEIGHTS (g)
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 4 mg/kg/day

ANIMAL		Treatment day									
No.	Sex	-7	1	4	8	11	15	18	22	25	29
16	M	118	183	-	-	-	-	-	-	-	-
17	M	122	189	-	-	-	-	-	-	-	-
18	M	131	205	-	-	-	-	-	-	-	-
19	M	133	207	233	-	-	-	-	-	-	-
20	M	137	216	235	-	-	-	-	-	-	-
	MEAN	128.2	200.0	234.0							
	S.D.	7.92	13.60	1.41							
	n	5	5	2							
36	F	119	172	185	-	-	-	-	-	-	-
37	F	130	169	-	-	-	-	-	-	-	-
38	F	133	172	179	205	222	236	245	263	280	285
39	F	123	159	171	-	-	-	-	-	-	-
40	F	120	156	165	193	216	248	265	277	291	-
	MEAN	125.0	165.6	175.0	199.0	219.0	242.0	255.0	270.0	285.5	285.0
	S.D.	6.20	7.57	8.79	8.49	4.24	8.49	14.14	9.90	7.78	-
	n	5	5	4	2	2	2	2	2	2	1

-: Animal died before the end of treatment.

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Table no.: 16

ABSOLUTE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: CONTROL
Dose: --
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
1	381	48	3.85	13	2.86	2.14	1.26	16.73	0.77	2.25	1.66	0.62	8
2	382	47	4.30	16	2.93	2.02	1.27	19.10	0.83	2.03	1.56	0.55	8
3	389	52	3.96	19	2.95	1.90	1.20	15.28	0.70	1.79	1.37	0.58	11
4	408	55	4.13	29	3.42	2.16	1.34	18.92	0.76	2.31	1.52	0.57	12
5	384	68	4.08	16	2.79	2.04	1.14	17.04	0.95	2.18	1.98	0.54	10
MEAN	388.8	54.0	4.06	18.6	2.99	2.05	1.24	17.41	0.80	2.11	1.62	0.57	9.8
S.D.	11.17	8.46	0.171	6.19	0.248	0.104	0.076	1.603	0.095	0.208	0.228	0.031	1.79
n	5	5	5	5	5	5	5	5	5	5	5	5	5

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Toxicology Department
Table no.: 17

ABSOLUTE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 1 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
6	381	74	4.46	21	3.03	1.95	1.26	15.57	1.02	2.14	1.77	0.70	11
7	397	61	4.89	23	3.39	2.09	1.34	18.19	1.08	2.09	2.14	0.74	12
8	381	63	4.39	21	2.75	2.10	1.62	18.89	0.86	2.30	1.51	0.88	11
9	394	55	4.00	26	3.04	2.08	1.34	16.82	0.81	1.61	1.80	0.64	14
10	395	59	4.05	21	3.12	2.13	1.37	21.17	1.07	1.66	1.80	0.74	12
MEAN	389.6	62.4	4.36	22.4	3.07	2.07	1.39	18.13	0.97	1.96	1.80	0.74	12.0
S.D.	7.92	7.13	0.360	2.19	0.229	0.070	0.137	2.127	0.125	0.307	0.224	0.088	1.22
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 18

ABSOLUTE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 2 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
11	376	81	4.35	19	3.04	1.94	1.36	17.78	0.75	1.98	1.71	0.67	12
12	391	66	4.13	28	2.66	1.86	1.37	16.25	0.77	2.15	1.64	0.49	12
13	372	60	4.15	26	2.88	2.12	1.39	16.92	1.32	2.22	1.73	0.74	15
14*	422	69	4.71	22	3.09	2.22	1.53	26.59	1.08	1.89	2.43	0.85	15
15	383	58	4.31	13	2.81	1.99	1.26	14.13	0.86	1.74	1.69	0.44	12
MEAN	380.5	66.3	4.24	21.5	2.85	1.98	1.35	16.27	0.93	2.02	1.69	0.59	12.8
S.D.	8.35	10.40	0.111	6.86	0.158	0.109	0.058	1.558	0.268	0.214	0.039	0.143	1.50
n	4	4	4	4	4	4	4	4	4	4	4	4	4

*: Animal died before the end of treatment. Not included in statistics.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 19

ABSOLUTE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 4 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
16*	183	38	2.08	16	1.58	1.84	0.91	11.49	0.61	0.34	1.41	0.76	7
17*	192	55	1.61	15	1.84	1.87	1.01	12.52	0.51	0.33	1.52	0.43	6
18*	210	46	2.29	15	1.96	1.93	1.22	14.06	0.64	0.45	1.65	0.65	9
19*	233	42	2.63	16	2.03	1.99	1.20	15.46	0.73	0.43	1.76	0.67	7
20*	235	53	2.51	21	2.03	1.77	1.22	15.51	0.72	0.63	1.91	0.58	12
MEAN													
S.D.													
n													

*: Animal died before the end of treatment. Not included in statistics.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 20

ABSOLUTE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: CONTROL
Dose: --
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
21	228	90	166	17	1.91	1.78	0.84	10.94	0.58	0.51	1.48	0.51	14
22	233	58	108	15	1.63	1.85	0.89	9.95	0.52	0.56	1.27	0.65	14
23	219	68	121	17	1.65	1.83	0.79	9.93	0.51	0.50	1.43	0.40	11
24	249	69	139	17	2.28	1.78	0.96	10.56	0.60	0.44	1.33	0.52	15
25	247	68	121	22	1.94	1.88	0.85	10.20	0.86	0.61	1.31	0.47	12
MEAN	235.2	70.6	131.0	17.6	1.88	1.82	0.87	10.32	0.61	0.52	1.36	0.51	13.2
S.D.	12.74	11.74	22.46	2.61	0.265	0.044	0.063	0.432	0.143	0.064	0.088	0.091	1.64
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 21

ABSOLUTE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 1 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
26	243	75	136	28	1.77	1.91	0.95	10.17	0.79	0.51	1.34	0.58	14
27	227	82	95	18	2.16	1.75	0.92	9.71	0.72	0.53	1.29	0.47	13
28	240	65	145	16	1.97	1.85	0.90	11.35	0.87	0.69	1.34	0.52	14
29	235	84	114	22	2.03	1.79	0.84	10.94	0.79	0.82	1.39	0.51	15
30	259	71	155	20	1.80	2.03	0.91	10.23	0.72	0.49	1.44	0.71	13
MEAN	240.8	75.4	129.0	20.8	1.95	1.87	0.90	10.48	0.78	0.61	1.36	0.56	13.8
S.D.	11.84	7.83	24.30	4.60	0.163	0.110	0.040	0.656	0.062	0.143	0.057	0.094	0.84
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 22

ABSOLUTE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 2 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
31*	170	40	87	14	1.41	1.73	0.71	10.35	0.51	0.43	1.16	0.66	7
32	241	66	111	15	2.10	2.09	1.07	11.07	0.69	0.50	1.37	0.78	16
33	232	59	141	20	1.98	1.99	0.92	10.57	0.89	0.43	1.40	0.51	17
34*	229	69	146	15	1.72	1.92	1.09	14.41	0.63	0.51	1.37	0.99	9
35	252	68	127	13	1.90	1.79	0.93	10.76	0.73	0.36	1.19	0.50	15
MEAN	241.7	64.3	126.3	16.0	1.99	1.96	0.97	10.80	0.77	0.43	1.32	0.60	16.0
S.D.	10.02	4.73	15.01	3.61	0.101	0.153	0.084	0.252	0.106	0.070	0.114	0.159	1.00
n	3	3	3	3	3	3	3	3	3	3	3	3	3

*: Animal died before the end of treatment. Not included in statistics.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 23

ABSOLUTE ORGAN WEIGHTS
. Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 4 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
36*	185	57	113	100	1.54	1.86	0.97	12.71	0.45	0.64	1.69	0.75	14
37*	176	45	115	16	1.57	1.72	0.90	12.78	0.45	0.29	2.98	0.56	11
38	285	94	96	28	2.07	1.97	1.11	13.35	0.75	0.95	1.74	0.75	15
39*	171	52	92	12	1.32	1.80	0.80	10.85	0.36	0.30	1.58	0.66	10
40*	304	113	166	17	2.06	2.05	1.32	18.97	0.78	0.49	1.73	0.79	18
MEAN	285.0	94.0	96.0	28.0	2.07	1.97	1.11	13.35	0.75	0.95	1.74	0.75	15.0
S.D.	-	-	-	-	-	-	-	-	-	-	-	-	-
n	1	1	1	1	1	1	1	1	1	1	1	1	1

