REPORT NO. CD-98/6289T

FOUR-WEEK TOXICITY STUDY IN RATS BY INTRAVENOUS ADMINISTRATION WITH A TWO-WEEK RECOVERY PERIOD.

TEST SUBSTANCE: IQB-9302.HCl

VOLUME II

REPORT NO. CD-98/6289T

FOUR-WEEK TOXICITY STUDY IN RATS BY INTRAVENOUS ADMINISTRATION WITH A TWO-WEEK RECOVERY PERIOD.

TEST SUBSTANCE: IQB-9302.HCl

Head Toxicology Department:	J. Zapatero Biologist
Study Director:	L. Canut Biologist
Histopathologist:	J. Alumà Medical Doctor and Surgeon
Haematology and Biochemistry:	M. de Luna Biologist
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: B. Befani Date Report Issued:	

CONTENTS

Volume I

CONTENTS (Cont.)

Volume I (Cont.)

CONTENTS (Cont.)

Volume I (Cont.)

HISTOPATHOLOGICAL REPORT

(Animals sacrificed at the end of the treatment period)

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	1 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	*		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	2 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	*		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	3 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	4 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	5 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	6 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	7 M

MICROSCOPIC OBSERVATIONS

LUNGS

Intraalveolar histiocytosis, focal

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	8 M

MICROSCOPIC OBSERVATIONS

KIDNEYS

Dilation of renal pelvis

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	9 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	*		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	10 M

MICROSCOPIC OBSERVATIONS

KIDNEYS

Dilation of renal pelvis

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	51 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	52 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	53 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	54 F

MICROSCOPIC OBSERVATIONS

LUNGS

Intraalveolar histiocytosis, focal

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	55 F

MICROSCOPIC OBSERVATIONS

LIVER

Microgranuloma

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	56 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)		
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	57 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	58 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	59 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	60 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 0.75 mg/kg/day	69 F

MICROSCOPIC OBSERVATIONS

KIDNEYS

Dilation of renal pelvis

THYMUS

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	1	
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			Skin			Vagina		
Lungs			Spinal cord			Injection site (tail)		
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 1.25 mg/kg/day	29 M

MICROSCOPIC OBSERVATIONS

KIDNEYS

Dilation of renal pelvis

TESTES

Tubular atrophy

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals			Oesophagus			Stomach		
Aorta			Ovaries			Testes	2	
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			Skin			Vagina		
Lungs			Spinal cord			Injection site (tail)		
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 1.25 mg/kg/day	79 F

MICROSCOPIC OBSERVATIONS

THYMUS

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	1	
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			Skeletal muscle			Uterus		
Liver			Skin			Vagina		
Lungs			Spinal cord			Injection site (tail)		
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 1.25 mg/kg/day	85 F

MICROSCOPIC OBSERVATIONS

KIDNEYS

Dilation of renal pelvis

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			Skin			Vagina		
Lungs			Spinal cord			Injection site (tail)		
Lymph nodes			Spleen					
Mammary gland			Sternum					

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	36 M

MICROSCOPIC OBSERVATIONS

LUNGS

Intraalveolar histiocytosis, focal

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	1	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	37 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	*		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	38 M

MICROSCOPIC OBSERVATIONS

LUNGS

Intraalveolar histiocytosis, focal

THYMUS

Multifocal congestion

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	39 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	40 M

MICROSCOPIC OBSERVATIONS

PITUITARY GLAND

Simple cyst

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	41 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	42 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	43 M

MICROSCOPIC OBSERVATIONS

KIDNEYS

Interstitial nephritis, focal

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	44 M

MICROSCOPIC OBSERVATIONS

SPLEEN

Lymphoid hyperplasia

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	*		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	45 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	*		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	86 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	87 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	88 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	89 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	90 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	91 F

MICROSCOPIC OBSERVATIONS

LIVER

Microgranuloma

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	92 F

MICROSCOPIC OBSERVATIONS

LIVER

Lymphocytary infiltrate, portal

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	93 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	94 F

