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8EHQ-99-14381

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Document Control Officer (TS-790)
Attn: Section 8 (e) Coordinator
Information Management Division
Office of Toxic Substances
Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

MR31353

Subject: 8EHQ-99-14381

To Whom It May Concern:

Enclosed is a copy of the final report for a study that our company submitted to the Environmental Protection Agency under Section 8(e) of the Toxic Substances Control Act on February 18, 1999. The study is a 90-day subchronic oral toxicity study in the rat with the test substance [

]. The generic name for the test substance is "long chain alkenylamide borate".

A copy of this letter and of the final report, with confidential business information deleted, is attached for EPA's use when responding to public inquiries on this matter.

If there are any questions on this submission, please contact me at the number shown on the top of this page.

Sincerely,

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Final report []

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NINETY DAY REPEATED DOSE
ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
SPL PROJECT NUMBER: [] []

AUTHORS: L J Jones
D Mullee
P N Brooks

STUDY SPONSOR:



RDLJR00060

ISSUED BY:

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SPL PROJECT NUMBER:

QUALITY ASSURANCE REPORT

The conduct of this study has been subjected to periodic inspections by Safeparm Quality Assurance Unit. Inspection findings are reported to Management/Study Directors on the day of inspection in each case. The dates of inspection are given below:

25, 26 June 1998

03 July 1998

04 August 1998

23 September 1998

This report has been audited by Safeparm Quality Assurance Unit. It is considered to be an accurate account of the data generated and of the procedures followed.

Date of Report Audit:

22 January 1999

J R Pateman CBiol MIBiol Dip RQA
For Safeparm Quality Assurance Unit



DATE:

15 MAR 1999

SPL PROJECT NUMBER:

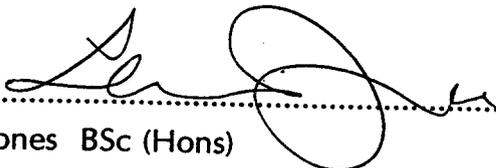
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GLP COMPLIANCE STATEMENT

I, the undersigned, hereby declare that the objectives laid down in the protocol were achieved and as nothing occurred to adversely affect the quality or integrity of the study, I consider the data generated to be valid. This report fully and accurately reflects the procedures used and data generated.

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1997 (SI 1997/654)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (Revised 1997, ENV/MC/CHEM (98) 17); and are in accordance with, and implement, the requirements of Directives 87/18/EEC and 88/320/EEC.

These international standards are acceptable to the United States Environmental Protection Agency and Food and Drug Administration, and fulfil the requirements of 40 CFR Part 792 and 21 CFR Part 58 (as amended).

 DATE: **15 MAR 1999**

L J Jones BSc (Hons)
Study Director

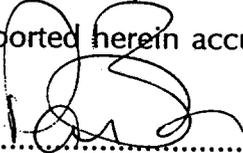
The following scientific and supervisory personnel were involved in the study under the overall supervision of the Study Director:

- T Blagden MIAT
- M Trussell HNC
- P W Thompson HNC
- N Doleman HNC

SPL PROJECT NUMBER:

AUTHENTICATION

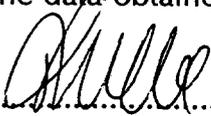
I, the undersigned, hereby declare that the macroscopic and microscopic pathology data presented in this report were compiled by me, or under my supervision, and that the results reported herein accurately reflect the data obtained.



DATE: **12 MAR 1999**

P N Brooks MSc BSc EurBiol CBiol MIBiol
EUROTOX Registered Toxicologist
Study Pathologist

I, the undersigned, hereby declare that the analytical data presented in this report were compiled by me or under my supervision and that the results reported herein accurately reflect the data obtained.



DATE: **12 MAR 1999**

D Mullee CChem MRSC
Head of Analytical Chemistry

Approved for issue:



DATE: **15 MAR 1999**

M P Blackwell BSc CBiol MIBiol FIAT
EUROTOX Registered Toxicologist
Head of Repeat Dose and Inhalation Toxicology

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ORAL (GAVAGE) TOXICITY STUDY
IN THE RAT**

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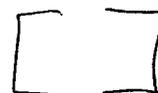
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PART I

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NINETY DAY REPEATED DOSE
ORAL (GAVAGE) TOXICITY STUDY
IN THE RAT

SPL PROJECT NUMBER: [] []

SUMMARY

STUDY SPONSOR : [] []

STUDY TITLE : NINETY DAY REPEATED
DOSE ORAL (GAVAGE) TOXICITY
STUDY IN THE RAT

TEST MATERIAL : [] []

1. The study was designed to investigate the systemic toxicity of the test material. It follows the testing method described in Commission Directive 87/302/EEC and complies with the recommendations of the OECD Guidelines for Testing of Chemicals No. 408 "Subchronic Oral Toxicity - Rodent: 90 day Study".