*: Animal died before the end of treatment. Not included in statistics.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 24

RELATIVE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: CONTROL
Dose: --
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
1	381	1.26	1.01	0.34	0.75	0.56	0.33	4.39	0.20	0.59	0.44	0.16	0.21
2	382	1.23	1.13	0.42	0.77	0.53	0.33	5.00	0.22	0.53	0.41	0.14	0.21
3	389	1.34	1.02	0.49	0.76	0.49	0.31	3.93	0.18	0.46	0.35	0.15	0.28
4	408	1.35	1.01	0.71	0.84	0.53	0.33	4.64	0.19	0.57	0.37	0.14	0.29
5	384	1.77	1.06	0.42	0.73	0.53	0.30	4.44	0.25	0.57	0.52	0.14	0.26
MEAN	388.8	1.39	1.05	0.48	0.77	0.53	0.32	4.48	0.21	0.54	0.42	0.15	0.25
S.D.	11.17	0.219	0.051	0.141	0.042	0.025	0.014	0.390	0.028	0.052	0.067	0.009	0.038
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 25

RELATIVE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 1 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
6	381	1.94	1.17	0.55	0.80	0.51	0.33	4.09	0.27	0.56	0.46	0.18	0.29
7	397	1.54	1.23	0.58	0.85	0.53	0.34	4.58	0.27	0.53	0.54	0.19	0.30
8	381	1.65	1.15	0.55	0.72	0.55	0.43	4.96	0.23	0.60	0.40	0.23	0.29
9	394	1.40	1.02	0.66	0.77	0.53	0.34	4.27	0.21	0.41	0.46	0.16	0.36
10	395	1.49	1.03	0.53	0.79	0.54	0.35	5.36	0.27	0.42	0.46	0.19	0.30
MEAN	389.6	1.60	1.12	0.57	0.79	0.53	0.36	4.65	0.25	0.50	0.46	0.19	0.31
S.D.	7.92	0.208	0.092	0.051	0.047	0.015	0.041	0.516	0.028	0.085	0.050	0.025	0.029
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 26

RELATIVE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 2 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
11	376	2.15	1.16	0.51	0.81	0.52	0.36	4.73	0.20	0.53	0.45	0.18	0.32
12	391	1.69	1.06	0.72	0.68	0.48	0.35	4.16	0.20	0.55	0.42	0.13	0.31
13	372	1.61	1.12	0.70	0.77	0.57	0.37	4.55	0.35	0.60	0.47	0.20	0.40
14*	422	1.64	1.12	0.52	0.73	0.53	0.36	6.30	0.26	0.45	0.58	0.20	0.36
15	383	1.51	1.13	0.34	0.73	0.52	0.33	3.69	0.22	0.45	0.44	0.11	0.31
MEAN	380.5	1.74	1.12	0.57	0.75	0.52	0.35	4.28	0.24	0.53	0.45	0.16	0.34
S.D.	8.35	0.283	0.042	0.179	0.056	0.037	0.017	0.461	0.072	0.062	0.021	0.042	0.044
n	4	4	4	4	4	4	4	4	4	4	4	4	4

*: Animal died before the end of treatment. Not included in statistics.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 27

RELATIVE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose:4 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
16*	183	2.08	1.14	0.87	0.86	1.01	0.50	6.28	0.33	0.19	0.77	0.42	0.38
17*	192	2.86	0.84	0.78	0.96	0.97	0.53	6.52	0.27	0.17	0.79	0.22	0.31
18*	210	2.19	1.09	0.71	0.93	0.92	0.58	6.70	0.30	0.21	0.79	0.31	0.43
19*	233	1.80	1.13	0.69	0.87	0.85	0.52	6.64	0.31	0.18	0.76	0.29	0.30
20*	235	2.26	1.07	0.89	0.86	0.75	0.52	6.60	0.31	0.27	0.81	0.25	0.51
MEAN													
S.D.													
n													

*: Animal died before the end of treatment. Not included in statistics.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 28

RELATIVE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: CONTROL
Dose: --
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
21	228	3.95	7.28	0.75	0.84	0.78	0.37	4.80	0.25	0.22	0.65	0.22	0.61
22	233	2.49	4.64	0.64	0.70	0.79	0.38	4.27	0.22	0.24	0.55	0.28	0.60
23	219	3.11	5.53	0.78	0.75	0.84	0.36	4.53	0.23	0.23	0.65	0.18	0.50
24	249	2.77	5.58	0.68	0.92	0.71	0.39	4.24	0.24	0.18	0.53	0.21	0.60
25	247	2.75	4.90	0.89	0.79	0.76	0.34	4.13	0.35	0.25	0.53	0.19	0.49
MEAN	235.2	3.01	5.59	0.75	0.80	0.78	0.37	4.39	0.26	0.22	0.58	0.22	0.56
S.D.	12.74	0.568	1.029	0.097	0.085	0.047	0.019	0.270	0.053	0.027	0.063	0.039	0.060
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 29

RELATIVE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 1 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
26	243	3.09	5.60	1.15	0.73	0.79	0.39	4.19	0.33	0.21	0.55	0.24	0.58
27	227	3.61	4.19	0.79	0.95	0.77	0.41	4.28	0.32	0.23	0.57	0.21	0.57
28	240	2.71	6.04	0.67	0.82	0.77	0.38	4.73	0.36	0.29	0.56	0.22	0.58
29	235	3.57	4.85	0.94	0.86	0.76	0.36	4.66	0.34	0.35	0.59	0.22	0.64
30	259	2.74	5.98	0.77	0.69	0.78	0.35	3.95	0.28	0.19	0.56	0.27	0.50
MEAN	240.8	3.14	5.33	0.86	0.81	0.77	0.38	4.36	0.33	0.25	0.57	0.23	0.57
S.D.	11.84	0.434	0.795	0.187	0.104	0.011	0.024	0.328	0.030	0.065	0.015	0.024	0.050
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 30

RELATIVE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 2 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
31*	170	2.35	5.12	0.82	0.83	1.02	0.42	6.09	0.30	0.25	0.68	0.39	0.41
32	241	2.74	4.61	0.62	0.87	0.87	0.44	4.59	0.29	0.21	0.57	0.32	0.66
33	232	2.54	6.08	0.86	0.85	0.86	0.40	4.56	0.38	0.19	0.60	0.22	0.73
34*	229	3.01	6.38	0.66	0.75	0.84	0.48	6.29	0.28	0.22	0.60	0.43	0.39
35	252	2.70	5.04	0.52	0.75	0.71	0.37	4.27	0.29	0.14	0.47	0.20	0.60
MEAN	241.7	2.66	5.24	0.67	0.82	0.81	0.40	4.47	0.32	0.18	0.55	0.25	0.66
S.D.	10.02	0.106	0.756	0.175	0.064	0.090	0.035	0.177	0.052	0.036	0.068	0.064	0.065
n	3	3	3	3	3	3	3	3	3	3	3	3	3

*: Animal died before the end of treatment. Not included in statistics.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 31

RELATIVE ORGAN WEIGHTS
Individual results

Study no.: CD-98/6288T
Test substance: IQB-9302.HCl
Dose: 4 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
36*	185	3.08	6.11	5.41	0.83	1.01	0.52	6.87	0.24	0.35	0.91	0.41	0.76
37*	176	2.56	6.53	0.91	0.89	0.98	0.51	7.26	0.26	0.16	1.69	0.32	0.63
38	285	3.30	3.37	0.98	0.73	0.69	0.39	4.68	0.26	0.33	0.61	0.26	0.53
39*	171	3.04	5.38	0.70	0.77	1.05	0.47	6.35	0.21	0.18	0.92	0.39	0.58
40*	304	3.72	5.46	0.56	0.68	0.67	0.43	6.24	0.26	0.16	0.57	0.26	0.59
MEAN	285.0	3.30	3.37	0.98	0.73	0.69	0.39	4.68	0.26	0.33	0.61	0.26	0.53
S.D.	-	-	-	-	-	-	-	-	-	-	-	-	-
n	1	1	1	1	1	1	1	1	1	1	1	1	1

*: Animal died before the end of treatment. Not included in statistics.