MICROSCOPIC OBSERVATIONS

KIDNEYS

Pyelitis, acute, non-specific

URINARY BLADDER

Cystitis, acute, non-specific

EYES

Lymphocytary infiltrate in Harder's gland, unilateral

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	95 F

MICROSCOPIC OBSERVATIONS

KIDNEYS

Pyelitis, acute, non-specific

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

HISTOPATHOLOGICAL REPORT

(Animals sacrificed at the end of the recovery period)

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	11 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	12 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	*		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	13 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	*		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	14 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	*		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	15 M

MICROSCOPIC OBSERVATIONS

LIVER

Hepatocytary vacuolisation, centrolobular

KIDNEYS

Dilation of renal pelvis

LUNGS

Intraalveolar histiocytosis, focal

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	61 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	62 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	63 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	64 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	Control	65 F

MICROSCOPIC OBSERVATIONS

PITUITARY GLAND

Simple cyst

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	46 M

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl	47 M
	2.25 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl	48 M
	2.25 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl	49 M
	2.25 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	*		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl	50 M
	2.25 mg/kg/day	

MICROSCOPIC OBSERVATIONS

LUNGS

Intraalveolar histiocytosis, focal

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries			Testes	2	
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate	1		Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles	2		Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus		
Liver	2	1	Skin	1		Vagina		
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	*		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl	96 F
	2.25 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl 2.25 mg/kg/day	97 F

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl	98 F
	2.25 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl	99 F
	2.25 mg/kg/day	

MICROSCOPIC OBSERVATIONS

KIDNEYS

Dilation of renal pelvis

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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

HISTOPATHOLOGICAL SECTION

HISTOPATHOLOGICAL REPORT

REPORT NO.	TEST SUBSTANCE	ANIMAL
CD-98/6289T	IQB-9302.HCl	100 F
	2.25 mg/kg/day	

MICROSCOPIC OBSERVATIONS

No histopathological alterations were observed.

Tissue samples observed:

	H&E	Sp.		H&E	Sp.		H&E	Sp.
Adrenals	2		Oesophagus	1		Stomach	1	
Aorta	1		Ovaries	2		Testes		
Brain	3		Pancreas	1		Thymus	1	
Eyes	2		Pituitary gland	1		Thyroid glands	2	
Femur	1		Prostate			Tissue masses		
Heart	1		Salivary gland	1		Tongue	1	
Intestine, large	3		Sciatic nerve	1		Trachea	1	
Intestine, small	3		Seminal vesicles			Urinary bladder	1	
Kidneys	2		Skeletal muscle	1		Uterus	3	
Liver	2	1	Skin	1		Vagina	1	
Lungs	2		Spinal cord	3		Injection site (tail)	1	
Lymph nodes	2		Spleen	1				
Mammary gland	1		Sternum	1				

H&E : Haematoxylin-eosin Sp.: Special techniques *: Tissue not examined

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	
HCB	< 1	(< 10)	p.p'DDD	< 5	
PCB	< 50	(< 50)	o.p'DDE	< 1	(Σ < 50)
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

FICHE CONTROLE

A04C Lot 80609

Date de Fabrication 09/06/1998

Date limite de vente 09/10/1998

Date limite d'utilisation 09/06/1999

Numéros des sacs :	1 à 1500

Quantité fabriquée ..... *(en tonnes)*	42
Contrôle de la composition centésimale	*Conforme*