The test material was administered by gavage to three groups, each of ten male and ten female Sprague-Dawley CrI:CD®BR strain rats, for ninety consecutive days, at dose levels of 50, 250 and 1000 mg/kg/day. A control group of ten males and ten females was dosed with vehicle alone (Arachis oil BP).

Clinical signs, bodyweight development, food and water consumption were monitored during the study. Haematology and blood chemistry were evaluated for all animals at the end of the study. Ophthalmoscopic examination was also performed on control group and high dose animals.

All animals were subjected to a gross necropsy examination and a comprehensive histopathological evaluation of tissues was performed.

The results are summarised as follows:

2. Mortality

There were no deaths during the study.

3. Clinical Observations

The clinically observable signs detected in test or control animals were all considered to be without toxicological significance.

Animals of either sex treated with 1000 mg/kg/day showed increased salivation approximately two minutes after dosing from Day 3 onwards. One male treated with 250 mg/kg/day also showed transient increased salivation on Day 31. Increased salivation was still apparent in some high dose individuals up to one hour after dosing as the study progressed. Accompanying observations included wet and/or red/brown staining of the external fur surface and occasional incidents of noisy respiration. Such observations are often reported when a test material formulation has an unpleasant taste or is slightly irritant and, in isolation, were considered not to be indicative of toxicity.

4. Bodyweight

A statistically significant reduction in bodyweight gain was detected for males treated with 1000 mg/kg/day during Week 2 and Week 10 of treatment.

No adverse effect on bodyweight gain was detected for 1000 mg/kg/day females or for animals of either sex treated with 250 or 50 mg/kg/day.

5. Food Consumption

A slight reduction in dietary intake was detected for males treated with 1000 mg/kg/day during the first three weeks of treatment. Food efficiency was slightly reduced during Week 10 only.

No adverse effect on food consumption was detected for 1000 mg/kg/day females or for animals of either sex treated with 250 or 50 mg/kg/day.

6. Water Consumption

Visual inspection of water bottles revealed no intergroup differences.

7. Ophthalmoscopy

There were no treatment-related ocular effects.

8. Haematology

Females treated with 1000 mg/kg/day showed reductions in haemoglobin and haematocrit together with reduced mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration when compared with controls.

No such changes were detected for 1000 mg/kg/day males or for animals of either sex treated with 250 or 50 mg/kg/day.

9. Blood Chemistry

A statistically significant reduction in plasma cholesterol was detected for animals of either sex treated with 1000 mg/kg/day when compared with controls, although in isolation, the toxicological significance of this finding is dubious.

No treatment-related effects were detected at 250 or 50 mg/kg/day.

10. Organ Weights

Females treated with 1000 mg/kg/day showed a statistically significant increase in liver and kidney weight, both absolute and relative to bodyweight, when compared with controls. The effect extended to the 250 mg/kg/day dose group with increases in both relative liver and kidney weight detected for females when compared with controls.

No adverse effect on organ weights was detected for the male treatment groups or for females treated with 50 mg/kg/day.

11. Necropsy

There were no treatment-related macroscopic changes detected at terminal kill.

12. Histopathology

The following treatment-related changes were observed:

Liver: Five females treated with 1000 mg/kg/day showed centrilobular hepatocyte enlargement in relation to treatment ($p < 0.05$). Hepatocyte enlargement is commonly observed in the rodent liver following the administration of xenobiotics and, in the absence of associated inflammatory or degenerative changes, is generally considered to be adaptive in nature. The condition was not observed amongst males, or amongst females from the remaining dose levels.

Kidneys: Five females dosed at 1000 mg/kg/day and one control female exhibited epithelial hypertrophy of inner cortical tubules. Although not quite attaining statistical significance, this minimal change was considered to be related to treatment at 1000 mg/kg/day for females, but was not associated with any degenerative changes. Such an effect of treatment was not observed for males or for females from the 250 or 50 mg/kg/day dose groups.

Thyroids: An increased incidence of follicular cell hypertrophy ($p < 0.05$), occasionally with associated colloid depletion, was observed in relation to treatment for females dosed at 1000 mg/kg/day. A similar effect was not observed for males or amongst females from the remaining treatment levels.