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	Control	1 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	Control	2 M

MICROSCOPIC OBSERVATIONS

KIDNEYS

Cyst, cortical, simple, unilateral

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	Control	3 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	Control	4 M

MICROSCOPIC OBSERVATIONS

LIVER

Microgranuloma

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	Control	5 M

MICROSCOPIC OBSERVATIONS

LIVER

Microgranuloma

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	Control	21 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid glands		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	Control	22 F

MICROSCOPIC OBSERVATIONS

LIVER

Microgranuloma

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid glands		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	Control	23 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid glands		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	Control	24 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid glands		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	Control	25 F

MICROSCOPIC OBSERVATIONS

LIVER

Microgranuloma

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid glands		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl	6 M
	1 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl	7 M
	1 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 1 mg/kg/day	8 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl	9 M
	1 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 1 mg/kg/day	10 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 1 mg/kg/day	26 F

MICROSCOPIC OBSERVATIONS

LIVER

Microgranuloma

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 1 mg/kg/day	27 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl	28 F
	1 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 1 mg/kg/day	29 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl	30 F
	1 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 2 mg/kg/day	11 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 2 mg/kg/day	12 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 2 mg/kg/day	13 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl	14 M
	2 mg/kg/day	

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

LIVER

Increase in number of hepatocytes undergoing mitosis

KIDNEYS

Lymphocytary infiltrate, interstitial, focal, subcapsular

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl	15 M
	2 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl	31 F
	2 mg/kg/day	

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 2 mg/kg/day	32 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 2 mg/kg/day	33 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 2 mg/kg/day	34 F

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

LIVER

Increase in number of hepatocytes undergoing mitosis

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 2 mg/kg/day	35 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys			Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 4 mg/kg/day	16 M

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

LIVER

Increase in number of hepatocytes undergoing mitosis

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 4 mg/kg/day	17 M

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

LIVER

Increase in number of hepatocytes undergoing mitosis

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 4 mg/kg/day	18 M

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

LIVER

Increase in number of hepatocytes undergoing mitosis

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 4 mg/kg/day	19 M

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

LIVER

Increase in number of hepatocytes undergoing mitosis

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 4 mg/kg/day	20 M

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 4 mg/kg/day	36 F

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

LIVER

Increase in number of hepatocytes undergoing mitosis

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 4 mg/kg/day	37 F

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 4 mg/kg/day	38 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 4 mg/kg/day	39 F

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

LIVER

Increase in number of hepatocytes undergoing mitosis

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6288T	IQB-9302.HCl 4 mg/kg/day	40 F

Died before end of treatment.

MICROSCOPIC OBSERVATIONS

LIVER

Microgranuloma

KIDNEYS

Slight pyelitis, chronic

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes		
Brain			Pancreas			Thymus		
Eyes			Pituitary gland			Thyroid gland		
Femur			Prostate			Tissue masses		
Heart			Salivary gland			Tongue		
Intestine, large			Sciatic nerve			Trachea		
Intestine, small			Seminal vesicles			Urinary bladder		
Kidneys	2		Skeletal muscle			Uterus		
Liver	2		Skin			Vagina		
Lungs			Spinal chord					
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques

APPENDIX I

DIET ANALYSIS CERTIFICATE

FICHE CONTROLE

A04C Lot 80507

Date de Fabrication 07/05/1998

Date limite de vente 07/09/1998

Date limite d'utilisation 07/05/1999

Numéros des sacs :	1 à 1250

Quantité fabriquée ..... *(en tonnes)*	41
Contrôle de la composition centésimale	*Conforme*

TECHNOLOGIE DES PELLETS

Diamètre ..... *(en mm)*	16.54	±	0.11	*(15.5 à 17.0)*
Résistance à l'écrasement ..... *(en Kgf / cm²)*	15.6	±	4.4	*(12 à 32)*
Résistance à l'abrasion ..... *(en %)*	96.9			*(> 96)*
Masse Spécifique ..... *(en g / l)*	700.0			
Poids ..... *(en g)*	5.709	±	0.784	
Longueur ..... *(en mm)*	22.70	±	3.90	*(18.0 à 26.0)*
Longueur < Diamètre..... *(en %)*	0.1			*(< 4)*
Nombre de pellets chauffés par Kg ..... *(/ Kg)*	0			*(< 1)*

CONTROLE DE LA QUALITE NUTRITIVE

Témoin incorporation mélange minéral ..... *(Na)*	Positif	
Témoin incorporation pré-mélange oligo-éléments *(Mn et Cu)*	Positif	
Témoin incorporation pré-mélange vitamines .. *(Vit.A et E)*	Positif	
Eau ..... *(en %)*	12.0	*(9 à 14)*
Protéines ..... *(en %)*	16.4	*(14.5 à 18.0)*
Lipides ..... *(en %)*	2.9	*(1.7 à 3.7)*
Glucides E.N.A. ..... *(en %)*	58.6	*(57.0 à 63.0)*
Dont Amidon ..... *(en %)*	46.2	*(35.0 à 53.0)*
" Sucres totaux ..... *(en %)*	1.9	
Cellulose WEENDE ..... *(en %)*	4.5	*(3.0 à 5.5)*
Hémicellulose ..... *(en %)*		
Cellulose vraie ..... *(en %)*		
Lignine ..... *(en %)*		
Minéraux totaux ..... *(en %)*	4.8	*(4.0 à 6.0)*
Dont Calcium ..... *(en mg / Kg)*	9 000	*(6 000 à 10 000)*
" Phosphore ..... *(en mg / Kg)*	4 800	*(4 500 à 7 000)*
" Sodium ..... *(en mg / Kg)*	2 500	*(1 500 à 3 500)*
" Potassium ..... *(en mg / Kg)*	5 600	*(5 500 à 8 500)*
" Manganèse ..... *(en mg / Kg)*	67	*(40 à 100)*
" Cuivre ..... *(en mg / Kg)*	16	*(8 à 35)*
" Vitamine A ..... *(en UI / Kg)*	5 600	*(4 000 à 11 000)*
" Vitamine C ..... *(en mg / Kg)*		
" Vitamine D3 ..... *(en UI / Kg)*	1 200	*(<= 3 000)*
" Vitamine E ..... *(en mg / Kg)*	30	

CONTROLE DES CONTAMINANTS

BACTERIOLOGIQUES		
Germes revivifiables .... *(/ g)*	3 200	*(< 100 000)*
Moisissures & levures .. *(/ g)*	< 10	*(< 1 000)*
Coliformes totaux ..... *(/ g)*	2	*(< 5)*
Coliformes fécaux ..... *(/ g)*	0	*(0)*
Anaérobies S.R. ..... *(/ g)*	80	*(< 100)*
Salmonelles ..... *(/ 25 g)*	0	*(0)*

MYCOTOXIQUES *(en µg / Kg)*		
Aflatoxines	< 1	*(< 5)*
Ochratoxines	< 12	*(< 200)*
Zéaralénone	< 50	*(< 1 000)*
Stérigmatocystine	< 30	*(< 300)*
Patuline		
Toxine T2		

METAUX LOURDS

Plomb ..... *(en µg / Kg)*	160	*(< 1 500)*
Mercure ... *(en µg / Kg)*	23	*(< 100)*
Arsenic ... *(en µg / Kg)*	50	*(< 1 000)*
Cadmium ... *(en µg / Kg)*	30	*(< 250)*
Sélénium .. *(en µg / Kg)*	210	*(< 600)*

DERIVES NITROSES

NO2 ..... *(en mg / Kg)*	0.5	*(Σ < 500)*
NO3 ..... *(en mg / Kg)*	18.0	
NDMA ..... *(en µg / Kg)*	1.6	*(< 10)*
NDEA ..... *(en µg / Kg)*	< 0.2	*(< 10)*
NDPA ..... *(en µg / Kg)*	< 0.3	*(< 10)*
NDBA ..... *(en µg / Kg)*	< 0.3	*(< 10)*
NPIP ..... *(en µg / Kg)*	< 0.3	*(< 10)*
NPYR ..... *(en µg / Kg)*	< 0.5	*(< 10)*
NMOR ..... *(en µg / Kg)*	< 0.6	*(< 10)*

PESTICIDES ORGANOS-CHLORES (en µg / Kg)

(Total < 200)

Lindane	1	*(< 100)*	Heptachlore	< 1	*(Σ < 10)*
a HCH	< 1	*(< 20)*	Heptachlore Epoxyde ...	< 1	
b HCH	< 5	*(< 10)*	Endrine	< 1	*(< 10)*
d HCH	< 5	*(< 100)*	o.p'DDD	< 5	*(Σ < 50)*
HCB	< 1	*(< 10)*	p.p'DDD	< 5	
PCB	< 50	*(< 50)*	o.p'DDE	< 1	
Aldrine	< 1	*(< 10)*	p.p'DDE	< 1	
Dieldrine	< 1	*(< 20)*	o.p'DDT	< 5	
Endosulfan	< 1	*(< 100)*	p.p'DDT	< 5	