TECHNOLOGIE DES PELLETS

Diamètre ..... *(en mm)*	16.41	±	0.09	*(15.5 à 17.0)*
Résistance à l'écrasement ..... *(en Kgf / cm²)*	16.7	±	1.3	*(12 à 32)*
Résistance à l'abrasion ..... *(en %)*	97.0			*(> 96)*
Masse Spécifique ..... *(en g / l)*	700.0			
Poids ..... *(en g)*	5.870	±	0.710	
Longueur ..... *(en mm)*	23.00	±	3.00	*(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 %)*	11.5	*(9 à 14)*
Protéines ..... *(en %)*	16.8	*(14.5 à 18.0)*
Lipides ..... *(en %)*	3.1	*(1.7 à 3.7)*
Glucides E.N.A. ..... *(en %)*	59.3	*(57.0 à 63.0)*
Dont Amidon ..... *(en %)*	48.8	*(35.0 à 53.0)*
" Sucres totaux ..... *(en %)*	1.7	
Cellulose WEENDE ..... *(en %)*	3.9	*(3.0 à 5.5)*
Hémicellulose ..... *(en %)*		
Cellulose vraie ..... *(en %)*		
Lignine ..... *(en %)*		
Minéraux totaux ..... *(en %)*	5.3	*(4.0 à 6.0)*
Dont Calcium ..... *(en mg / Kg)*	8 600	*(6 000 à 10 000)*
" Phosphore ..... *(en mg / Kg)*	5 600	*(4 500 à 7 000)*
" Sodium ..... *(en mg / Kg)*	1 900	*(1 500 à 3 500)*
" Potassium ..... *(en mg / Kg)*	7 000	*(5 500 à 8 500)*
" Manganèse ..... *(en mg / Kg)*	79	*(40 à 100)*
" Cuivre ..... *(en mg / Kg)*	16	*(8 à 35)*
" Vitamine A ..... *(en UI / Kg)*	6 600	*(4 000 à 11 000)*
" Vitamine C ..... *(en mg / Kg)*		
" Vitamine D3 ..... *(en UI / Kg)*	900	*(<= 3 000)*
" Vitamine E ..... *(en mg / Kg)*	30	

CONTROLE DES CONTAMINANTS

BACTERIOLOGIQUES		
Germes revivifiables .... *(/ g)*	100	*(< 100 000)*
Moisissures & levures .. *(/ g)*	< 10	*(< 1 000)*
Coliformes totaux ..... *(/ g)*	0	*(< 5)*
Coliformes fécaux ..... *(/ g)*	0	*(0)*
Anaérobies S.R. ..... *(/ g)*	< 10	*(< 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)	360	(< 1 500)
Mercure ... (en µg / Kg)	40	(< 100)
Arsenic ... (en µg / Kg)	30	(< 1 000)
Cadmium ... (en µg / Kg)	70	(< 250)
Sélénium .. (en µg / Kg)	180	(< 600)

DERIVES NITROSES

NO2 ..... (en mg / Kg)	0.5	
NO3 ..... (en mg / Kg)	9.5	(Σ < 50)
NDMA ..... (en µg / Kg)	1.3	(< 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	2	(< 100)	Heptachlore	< 1	
a HCH	< 1	(< 20)	Heptachlore Epoxyde ...	< 1	(Σ < 10)
b HCH	< 5	(< 10)	Endrine	< 1	(< 10)
d HCH	< 5	(< 100)	o.p'DDD	< 5	
HCB	< 1	(< 10)	p.p'DDD	< 5	
PCB	< 50	(< 50)	o.p'DDE	< 1	
Aldrine	< 1	(< 10)	p.p'DDE	< 1	(Σ < 50)
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	20	(< 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

17/07/98

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).

186.

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

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 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

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)

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.

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 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

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)

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**

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)

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**

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)

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

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)

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.

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)

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

ych

195.

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)

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

TEST SUBSTANCE 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

IQB - 9302. HCl (muestra del 19.01.99)

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 0.5%. El tiempo de retención es 4.48.

$$\frac{98.4 - (98.4 \times 0.01 \times 0.66)}{100 \text{ mL}} \times \frac{5 \text{ mL}}{10 \text{ mL}} \times \frac{100.7}{100} = 0.492 \text{ mg / mL}$$

Soluciones problema:

- Se inyecta directamente dos veces un blanco de Suero Fisiológico 98/6289T, comprobándose que no interfiere en la cuantificación del problema.

- Se inyecta directamente dos veces la muestra 98/6289T, IQB-9302.HCl **0.211 mg/mL** en SF.