Lungs: The incidence of groups of alveolar macrophages was increased in relation to treatment for females treated with 1000 mg/kg/day ($p < 0.01$). A similar effect was not observed amongst males or for females from the 250 or 50 mg/kg/day dose groups.

Mesenteric lymph nodes: Sinus histiocytosis was observed for animals of either sex treated with 1000 mg/kg/day ($p < 0.001$). Histiocytes were generally foamy in appearance. Other lymphoid tissues including spleen, thymus, cervical lymph nodes, and Peyer's patches were not affected and the condition did not involve animals from the remaining treatment groups.

13. Conclusion

Oral administration of the test material, [] [] to rats for a period of ninety consecutive days at dose levels of up to 1000 mg/kg/day resulted in treatment-related changes at 1000 amongst animals of either sex and at 250 mg/kg/day amongst females only. No such changes were detected in animals treated with 50 mg/kg/day and for this reason the "No Observed Effect Level" (NOEL) was considered to be 50 mg/kg/day.

The effects detected at 250 mg/kg/day, however, were confined to marginal liver and kidney weight increases amongst females only and in the absence of any supporting histopathological correlates, these were considered not to represent an adverse health effect.

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**NINETY DAY REPEATED DOSE
ORAL (GAVAGE) TOXICITY STUDY IN THE RAT**

1. INTRODUCTION

The study was performed according to the protocol presented in Appendix IX and was designed to investigate the systemic toxicity of the test material, by repeated oral administration to the Sprague-Dawley Crl:CD®BR strain rat for a period of ninety consecutive days at dose levels of 50, 250 and 1000 mg/kg/day.

The study was designed to follow the testing method described in Commission Directive 87/302/EEC and complies with the recommendations of the OECD Guidelines for Testing of Chemicals No. 408 "Sub-Chronic Oral Toxicity - Rodent: 90 day Study".

The rat was selected for this study as it is a readily available rodent species historically used in safety evaluation studies and is acceptable to appropriate regulatory authorities.

The dose levels were chosen based on the results of the range-finding study presented in Part II of this report. The oral route was selected as the most appropriate route of exposure, based on the physical properties of the test material, and the results of the study are believed to be of value in predicting the likely toxicity of the test material to man.

The study was performed between 05 March 1998 and 15 December 1998.

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2. TEST MATERIAL AND EXPERIMENTAL PREPARATION

2.1 Description, Identification and Storage Conditions

Sponsor's identification : []
Date received : 12 January 1998
Description : amber viscous liquid
Storage conditions : ambient conditions in the dark

Data relating to the identity, purity and stability of the test material are the responsibility of the Sponsor.

2.2 Experimental Preparation

For the purpose of this study the test material was prepared at the appropriate concentrations as a solution in Arachis oil BP. The stability of the test material formulations was determined by Safepharm Analytical Laboratory. Results are given in Appendix XI and show the formulations to be stable for at least fourteen days. Formulations were therefore prepared weekly and stored at approximately +4°C in the dark.

Samples were taken of each test material formulation and were analysed for concentration of [] at Safepharm Analytical Laboratory. The method used for analysis of formulations and the results obtained are given in Appendix XI. The results indicate that the prepared formulations were within $\pm 10\%$ of the nominal concentration.

3. METHODS

3.1 Animals and Animal Husbandry

A sufficient number of male and female Sprague-Dawley Crl:CD®BR strain rats were obtained from Charles River (UK) Limited, Margate, Kent. On receipt the animals were examined for signs of ill-health or injury. The animals were acclimatised for ten days during which time their health status was assessed. A

SPL PROJECT NUMBER:

total of eighty animals (forty males and forty females) were accepted into the study. At the start of treatment the males weighed 168 to 224g, and the females weighed 151 to 192g, and were approximately six to seven weeks old.

The animals were housed in groups of up to four by sex in polypropylene grid-floor cages suspended over trays lined with absorbent paper. The animals were allowed free access to food and water. A pelleted diet (Rat and Mouse SQC Expanded Diet No. 1, Special Diets Services Limited, Witham, Essex, UK) was used. Certificates of analysis of the batches of diet are given in Appendix X. Mains water was supplied from polycarbonate bottles attached to the cage. The diet and drinking water were considered not to contain any contaminant at a level that might have affected the purpose or integrity of the study.