PESTICIDES ORGANOS-PHOSPHORES (en µg / Kg)

(Total < 7 000)

Acéphate	< 45	*(< 5 000)*	Iodofenphos	< 25	*(< 5 000)*
Azinphos éthyl	< 50	*(< 5 000)*	Malathion	50	*(< 5 000)*
Azinphos méthyl	< 50	*(< 5 000)*	Méthamidophos	< 15	*(< 5 000)*
Bromophos éthyl	< 10	*(< 5 000)*	Méthidathion	< 25	*(< 5 000)*
Bromophos méthyl	< 20	*(< 5 000)*	Mévinphos	< 10	*(< 5 000)*
Carbophénothion éthyl .	< 50	*(< 5 000)*	Monocrotophos	< 90	*(< 5 000)*
Carbophénothion méthyl	< 20	*(< 5 000)*	Naled	< 15	*(< 5 000)*
Chlorfenvinphos	< 10	*(< 5 000)*	Oxydéméton méthyl	< 400	*(< 5 000)*
Chlorméphos	< 10	*(< 5 000)*	Parathion éthyl	< 20	*(< 5 000)*
Chlorpyriphos éthyl ...	< 15	*(< 5 000)*	Parathion méthyl	< 20	*(< 5 000)*
Chlorpyriphos méthyl ..	< 15	*(< 1 500)*	Phosalone	< 50	*(< 5 000)*
Chlorthiofos	< 15	*(< 5 000)*	Phosmet	< 50	*(< 5 000)*
Diazinon	< 15	*(< 5 000)*	Phosphamidon	< 25	*(< 5 000)*
Dichlofenthion	< 10	*(< 5 000)*	Profénofos	< 50	*(< 5 000)*
Dichlorvos	< 20	*(< 5 000)*	Prothoate	< 20	*(< 5 000)*
Diéthion	< 15	*(< 5 000)*	Pyridaphenthion	< 15	*(< 5 000)*
Diméfox	< 10	*(< 5 000)*	Pyrimiphos éthyl	< 20	*(< 5 000)*
Diméthoate	< 30	*(< 1 000)*	Pyrimiphos méthyl	< 15	*(< 2 500)*
Dioxathion	< 15	*(< 5 000)*	Sulfotep	< 20	*(< 5 000)*
Disulfoton	< 30	*(< 5 000)*	Téméphos	< 15	*(< 5 000)*
Ethoprophos	< 20	*(< 5 000)*	Tétrachlorvinphos	< 30	*(< 5 000)*
Fenchlorphos	< 20	*(< 5 000)*	Thiométhon	< 40	*(< 5 000)*
Fénitrothion	< 15	*(< 5 000)*	Triazophos	< 30	*(< 5 000)*
Fenthion	< 30	*(< 5 000)*	Trichlorfon	< 10	*(< 5 000)*
Fonofos	< 20	*(< 5 000)*	Trichloronate	< 25	*(< 5 000)*
Formothion	< 20	*(< 5 000)*			
Hepténophos	< 30	*(< 5 000)*			

PYRETHRINOIDES DE SYNTHESE (en µg / Kg)

..... ND ..... ND ..... ND

REMARQUES

Laboratoire Contrôle AQ
Le Responsable

10/06/98

Le Responsable AQ

P.O

APPENDIX II

WATER ANALYSIS CERTIFICATE

LABORATORIO DR. OLIVER RODÉS, S.A.

Consell de Cent, 304 - 08007 Barcelona
Tel. 93 488 04 00 - Fax 93 488 15 45

Fundado en 1902

ANALYSIS OF WATER

Reg. nº: Q-62.984

Applications to:	CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. (C.I.D.A.S.A.L.) c/ Argenters, 6 08130 SANTA PERPETUA DE MOGODA (Barcelona)
Reference sampling point:	**"INTERIOR WATER MAIN"**, C.I.D.A.S.A.L., Polígono Industrial Santiga, SANTA PERPETUA DE MOGODA (Barcelona)
Sampling point:	**"Pipe project laboratory"**
Sample taken by:	Water was collected by technician laboratory personnel in appropiate containers.
Sampling date:	October 8th.1998
Type of water analysis:	**Potability "COMPLETO"**. According to the laws: "Art. 23.3., of the "Real Decreto 1138/1990" and the "Directiva 80/778/CEE" (B.O.E. de 20 septiembre 1990)". Physical characteristics, chemical composition and comprehensive chemical analysis, except radioactivity (Appendix G).

LABORATORIO DR. OLIVER RODÉS, S.A.

Consell de Cent, 304 - 08007 Barcelona
Tel. 93 488 04 00 - Fax 93 488 15 45

Fundado en 1902

Reg. nº: Q-62.984

"INTERIOR WATER MAIN" - C.I.D.A.S.A.L.
SANTA PERPETUA DE MOGODA (Barcelona)

ANNEX A: ORGANOLEPTIC PARAMETERS

Parameters	Results		Maximum admissible concentration
Colour (Pt/Co)	5,-	mg/l	20
Turbidity	0,2	U.N.F.	6
Odour (at 25ºC)	No foreign odour		Dilution 1/3
Taste (at 25ºC)	No foreign taste		Dilution 1/3

ANNEX B: PHYSICAL AND CHEMISTRY PARAMETERS IN RELATION TO THE WATER'S NATURAL STRUCTURE

Parameters	Results		Maximum admissible concentration
Temperature (*in situ*)	20,-	ºC	25
Hydrogen ion concentration (pH)	8,00		9,5
Conductivity at 20ºC	1.165,-	microS.cm^{-1}	----
Alkalinity (CO_3Ca) (T.A.C.)	158,6	mg/l	----
Chlorides (Cl)	224,8	mg/l	----
Sulphates (SO_4)	132,2	mg/l	250
Calcium (Ca)	89,8	mg/l	----
Magnesium (Mg)	25,3	mg/l	50
Sodium (Na)	125,1	mg/l	150
Potassium (K)	27,2	mg/l	12
Aluminium (Al)	0,09	mg/l	0,2
Total hardness (CO_3Ca)	328,0	mg/l	----
Total hardness	32,8	ºF	----
Dry residue (at 180ºC)	814,-	mg/l	1.500

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"INTERIOR WATER MAIN" - C.I.D.A.S.A.L.
SANTA PERPETUA DE MOGODA (Barcelona)

ANNEX C: PARAMETERS CONCERNING UNDESIRABLE SUBSTANCES

Parameters	Results	Maximum admissible concentration
Nitrates (NO_3)	10,9	50
Nitrites (NO_2)	<0,02	0,1
Ammonium (NH_4)	<0,02	0,5
Kjeldahl Nitrogen (N)	<1,-	1
Oxidizability (O_2) MnO_4K	1,8	5
Residual chlorine (*in situ*) (Cl_2)	0,70	Positive
Hydrogen sulphide (S)	Undetectable	Undetectable

Parameters	Results	Maximum admissible concentration
Phenols (phenol index)(C_6H_5OH)	<1,-	0,5
Surfactants (lauryl sulphate)	<40,-	200
Iron (Fe)	<30,-	200
Manganese (Mn)	<20,-	50
Phosphorus (P_2O_3)	<900,-	5.000
Silver (Ag)	<10,-	10
Fluorides (F)	200,-	700 a 1.500 dependent on T. ºC

97.

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SANTA PERPETUA DE MOGODA (Barcelona)

HALOGENATED VOLATILE ORGANIC COMPOUNDS:

Halophorms	Results in micrograms/l	(1) .
Chloroform	14,-	--
Bromodichloromethane	42,-	--
Dibromochloromethane	86,-	--
Bromoform	62,-	--
Total	**204,-**	**100** (2)
Other compounds		
Trichloroethylene	<1,-	--
Tetrachloroethylene	<1,-	--
Total	**<10,-**	**10**
1,2-Dichloroethane	<2,5	**3**

Other compounds non limited in (1)	Results in micrograms/l
1,1-Dichloroethylene	<1,-
Methylene Chloride	<2,-
trans-1,2-Dichloroethylene	<2,-
c-1,2-Dichloroethylene	<2,5
1,1,1-Trichloroethane	<1,-
Carbon Tetrachloride	<1,-
1,2-Dichloropropane	<2,5
c-1,3-Dichloropropene	<1,-
1,1,2,2-Tetrachloroethane	<1,-
1,3-Dichlorobenzene	<1,-
1,4-Dichlorobenzene	<1,-
1,2-Dichlorobenzene	<1,-

(1) Values indicated in the "COMMON POSITION" (CE) Number 13/98 relative to the publication of the Directive relative to the **quality of waters for human consumption**, published in the Official Journey of the European Communities, last 26th of March, 1998.