  Los resultados son: 0.205 mg/mL - 0.208 mg/ mL

  Tiempo de retención 4.52

- Se inyecta directamente dos veces la muestra 98/6289T, IQB-9302.HCl **0.352 mg/mL** en SF.

  Los resultados son: 0.335 mg/mL - 0.337 mg/ mL

  Tiempo de retención 4.50 - 4.48

  Se inyecta directamente dos veces la muestra 98/6289T, IQB-9302.HCl **0.634 mg/mL** en SF. Los resultados son: 0.617 mg/mL - 0.611 mg/ mL

  Tiempo de retención 4.45

29.C.99

Emiliano Rodríguez
Responsable Control Calidad

INIBSA LABORATORIOS

IQB - 9302. HCl (muestra del 02.02.99)

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 4.47.

$$\frac{51.1 - (51.1 \times 0.01 \times 0.66)}{50\ mL} \times \frac{5\ mL}{10\ mL} \times \frac{100.7}{100} = 0.511\ mg / mL$$

Soluciones problema:

- Se inyecta directamente la muestra 98/6289T, IQB-9302.HCl **0.211 mg/mL** en SF.

  El resultado es: 0.207 mg/mL

  Tiempo de retención 4.51

- Se inyecta directamente la muestra 98/6289T, IQB-9302.HCl **0.352 mg/mL** en SF.

  El resultado es: 0.341 mg/mL

  Tiempo de retención 4.48

- Se inyecta directamente la muestra 98/6289T, IQB-9302.HCl **0.634 mg/mL** en SF.

  El resultado es: 0.618 mg/mL

  Tiempo de retención 4.43

29.6.99

Emiliano Rodríguez
Responsable Control Calidad

APPENDIX V

EXPERIMENTAL PROTOCOL

PROTOCOL NO. CD-98/6289T

FOUR-WEEK TOXICITY STUDY IN RATS BY INTRAVENOUS ADMINISTRATION WITH A TWO-WEEK RECOVERY PERIOD.

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 for a period of 4 weeks. This Study should provide a rational base for the evaluation of the toxicological risk to man, and indicate potential target organs.

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 :	Two groups (Control and high dose) composed of 15 males and 15 females each and a further two groups (intermediate and low dose) composed of 10 males and 10 females each.
Total no. of animals :	100.
Administration route :	Intravenous. This route has been chosen because it is the proposed route for administration to humans.
Duration of treatment :	4 weeks.
Frequency of administration :	Once a day, seven days a week.
Recovery period:	2 weeks.
Dose levels:	Control (only vehicle) : Low : Intermediate : High :

The doses to be used will be selected after a discussion with the Sponsor of the results obtained for a preliminary Study and will be specified in a protocol amendment.

Volume of administration : 4 mL/kg.

Proposed Study dates : The Study dates will be determined at a later date and specified in 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 120 Sprague-Dawley Crl:CD (SD) BR rats (60 males and 60 females) approximately 28 days old, 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 and housed 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, 100 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 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 undergo a veterinary inspection. 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 where this number is reduced by death. 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 22 ± 3°C. 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 artificial and 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 equalized.

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 and the stability of the test substance will be added to this protocol as an amendment.

It will be the responsibility of the Sponsor to ensure the identity, 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. This route has been chosen because it is the expected route for human administration.

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

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

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.

The rats will be distributed among the four groups as follows:

Group	Dose level	Colour code	Total no. of animals	No. of animals sacrificed	
				at end of admin. period	at end of recovery period
1	Control (vehicle)	White	15 M + 15 F	10 M + 10 F	5 M + 5 F
2	Low	Blue	10 M + 10 F	10 M + 10 F	
3	Intermediate	Green	10 M + 10 F	10 M + 10 F	
4	High	Red	15 M + 15 F	10 M + 10 F	5 M + 5 F

The Control group will only receive the vehicle at the same volume and following the same pattern of administration as that of the remaining treatment groups.

3.6. Preparation of the formulations

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

3.7. Analysis of the formulation

Before the start of the treatment period and in the course of the 1st and 3rd weeks of administration, samples of the formulations prepared will be taken and these will be sent to LABORATORIOS INIBSA, S.A. for analysis.

3.8. Recovery period

Five males and five females of the Control and of the high-dose group will be selected at random to undergo a recovery period of 2 weeks after the last administration.

The aim of the recovery period is to study the evolution of the possible alterations recorded during the treatment period.

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 6. If any rat is found dead outside normal working hours, its body will be kept in a refrigerator (+4°C to 8°C), 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 frequency of the observations will be increased depending on the response obtained. The observations will be continued at the week-ends. Observations will include 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, daily during treatment, 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.

4.5. Water intake

The amount of water consumed will be noted by visual examination. In addition, the water consumed in each cage will be measured daily for a period of 5 days, during the 3rd week treatment.

4.6. Ophthalmoscopy

Before the start of treatment, the eyes of all the animals will be examined. These examinations will include the cornea, the conjunctivae, the sclerotica, the iris and the fundus.

The observation will be conducted using an indirect ophthalmoscope.

Additional examinations will be made, before the end of treatment and before the end of the recovery period, of the eyes of the animals from the Control and high dose groups. If any anomaly related to the treatment is observed, the examination will be extended to include the remaining animals.

The pupils of the rats will be dilated by instillation of one drop of 1% cyclopentholate chlorhydrate eyedrops before each examination.

5. LABORATORY STUDIES

During the 4th week of treatment, samples of blood will be withdrawn under light ether anaesthesia from the orbital sinus of 10 males and 10 females of each group. These animals will have been previously fasted for 16 hours before extracting the blood samples.

In addition, blood samples will be taken and analysed at the end of the recovery period.

The blood samples will be taken from each animal between approximately 7:30 and 10:00 in the morning to reduce biological variation caused by circadian rhythms.

Similarly, samples will be taken of the urine produced over 16 hours by 10 males and 10 females from each treatment group. To this end the rats will be deprived of food and water for 16 hours.

5.1. Haematology

The following determinations will be performed:

Parameter	Method/Instrumentation	Units
Erythrocyte count	Haematological counter. SYSMEX F-800	$10^6/\mu L$
Haemoglobin	Haematological counter. SYSMEX F-800	g/100 mL
Haematocrit	Haematological counter. SYSMEX F-800	%
Mean corpuscular volume (MCV)	Calculation. SYSMEX F-800	fL
Mean corpuscular haemoglobin (MCH)	Calculation. SYSMEX F-800	pg
Mean corpuscular haemoglobin concentration (MCHC)	Calculation. SYSMEX F-800	g/100 mL
Reticulocyte count*	New methylene blue stain. Microscope	%
Total leukocyte count	Haematological counter. SYSMEX F-800	$10^3/\mu L$
Differential leukocyte count - Neutrophils - Lymphocytes - Eosinophils - Basophils - Monocytes	May Grünwald-Giemsa stain. Microscope	$10^3/\mu L$
Platelet count	Haematological counter. SYSMEX F-800	$10^3/\mu L$
Prothrombin time	Coagulometer. KC-4A	s

* Slides will be prepared, and these will be examined if there are any signs of anaemia.

5.2. Biochemistry

The following serum determinations will be carried out:

Parameter	Method/Instrumentation	Unit
Glucose	Glucose dehydrogenase. COBAS MIRA	mg/100 mL
Urea	Urease. GLDH. COBAS MIRA	mg/100 mL
Creatinine	Jaffé. COBAS MIRA	mg/100 mL
Total bilirubin	Jendrassik-Grof reaction. COBAS MIRA	mg/100 mL
Aspartate aminotransferase (AST/GOT)	Malate dehydrogenase. DGKC. COBAS MIRA	U/L
Alanine aminotransferase (ALT/GPT)	Lactate dehydrogenase. DGKC. COBAS MIRA	U/L
Sorbitol dehydrogenase (SDH)	Reduction of fructose COBAS MIRA	U/L
Alkaline phosphatase	p-nitrophenylphosphate. DGKC. COBAS MIRA	U/L
Total cholesterol	CHOD-PAP. COBAS MIRA	mg/100 mL
Sodium	Ion selective electrode. NOVA I	mmol/L
Potassium	Ion selective electrode. NOVA I	mmol/L
Chloride	Coulombimetric. CORNING 925	mmol/L
Calcium	MTB. COBAS MIRA	mg/100 mL
Inorganic phosphorus	Phosphomolybdate without deproteinization. COBAS MIRA	mg/100 mL
Total protein	Biuret. COBAS MIRA	g/100 mL
Albumin	Bromocresol green. COBAS MIRA	g/100 mL