(2) The proposal is 150 micrograms/litre from the 5th year of the publication of the Directive and 100 micrograms/litre from the from the 10th year of the publication of the Directive.

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"INTERIOR WATER MAIN" - C.I.D.A.S.A.L.
SANTA PERPETUA DE MOGODA (Barcelona)

ANNEX D: PARAMETERS CONCERNING TOXIC SUBSTANCES

Parameters	Results in micrograms/l	Maximum admissible concentration
Arsenic (As)	<5,-	50
Cadmium (Cd)	<5,-	5
Cyanides (CN)	<10,-	50
Chromium (Cr)	<20,-	50
Mercury (Hg)	<1,-	1
Nickel (Ni)	<20,-	50
Lead (Pb)	<50,-	50
Antimony (Sb)	<5,-	10
Selenium (Se)	<5,-	10

Polycyclic aromatic hydrocarbons:

Fluoranthene		
Benzo 3,4 fluoranthene		
Benzo 11,12 fluoranthene		
Benzo 3,4 pyrene		
Benzo 1,12 perylene		
Indeno (1,2,3-cd) pyrene		
Total	**<0,2**	0,2

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"INTERIOR WATER MAIN" - C.I.D.A.S.A.L.
SANTA PERPETUA DE MOGODA (Barcelona)

Organophosphorus pesticides:

Parameters	Results in micrograms/l	Maximum admissible concentration (provisional)
Dichlorvos	<0,1	0,1
Methamidophos	<0,1	0,1
Mevinphos	<0,1	0,1
Phorate	<0,1	0,1
Naled	<0,1	0,1
Diazinon	<0,1	0,1
Disulfoton	<0,1	0,1
Dimethoate	<0,1	0,1
Dichlofenthion	<0,1	0,1
Fenchlorphos	<0,1	0,1
Methyl-parathion	<0,1	0,1
Fenitrothion	<0,1	0,1
Chlorpyriphos	<0,1	0,1
Ethilparathion	<0,1	0,1
Malathion	<0,1	0,1
Methyl-bromophos	<0,1	0,1
Ethyl-bromophos	<0,1	0,1
Clorfenvinphos	<0,1	0,1
Tetrachlorvinphos	<0,1	0,1
Methidathion	<0,1	0,1
Ethion	<0,1	0,1
Fosalone	<0,1	0,1
Methyl-azinphos	<0,1	0,1
Ethyl-azinphos	<0,1	0,1
Coumaphos	<0,1	0,1
Total	**<0,5**	**0,5**

100.

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Organochlorine pesticides:

Parameters	Results in micrograms/l	Maximum admissible concentration (provisional)
Alfa - HCH	<0,1	0,1
Beta - HCH	<0,1	0,1
Gamma - HCH	<0,1	0,1
Delta - HCH	<0,1	0,1
Epsilon - HCH	<0,1	0,1
Heptaclor	<0,1	0,1
Aldrin	<0,1	0,1
Heptaclor epoxide	<0,1	0,1
op' - DDE	<0,1	0,1
Endosulfan I	<0,1	0,1
Dieldrin	<0,1	0,1
pp' - DDE	<0,1	0,1
op' - DDD	<0,1	0,1
Endrin	<0,1	0,1
Endosulfan II	<0,1	0,1
pp' - DDD	<0,1	0,1
op' - DDT	<0,1	0,1
Endrin aldehyde	<0,1	0,1
Endosulfan sulphate	<0,1	0,1
pp' - DDT	<0,1	0,1
Total	**<0,5**	**0,5**

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"INTERIOR WATER MAIN" - C.I.D.A.S.A.L.
SANTA PERPETUA DE MOGODA (Barcelona)

ANION-CATION BALANCE

ANIONS	mg/l	meq/l
Bicarbonates (CO_3H)	193,5	3,17
Carbonates (CO_3)	0,0	0,00
Sulphates (SO_4)	132,2	2,75
Chlorides (Cl)	224,8	6,34
Nitrates (NO_3)	10,9	0,18
Fluorides (F)	0,2	0,01
Nitrites (NO_2)	<0,02	0,00
	Total	12,45

CATIONS	mg/l	meq/l
Calcium (Ca)	89,8	4,48
Magnesium (Mg)	25,3	2,08
Sodium (Na)	125,1	5,44
Potassium (K)	27,2	0,70
Iron (Fe)	<0,03	0,00
Manganese (Mn)	<0,02	0,00
Ammonium (NH_4)	<0,02	0,00
	Total	12,70

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"INTERIOR WATER MAIN" - C.I.D.A.S.A.L.
SANTA PERPETUA DE MOGODA (Barcelona)

CONCLUSIONS

The results obtained in the analysis carried out allow as to conclude that the following water: "**"INTERIOR WATER MAIN"** in C.I.D.A.S.A.L., in the municipality of SANTA PERPETUA DE MOGODA (Barcelona), can be classified as follows:

Medium mineralized water.

Its main components are: Bicarbonates, sulphates, chlorides, calcium and sodium.

In a lower proportion we find: Nitrates, magnesium and potassium.

In small amounts we find: Fluorides and aluminium.

Its content of calcium and magnesium make this water as hard water.

CLASSIFICATION according to the Spanish law, the "Reglamentación Técnico-Sanitaria para las Aguas Potables de Consumo Público (Real Decreto 1138/1990, B.O.E. de 20 septiembre 1990)":

We have found an absence of the investigated toxic substances (see Appendix D of this report of results) in an amount superior to the "maximum allowed concentration", established by the current Legislation.

The amount of potassium exceeds the "maximum allowed concentration" (12,- mg/l) established by the "Real Decreto 1138/1990, B.O.E. de 20 septiembre 1990".

This parameter can be found in Appendix B: "Physical and chemistry characteristics in relationship with the natural structure of the waters".

The consumption of this water, with its content of potassium, does not represent any risk for the health of the consumer.

The results obtained in all the other parameters are in accordance with the current Legislation.

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Tel. 93 488 04 00 - Fax 93 488 15 45

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SANTA PERPETUA DE MOGODA (Barcelona)

The above mentioned Technical and Health Regulation, which is currently in force, regulates (parameter 32) the halogenated volatile organic compounds, indicating that the presence of haloforms will be reduced as much as possible, although it does not indicate the "maximum allowed concentration".

These values are those proposed by the Proposal of future European Directive, and they will be subject to transposition to the Technical and Health Regulation.

Reference methods of analysis:

Residual chlorine: Colorimetry - DPD.
Colour: Colorimetry. Scale Pt/Co.
Turbidity: Formazine test.
Odour and taste: Successive dilutions, tested at a 25ºC.
Hydrogen ion concentration (pH) and conductivity: Electrometry.
Temperature: Thermometry.
Alkalinity, bicarbonates and carbonates: Volumetry.
Chlorides and sulphates: Ion chromatography.
Calcium, magnesium and total hardness: Complexometry.
Sodium, potassium, aluminium, iron, manganese, silver, arsenic, cadmium, antimony, selenium, chromium, mercury, nickel and lead: Atomic absorption.
Dry residue: Gravimetry - Dessication at 180ºC.
Nitrates: Molecular absorption spectroscopy U.V.
Nitrites, ammonium, phosphorus, phenol index, surfactants and cyanides: Absorption spectroscopy.
Kjeldahl Nitrogen: Decomposotion. Distillation. Volumetry.
Oxidizability: Boiling with $KMnO_4$ in acid medium.
Hydrogen sulphide: Organoleptic - Iodometry.
Fluorides: Specific electrode.
Halogenated volatile organic compounds: Head-Space - Gas chromatography ECD.
Organophosphorus pesticides: Gas chromatography NPD.
Organochlorine pesticides: Gas chromatography ECD.
Polycyclic aromatic hydrocarbons: Mass spectrometry.

Barcelona, May 8th. 1998

M.C. Pastor
Technician Director

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Tel. 93 488 04 00 - Fax 93 488 15 45

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NOTAS:

Los valores indicados con el signo "<" indican que el resultado obtenido no supera el límite de detección del método analítico correspondiente.

El/los presente/s dictamen/es de resultados solamente da/n fe de la/s muestra/s analizada/s.