The albumin/globulin ratios will be calculated using the total protein and albumin values.

5.3. Analysis of urine

The following determinations will be made:

Parameters	Method
Colour Volume	Macroscopic observation
Specific gravity	Refractometry
pH Proteins Glucose Bilirubin Ketones Urobilinogen Haemoglobin	Combur 8 test

The Combur 8 test is a strip reagents kit obtained from Boehringer Mannheim and it is used as a qualitative indicator of the concentration of the different parameters. The results are presented using the following scale:

0 = negative
+ = small quantity of the parameter analyzed
++ = moderate quantity of the parameter analyzed
+++ = large quantity of the parameter analyzed

The urinary sediment will be examined for the detection of:

- Epithelial cells
- Leukocytes
- Erythrocytes
- Organisms (bacteria, etc.)
- Crystals
- Other abnormal constituents (casts, sperm, etc.)

6. TERMINAL STUDIES

6.1. Sacrifice and macroscopic examination

On completion of the 4 weeks of treatment, all surviving rats will be sacrificed by CO_2 inhalation, except those animals that will be selected to undergo the recovery period. A full autopsy will be performed on all animals and 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 three 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.

6.2. Organ weights

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

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

6.3. 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 and optic nerves which will be preserved in Davidson's fixative:

Adrenals
Aorta
Bone (sternum)
Brain (bulbar, cerebellar and cortical sections)
Caecum
Colon
Eyes and optic nerves
Femur (with joint)
Heart
Injection site (tail)
Kidneys
Liver
Lungs and mainstem bronchi
Lymph nodes (submandibular and mesenteric)
Mammary gland
Oesophagus
Ovaries
Pancreas
Pituitary gland
Prostate
Rectum
Salivary glands
Sciatic nerve
Seminal vesicles
Skeletal muscle
Skin (abdominal)
Small intestine (duodenum, ileum, jejunum)
Spinal cord (cervical, thoracic and lumbar)
Spleen
Stomach
Testes and epididymides
Thymus
Thyroid 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.

6.4. Histopathological examination

Samples of the above-mentioned organs and tissues, except the marrow smear of which no examination is planned, will be embedded in paraffin-wax, sectioned and stained with haematoxylin-eosin (phloxine variant).

Sections of liver obtained after freezing will be stained using the Fat Red 7B method for examination of fat.

Initially, the microscopic examination will be restricted to:

I. Tissues of animals which have died, so as to determine the cause of death.
II. All animals pertaining to the Control and high dose groups.
III. All organs and tissues of animals from the low and intermediate dose groups which show any macroscopic alterations.

In addition, the tissues of animals in the intermediate and low dose groups will be examined where anomalies have been found in the high dose group.

7. STATISTICAL ANALYSIS

Bodyweight, organ weight, the results of the haematological and clinical biochemical analyses, and urinary volume, pH and specific gravity, 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.

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

---

[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 replications.
Biometrics 12, 307 (1956)

8. 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 its composition, concentration and purity.
- The vehicle or excipient.
- The experimental protocol.
- The amendments to the protocol.
- A description of the animals used, including species, strain, supplier, housing, sex, bodyweight range, age, group distribution and method of identification.
- Food and water analysis certificates.
- 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 clinical signs, food intake, bodyweights, analytical results and organ weights.
- Individual tables showing bodyweights, analytical results, organ weights and histopathological findings.
- Statistical analysis.
- Norms or Directives followed.