AUTORIZACIONES Y CERTIFICACIONES OBTENIDAS:

- Ministerio de Sanidad y Consumo.
  Dirección General de Control y Análisis de la Calidad.
  Autorizado para análisis y controles de aguas y microbiología alimentaria.
- Ministerio de Sanidad y Consumo.
  Dirección General de Farmacia y Productos Sanitarios.
  Autorizado para análisis de control de: Cosméticos, dentífricos, insecticidas, plantas medicinales y material estéril.
- Ministerio de Obras Públicas, Transportes y Medio Ambiente.
  Dirección General de Calidad de las Aguas.
  Declarado Empresa Colaboradora de los Organismos de Cuenca en Control de Vertidos de Aguas Residuales, Grupos 1, 2 y 3.
- Generalitat de Catalunya.
  Departament d'Agricultura, Ramaderia i Pesca.
  Acreditado para análisis de: Platos preparados y precocinados, huevos y derivados, aguas y hielo, pastas y galletas, microbiología alimentaria, metales (trazas), residuos de plaguicidas y contaminantes orgánicos.
- Generalitat de Catalunya.
  Departament de Medi Ambient.
  Declarado Establiment Tècnic Auxiliar de la Junta de Sanejament para análisis y control de vertidos de aguas residuales, Nivel A.
- Generalitat de Catalunya.
  Departament de Sanitat i Seguretat Social.
  Autorizado como Laboratorio de Salud Ambiental y Alimentaria.
- Department of Health & Human Services. USA.
  FDA, Food and Drug Administration.
  Clasificado para análisis de aguas utilizadas en la fabricación de productos químico-farmacéuticos.
- **Empresa Certificada según Norma UNE-EN-ISO 9002.**
  Fundación Calitax para el Fomento y Control de la Calidad.
  Toma de muestras, análisis físico-químicos de aguas (naturales, potables, minerales, residuales, industriales), análisis microbiológicos de aguas, alimentos, cosméticos, superficies, aire y productos industriales.

APPENDIX III

PRODUCT ANALYSIS CERTIFICATE

LEBSA

LABORATORIOS ESPINOS Y BOFILL, S.A.
Investigación y síntesis de productos químicos
Ctra. de l'Hospitalet, 30
08940 Cornellá (Barcelona)
Apartado 14.012 de Barcelona
Teléfono 93 377 00 51 Fax 93 377 51 58
E-mail: lebsa@sefes.es
Telex. 93051 LEB-E

CERTIFICATE OF ANALYSIS

PRODUCT: IQB-9302.HCl

CONTROL #: 9810034

LOT #: 9454.001

DATE: 8th Oct.1998

ANALYTICAL DATA	SPECIFICATIONS	RESULT
Appearance	White powder	Conforms
Identification		
I.R. Spectrum	Similar to standard	Conforms
Chlorides	To pass test	Conforms
Appearance of solution	Clear and colourless	Conforms
Acidity or alkalinity	To pass test	Conforms
Related substances	Not more than 0.5%	Conforms
2,6-Dimethylaniline	Not more than 100ppm	Conforms
Heavy metals	Not more than 10 ppm	Conforms
Loss on drying	Not more than 1.0%	0.35%
Sulphates ash	Not more than 0.1%	0.04%
Assay	98.5 - 101.0%	101.0%
Residual Isopropanol	Not more than 0.5%	0.23%

Analyst
Silvia Dieguez

Analytical Department Manager
Anna Pons

R.M. Barcelona, Insc. 1ª, Sec. 2ª, L. 1.025, T. 1.594, F. 171, H. 13.690 - CIF/VAT - ESA/ 08150450

APPENDIX IV

FORMULATION ANALYSIS RESULTS

INIBSA LABORATORIOS

28.10.98

IQB - 9302. HCl

Solución patrón:

Se inyecta por triplicado una solución patrón IQB-9302.HCl, Lote: 9454.001 (control 9810034) LEBSA. El CV de las tres inyecciones es 0.17%. El tiempo de retención es 4.16.

$$\frac{100.1 \text{ mg}}{100 \text{ mL}} \times \frac{5 \text{ mL}}{10 \text{ mL}} = 0.500 \text{ mg / mL}$$

Soluciones problema:

- Se inyecta directamente dos veces la muestra 98/6288T, IQB-9302.HCl **0.25 mg/mL** en SF.

  Los resultados son: 0.27 mg/mL - 0.27 mg/ mL

  Tiempo de retención 4.19

- Se inyecta directamente dos veces la muestra 98/6288T, IQB-9302.HCl **0.50 mg/mL** en SF.

  Los resultados son: 0.54 mg/mL - 0.55 mg/ mL

  Tiempo de retención 4.15 - 4.14

- Se inyecta dos veces la muestra 98/6288T, IQB-9302.HCl **1 mg/mL** en SF. Se diluye 1.0 mL de muestra hasta 2.0 mL en un matraz aforado con agua ultrapura.

  Los resultados son: 1.06 mg/mL - 1.07 mg/ mL

  Tiempo de retención 4.15 - 4.14

Emiliano Rodríguez
Responsable Control Calidad

INIBSA LABORATORIOS

05.11.98

IQB - 9302. HCl (muestra del 03.11.98)

Solución patrón:

Se inyecta por triplicado una solución patrón IQB-9302.HCl, Lote: 9454/R.E-1 Standard (control 9810071) LEBSA, con humedad = 0.66% y riqueza 100.7%. El CV de las tres inyecciones es 0.67%. El tiempo de retención es 4.21.

$$\frac{100.4 - (100.4 \times 0.01 \times 0.66)}{100 \text{ mL}} \times \frac{5 \text{ mL}}{10 \text{ mL}} \times \frac{100.7}{100} = 0.502 \text{ mg / mL}$$

Soluciones problema:

- Se inyecta directamente dos veces un blanco de Suero Fisiológico 98/6288T, comprobándose que no interfiere en la cuantificación del problema.

- Se inyecta directamente dos veces la muestra 98/6288T, IQB-9302.HCl **0.25 mg/mL** en SF.

  Los resultados son: 0.27 mg/mL - 0.27 mg/ mL

  Tiempo de retención 4.24

- Se inyecta directamente dos veces la muestra 98/6288T, IQB-9302.HCl **0.50 mg/mL** en SF.

  Los resultados son: 0.55 mg/mL - 0.56 mg/ mL

  Tiempo de retención 4.20

- Se inyecta dos veces la muestra 98/6288T, IQB-9302.HCl **1 mg/mL** en SF. Se diluye 1.0 mL de muestra hasta 2.0 mL en un matraz aforado con agua ultrapura.

  Los resultados son: 1.03 mg/mL - 1.04 mg/ mL

  Tiempo de retención 4.21

5.11.98

Emiliano Rodríguez
Responsable Control Calidad

INIBSA LABORATORIOS

IQB - 9302. HCl (muestra del 18.11.98)

Solución patrón:

Se inyecta por triplicado una solución patrón IQB-9302.HCl, Lote: 9454/R.E-1 Standard (control 9810071) LEBSA, con humedad = 0.66% y riqueza 100.7%. El CV de las tres inyecciones es 0.2%. El tiempo de retención es 4.30.

$$\frac{99.8 - (99.8 \times 0.01 \times 0.66)}{100\ mL} \times \frac{5\ mL}{10\ mL} \times \frac{100.7}{100} = 0.499\ mg / mL$$

Soluciones problema:

- Se inyecta directamente un blanco de Suero Fisiológico 98/6288T, comprobándose que no interfiere en la cuantificación del problema.

- Se inyecta directamente la muestra 98/6288T, IQB-9302.HCl **0.25 mg/mL** en SF.

  El resultado es: 0.28 mg/mL

  Tiempo de retención 4.33

- Se inyecta directamente la muestra 98/6288T, IQB-9302.HCl **0.50 mg/mL** en SF.

  El resultado es: 0.54 mg/mL

  Tiempo de retención 4.28

- Se inyecta la muestra 98/6288T, IQB-9302.HCl **1 mg/mL** en SF. Se diluye 1.0 mL de muestra hasta 2.0 mL en un matraz aforado con agua ultrapura.

  El resultado es: 1.04 mg/ mL

  Tiempo de retención 4.29

19.11.98

Emiliano Rodríguez
Responsable Control Calidad

APPENDIX V

EXPERIMENTAL PROTOCOL

PROTOCOL NO. CD-98/6288T

FOUR-WEEK INTRAVENOUS DOSE-RANGE-FINDING STUDY IN RATS.

TEST SUBSTANCE: IQB-9302.HCl

Protocol prepared by :

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Centro Industrial Santiga
c/Argenters, 6
08130-SANTA PERPÈTUA DE MOGODA
(Barcelona)
Spain
Tel. : 34 3 719 03 61
Fax : 34 3 718 96 67

For:

LABORATORIOS INIBSA, S.A.
c/Loreto, 8
08029-BARCELONA
Spain
Tel.: 34 93 321 54 08
Fax : 34 93 843 96 95

The aim of this Study is to evaluate the toxicity of the test substance IQB-9302.HCl, a local anaesthetic, when administered intravenously to rats during a period of four weeks, so as to determine the adequate dose levels for a four-week toxicity Study.

SUMMARY

Test substance :	IQB-9302.HCl, a local anaesthetic.
Animals :	Sprague Dawley rats. The rat has been chosen because it is an accepted rodent species for the study of toxicity and there is sufficient information available to justify its use.
Age at start of treatment :	6-8 weeks.
Group sizes :	4 groups of 5 males and 5 females.
Total no. of animals :	40.
Administration route :	Intravenous. This route has been chosen because it is the proposed route for administration to humans.
Dose levels:	Control (physiological saline): Low : 1 mg/kg/day Intermediate: 2 mg/kg/day High : 4 mg/kg/day
Volume of administration :	4 mL/kg.
Duration of treatment :	Four weeks.
Frequency of administration :	Once a day, seven days a week.
Proposed Study dates :	To be decided and added to this protocol as a protocol amendment.

PERSONNEL

For CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L.

Study Director : L. Canut

Deputy Study Director : A. Tortajada

Head of Department of Toxicology : J. Zapatero

Quality Assurance Unit Manager : A. Flores

For LABORATORIOS INIBSA, S.A.

Sponsor's Monitoring Scientist : A. Galiano

EXPERIMENTAL PROCEDURE

1. ANIMALS

1.1. Supply

A total of 50 rats of the strain Sprague-Dawley Crl:CD (SD) BR (25 males and 25 females) with an age of approximately 28 days bred by CHARLES RIVER, will be supplied by CRIFFA, S.A. (c/Paraires, 1-7, Nave 5, Polígono Industrial Santiga, 08130-SANTA PERPÈTUA DE MOGODA, Barcelona, Spain). The females will be nulliparous and not pregnant.

On arrival, the animals will be distributed at random in Makrolon cages (55 x 32.7 x 19 cm), according to sex, so that each cage contains a maximum of 5 animals of the same sex. During the acclimatization period, 40 rats selected from the total number supplied will be distributed among the experimental groups using a random distribution method. This procedure allows approximate equalization of initial bodyweights whilst allowing random allocation to experimental groups.

All the animals will be subjected to a prior period of observation and acclimatization of at least 2 weeks between the date of arrival and the start of treatment. During this period the animals will be inspected by a Veterinary Surgeon. Rats showing symptoms of ill-health or other anomalies will be rejected and will be replaced by other animals from the same batch.

1.2. Identification

The rats will be individually identified by a number tattooed on the ear.

1.3. Housing

The rats will be housed in Makrolon cages (55 x 32.7 x 19 cm) placed on shelves. The cages will have sawdust on the floor (Ultrasorb, Panlab, S.L.) as litter. From the week before the start of dosing, each cage will contain a maximum of 5 rats of the same sex and treatment group except when the quantity is reduced by mortalities. Each cage will be identified by a coloured card according to the dose level.

On this card will be indicated the cage number, the number and sex of the animals contained, the Study number, the test substance code, the dose level, the administration route, the date of arrival and the start of the treatment of the animals, and the name of the Study Director.

The temperature and the relative humidity of the animal house will be continuously recorded. The temperature will be kept at between 19 and 25ºC. The relative humidity will be maintained at 55 ± 10%. Levels of less than 40% and more than 70% will be avoided for prolonged periods. Lighting will be controlled to supply a 12 hours light (7:00 to 19:00 hours) and 12 hours dark cycle in a 24-hour period.

The cages corresponding to each experimental group will be arranged on the shelving in such a way that external factors such as environmental conditions are as far as possible equalised.

2. DIET AND WATER

2.1. Diet

All the rats will have free access to the dried, pelleted standard rat diet UAR A04C (Usine d'Alimentation Rationnelle, 91360-Villemoisson sur Orge, France). Each batch is analyzed by the manufacturer for composition and to detect possible contaminants.

2.2. Water

Water, supplied by Compañía de Aguas de Sabadell, S.A. will be available to the animals *ad libitum* by means of bottles. The water used is analyzed periodically to detect the presence of any contaminants.

3. TEST SUBSTANCE

3.1. Identification

The batch number of the product will be added to this protocol as an amendment.

It will be the responsibility of the Sponsor to ensure the identity, concentration, purity and stability of the test substance, and sufficient documentation will be supplied to Centro de Investigación y Desarrollo Aplicado, S.A.L. to verify this. On completion of the Study, a sample of the test substance will be retained in the Centro de Investigación y Desarrollo Aplicado, S.A.L. archives for 5 years, starting from the date of the issuing of the Final Report or until its expiry date. The remainder will be returned to the Sponsor.

3.2. Administration route and procedure

The test substance IQB-9302.HCl will be administered intravenously, by bolus, in the tail vein, using either a 25 G (0.5 x 16 mm) or a 23 G (0.6 x 25 mm) sterile disposable needle.

The velocity of injection will be 0.1 mL/second approximately.

This route has been chosen because it is the proposed route for administration to humans.

The quantity of the substance administered to each animal will be calculated daily from its bodyweight.

The rats belonging to the Control group will be treated with the vehicle (physiological saline), at the same administration volume as the rest of the treatment groups.

3.3. Administration volume

The volume of administration will be 4 mL/kg.

3.4. Frequency and duration of treatment

Once a day, seven days per week, for 4 weeks.

3.5. Dose levels and group size

Four treatment groups will be formed, including the Control group, each composed of five males and five females.

The rats will be allocated to the four treatment groups as follows:

Treatment Group	Treatment	Dose level (mg/kg/day)	Colour code	Number of animals	
				M	F
1	Physiological saline	-	White	5	5
2	IQB-9302.HCl	1	Blue	5	5
3	IQB-9302.HCl	2	Green	5	5
4	IQB-9302.HCl	4	Red	5	5

3.6. Preparation of the formulations

The test substance will be prepared daily and will be dissolved or suspended in physiological saline.

3.7. Analysis of the formulation

Before the start of the treatment period and in the course of the first and third weeks of administration, samples of the formulations prepared will be taken and these will be sent to LABORATORIOS INIBSA, S.A. for analysis.

4. OBSERVATIONS

4.1. Mortality

Any rat showing signs of extreme debility, especially if it is moribund, will be isolated, to avoid cannibalism. Rats found *in extremis* will be sacrificed to avoid the autolysis of the tissues and will be subjected to the terminal procedures described in section 5. If any rat is found dead outside normal working hours, its body will be kept in a refrigerator (+4ºC), the time of death will be recorded or, if this is not possible, the time at which it was found dead, and an autopsy will be conducted as soon as possible.

4.2. Clinical signs

All rats will be examined at least twice a day so as to record any signs of ill-health or behavioural changes. The observations will be made more frequently depending on the response obtained. These observations will be continued at the week-ends. The observations will include but will not be limited to changes in skin and fur, eyes and mucous membranes, respiratory, circulatory, autonomous and central nervous systems, somatomotor activity and behaviour pattern.

4.3. Bodyweight

The bodyweight of all the rats will be recorded one week before the start of administration, thereafter daily, and before sacrifice.

Group mean bodyweights will be calculated from the individual animal weights.

4.4. Food intake

Before the start of treatment and subsequently once per week, the quantity of food consumed in each cage will be recorded and the mean weekly intake per rat calculated.

5. TERMINAL STUDIES

5.1. Sacrifice and macroscopic examination

On completion of the 4 weeks of treatment, all the surviving rats will be sacrificed by CO_2 inhalation. A full autopsy will be performed on all animals. This will include examination of the external surface of the body, all orifices, cranial, thoracic and abdominal cavities and their contents both *in situ* and after evisceration.

Because the total number of animals exceeds the number which can be sacrificed in one day, the autopsies will be carried out on two consecutive days. However, each rat will continue to receive the test substance until the day before its sacrifice. The order in which the animals are sacrificed will be determined at random.