- Description of whatever circumstances could have affected the quality or integrity of the Study.
- 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.

Two months after the sacrifice of all the animals, the Sponsor will be sent a complete Draft Report, in English, which will not have 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 in English, and two copies will be sent to the Sponsor.

9. DIRECTIVES

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

- Directive 91/507/EEC on norms and analytical, toxicopharmacological and clinical protocols, for the testing of medicines (third part of the Annex, referring to toxicological and pharmacological tests), and Annex I of Recommendation 83/571/EEC.
- Directive 92/69/EEC. Annex. Part B. Method B.7. Toxicity by continuous (28 day) oral administration.

10. 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.

11. 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..

12. ARCHIVES

All the documentation pertaining to the Study, will be kept for at least five years at Centro de Investigación y Desarrollo Aplicado, S.A.L.

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 the histological preparations and embedded tissues will also be kept for this period of time. All the tissues preserved in formalin will be kept for the two years following the end of the Study.

13. 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.

14. PERSONNEL

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

15. 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-98/6289T

FOUR-WEEK TOXICITY STUDY IN RATS BY INTRAVENOUS ADMINISTRATION WITH A TWO-WEEK RECOVERY PERIOD.

TEST SUBSTANCE: IQB-9302.HCl

No. of pages in protocol : 20

For LABORATORIOS INIBSA, S.A.

Protocol accepted by _____ signature 9 October 98 date

A. GALIANA

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 NO. : CD-98/6289T DATE OF AMENDMENT : 18.JAN.99

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: 30th December 1998

Treatment period: 18th January to 14th February 1999

Recovery period: 15th February to 28th February 1999

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

3.2. Administration route and procedure

The second paragraph will be modified as follows:

The duration of injection procedure will be 2 minutes approximately.

3.5. Dose levels and group size

As stated in the experimental protocol and to complete the information therein, the dose levels will be the following:

Group	Treatment	Dose (mg/kg/day)
1	CONTROL (Physiological saline)	-
2	IQB-9302.HCl	0.75
3	IQB-9302.HCl	1.25
4	IQB-9302.HCl	2.25

PROTOCOL NO. : CD-98/6289T
DATE OF AMENDMENT : 18.JAN.99
TEST SUBSTANCE: IQB-9302.HCl
SPECIES : SPRAGUE-DAWLEY RAT

3.7. Analysis of the formulation

The paragraph will be modified as follows:

In the course of the 1st and 3rd weeks of administration, samples of the formulations prepared will be taken and these will be sent to LABORATORIOS INIBSA, S.A. for analysis.

4.5. Water intake

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

In addition, the water consumed in each cage will be measured daily for a period of 5 days, during the 3rd week treatment and, subsequently, during the second week of the recovery period.

FOR CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.I.
HEAD TOXICOLOGY DEPT. :
STUDY DIRECTOR :
QUALITY ASSURANCE UNIT :
DATE : 18 January 1999

FOR THE SPONSOR
SCIENTIFIC MONITOR :
DATE : 18 January 1999

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

PROTOCOL AMENDMENT (No. 2) (page 1 of 1)

PROTOCOL NO. : CD-98/6289T | DATE OF AMENDMENT : 02.FEB.99

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

AMENDMENT

3.6. Preparation of the formulations

To complete the information included in this section the following paragraph will be added:

The doses to be tested refer to the concentration of the base form of the test substance. Taking into account that the molecular weight of the test substance is 286.42 and of the hydrochloride form is 322.88, a factor of 1.127 will be used for the preparation of the formulations.

5. LABORATORY STUDIES

The fourth paragraph will be modified as follows:

"Similarly, samples will be taken of urine produced over 16 hours by 10 males and 10 females from each treatment group. To this end, the rats will be deprived of food for 16 hours."

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

HEAD TOXICOLOGY DEPT. :

STUDY DIRECTOR :

QUALITY ASSURANCE UNIT :

DATE : 2 February 1999

FOR THE SPONSOR

SCIENTIFIC MONITOR :

DATE : 3 Feb 99

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

BQ/147