5.2. Organ weights

Following macroscopic examination, the following organs will be weighed after removal of superficial fat:

- Adrenals
- Brain
- Heart
- Kidneys
- Liver
- Lungs
- Ovaries
- Pituitary
- Spleen
- Testes and epididymides
- Thymus
- Thyroid
- Uterus

5.3. Procedure for obtaining histological samples

Samples of the following organs and tissues will be taken and fixed in 10% neutral-buffered formalin, with the exception of the eyes which will be preserved in Davidson's fixative:

Adrenal glands
Aorta
Bone (sternum)
Brain (bulbar, cerebellar and cortical sections)
Caecum
Colon
Eyes and optic nerves
Femur (with joint)
Heart (with papillary muscle)
Injection site (tail)
Kidneys
Liver
Lungs (with mainstem bronchi)
Lymph nodes (submandibular and mesenteric)
Mammary gland
Oesophagus
Ovaries
Pancreas
Pituitary
Prostate
Salivary gland
Sciatic nerve
Seminal vesicles
Skeletal muscle

Skin (abdominal)
Small intestine (duodenum, ileum and jejunum)
Spinal cord (cervical, thoracic and lumbar)
Spleen
Stomach
Testes and epididymides
Thymus
Thyroids and parathyroids
Tissue masses or tumours (including regional lymph nodes)
Tongue
Trachea
Urinary bladder
Uterus (corpus and cervix)
Vagina
Whatever other organ or tissue showing macroscopic alterations.

A marrow smear from the femur will be prepared, air-dried and fixed in anhydrous methanol.

5.4. Histopathological examination

Samples of the liver and kidneys, as well as any organ or tissue that presents any macroscopic alteration will be embedded in paraffin-wax, sectioned and stained with haematoxylin-eosin (phloxine variant).

Initially, the microscopic examination will be restricted to:

I. The observation of the liver and kidneys of the animals treated with IQB-9302.HCl at the high dose and the Control group animals.
II. All organs and tissues which show any macroscopic alterations.

6. STATISTICAL ANALYSIS

The bodyweights and organ weights will be evaluated by a one-way analysis of variance ($p<0.05$) and, if found significant, the degree of significance will be evaluated using the Duncan-Kramer[(1)] method ($p < 0.05$).

(1) a) Duncan D.B., Multiple Range and Multiple F Test

Other statistical methods will be used when considered appropriate, and the evaluations will take the dose-response relationship into account.

7. REPORT

A Final Report, in English, containing all the data generated during the course of this Study will be prepared, in accordance with Good Laboratory Practice regulations.

This will contain the following information:

- The title, the aim of the Study and a summary of the results.
- The name and address of the Sponsor and of the test facilities, and the Study schedule.
- The names and signatures of all personnel involved in the Study, including the Study Director and other scientists.
- The name or code of the test substance and the vehicle or excipient, and its composition, concentration and purity.
- The experimental protocol.
- The amendment to the protocol.
- A description of the animals used, including species, strain, supplier, housing, sex, bodyweight range, age, group distribution and method of identification.
- A description of the dose levels, frequency and route of administration, the galenic form used, and the duration of the treatment period.
- A description of all methods.
- A description of all the results.
- A summary and evaluation of the toxic phenomena observed.
- Figures showing bodyweights.
- A summary in tabular form of food intake, bodyweights and organ weights.

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b) Kramer C.Y., Biometrics 11, 1-42 (1955)
Extension of Multiple Range test to group means with unequal number of replications.
Biometrics 12, 307 (1956)

- Individual tables showing bodyweights and organ weights.
- Description of whatever circumstances could have affected the quality or integrity of the Study.
- A proposal for the doses to be used in the following four-week main toxicity Study.
- Food and water analysis certificates.
- Statistical analysis.
- Norms or Directives followed.
- Statement of Compliance, signed by the Study Director.
- Quality Assurance Statement, signed by the QAU Manager.
- Locations of archives containing all raw data, samples, test substances and the Final Report.

The Sponsor will be sent a complete Draft Report which has not been checked by the Quality Assurance Unit.

Once the Draft Report has been discussed with the Sponsor, and checked by the Quality Assurance Unit, the Final Report will be issued and two copies will be sent to the Sponsor.

8. DIRECTIVES

The Study procedures described in this protocol are in accordance with the following Directive:

- Directive 91/507/EEC relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products (Annex, Part 3 referring to Toxicological and Pharmacological testing) and Annex I of recommendation 83/571/EEC.

9. GOOD LABORATORY PRACTICE

This Study will be carried out according to the Good Laboratory Practice regulations published by the OECD (OECD Principles of Good Laboratory Practice, C (81) 30 (Final), Paris, 12th May, 1981. Annex 2), and adopted by the EEC (now EU) according to

Directive 87/18/EEC of 18th December 1986 and in Spain by Real Decreto 822/1993, of 28th May.

The Study will be assessed to assure compliance with Standard Operating Procedures. Study procedures will be inspected periodically by the Quality Assurance Unit, and the inspection dates included in the Report. The data contained in the Report will be audited to ensure accuracy and a statement signed by the Quality Assurance Manager will be included in the Report.

10. STANDARD OPERATING PROCEDURES

All procedures will be carried out according to the Standard Operating Procedures of Centro de Investigación y Desarrollo Aplicado, S.A.L..

11. ARCHIVES

All the data obtained during the Study will be kept for at least five years in the Centro de Investigación y Desarrollo Aplicado, S.A.L. archives.

The following documents, amongst others, will be kept:

- The Protocol and any amendments.
- Work schedule.
- Documentation relating to the test substance.
- Documentation relating to animals used.
- Notebooks, registers and other raw Study data.
- The Final Report.

No material relating to this Study will be disposed of without the prior written consent of the Sponsor.

All histological preparations and tissues will also be stored for this same period. All tissues preserved in formalin will be stored for a period of two years following completion of the Study.

12. PROTOCOL AMENDMENTS

Any changes or revision of the protocol will only be implemented following formal authorization from the Sponsor, after discussions between Centro de Investigación y Desarrollo Aplicado S.A.L. and the Sponsor's Monitoring Scientist.

Any alteration agreed to will be documented, signed, dated and presented in the form of an amendment to this protocol.

13. PERSONNEL

The personnel involved will be designated before the start of the Study.

14. TESTING LABORATORY

This Study will be carried out in the Toxicology Department laboratories and animal facilities at Centro de Investigación y Desarollo Aplicado, Centro Industrial Santiga, c/Argenters 6, 08130-SANTA PERPÈTUA DE MOGODA, Barcelona (Spain).

The histopathological examination of the histological preparations will be carried out in the Centro de Histopatología Veterinaria, c/Castellnou, 21, 08017-BARCELONA, Spain.

PROTOCOL NO. CD-98/6288T

FOUR-WEEK INTRAVENOUS DOSE-RANGE-FINDING STUDY IN RATS.

TEST SUBSTANCE: IQB-9302.HCl

No. of pages in protocol : 15

For LABORATORIOS INIBSA, S.A.

Protocol accepted by ALVARO GALIANO signature 9 October 98 date

For CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L.

Study Director _____ signature 1 October 1998 date

L. Canut

Head Toxicology

Department _____ signature 1 October 1998 date

J. Zapatero

Quality Assurance Unit _____ signature 1 October 1998 date

A. Flores

APPENDIX VI

PROTOCOL AMENDMENT

PROTOCOL AMENDMENT (No. 1) (page 1 of 1)

PROTOCOL NO. : CD-98/6288T DATE OF AMENDMENT : 28.OCT.98

TEST SUBSTANCE: IQB-9302.HCl SPECIES : SPRAGUE-DAWLEY RAT

AMENDMENT

SUMMARY

As stated in the experimental protocol and to complete the information therein, the proposed Study dates are as follows:

Arrival of animals and start of acclimatization period: 21st October 1998
Start of treatment: 2nd November 1998
End of treatment: 29th November 1998
Draft Report: January 1999

1. ANIMALS

1.1. Supply

The first sentence of the third paragraph will be modified as follows:

"All the animals will be subjected to a prior period of observation and acclimatization of 12 days between the date of arrival and the start of treatment."

3. TEST SUBSTANCE

3.1. Identification

As specified in this Section, the batch number of the test substance will be added as follows:

Test substance	Batch no.
IQB-9302.HCl	9454.001

FOR CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.I.

HEAD TOXICOLOGY DEPT.:

STUDY DIRECTOR :

QUALITY ASSURANCE UNIT :

DATE : 29 octubre 1998

FOR THE SPONSOR

SCIENTIFIC MONITOR :

DATE : 29 Oct 1998

CIRCULATION : JZ, QAU, LC, Sponsor (2)