The animals were housed in a single air-conditioned room within the Safepharm Barrier Maintained Rodent Facility. The rate of air exchange was at least fifteen air changes per hour and the low intensity fluorescent lighting was controlled to give twelve hours continuous light and twelve hours darkness. Environmental conditions were continuously monitored by a computerised system, and print-outs of hourly mean temperatures and humidities were included in the study records. The temperature and relative humidity were controlled to remain within target ranges of $21 \pm 2^{\circ}\text{C}$ and $55 \pm 15\%$ respectively. Occasional deviations from these targets were considered not to have affected the purpose or integrity of the study.

The animals were randomly allocated to treatment groups using random letter tables, and the group mean bodyweights were then determined to ensure similarity between the treatment groups. The cage distribution within the holding rack was also randomised. The animals were uniquely identified within the study by an ear punching system routinely used in these laboratories.

3.2 Procedure

Animals were allocated to treatment groups as follows:

TREATMENT GROUP	DOSE LEVEL (mg/kg/day)	TREATMENT VOLUME (ml/kg)	CONCENTRATION (mg/ml)	NUMBER OF ANIMALS	
				MALE	FEMALE
Control	0	2	0	10 (1-10)	10 (11-20)
Low	50	2	25	10 (21-30)	10 (31-40)
Intermediate	250	2	125	10 (41-50)	10 (51-60)
High	1000	2	500	10 (61-70)	10 (71-80)

The numbers in parentheses () show the individual animal numbers allocated to each treatment group.

The test material was administered daily, for ninety consecutive days, by gavage using a stainless steel cannula attached to a disposable plastic syringe. Control animals were treated in an identical manner with 2 ml/kg/day of Arachis oil BP.

The volume of test and control material administered to each animal was based on the most recent bodyweight and was adjusted at weekly intervals.

3.3 Observations

3.3.1 Clinical Observations

All animals were examined for overt signs of toxicity, ill-health or behavioural change immediately before dosing and one and five hours after dosing during the working week wherever possible. Animals were observed immediately before dosing and one hour after dosing at weekends and public holidays. All observations were recorded.

3.3.2 Bodyweight

Individual bodyweights were recorded on Day 0 (the day before the start of treatment) and at weekly intervals thereafter. Bodyweights were also recorded at terminal kill.

--	--

3.3.3 Food Consumption

Food consumption was recorded for each cage group at weekly intervals throughout the study.

3.3.4 Water Consumption

Water intake was observed daily, for each cage group, by visual inspection of the water bottles for any overt changes.

3.3.5 Ophthalmoscopic Examination

The eyes of all control and high dose animals were examined pre-treatment and before termination of treatment (during Week 12). Examinations included observation of the anterior structures of the eye, pupillary and corneal blink reflex and, following pupil dilation with 0.5% Tropicamide solution ("Mydriacyl" - Alcon Laboratories (UK) Ltd., Imperial Way, Watford, Hertfordshire), detailed examination of the internal structure of each eye using a direct ophthalmoscope.

3.3.6 Laboratory Investigations

Haematological and blood chemical investigations were performed on all animals from each test and control group at the end of the study (Day 90). Blood samples were obtained from the lateral tail vein. Where necessary repeat samples were obtained by cardiac puncture at termination on Day 91. Animals were not fasted prior to sampling.

The methods used for haematological and blood chemical investigations are given in Appendix XII and normal ranges are shown in Appendix XIV.

3.3.6.1 Haematology

The following parameters were measured on blood collected into tubes containing potassium EDTA anti-coagulant:

- Haemoglobin (Hb)
- Erythrocyte count (RBC)
- Haematocrit (Hct)
- Erythrocyte indices
 - mean corpuscular haemoglobin (MCH)
 - mean corpuscular volume (MCV)
 - mean corpuscular haemoglobin concentration (MCHC)

Total leucocyte count (WBC)

- Differential leucocyte count
- neutrophils (Neut)
 - lymphocytes (Lymph)
 - monocytes (Mono)
 - eosinophils (Eos)
 - basophils (Bas)

Platelet count (PLT)

- Reticulocyte count (Retic)
- Cresyl blue stained slides were prepared but reticulocytes were not assessed

Prothrombin time (CT) was assessed by 'Hepato Quick' and Activated partial thromboplastin time (APTT) was assessed by 'Preci Clot' using samples collected into sodium citrate solution (0.11 mol/l).

3.3.6.2 Blood Chemistry

The following parameters were measured on plasma from blood collected into tubes containing lithium heparin anti-coagulant:

- | | |
|-----------------------------|-----------------------------------|
| Urea | Chloride (Cl ⁻) |
| Glucose | Calcium (Ca ⁺⁺) |
| Total protein (Tot.Prot) | Inorganic phosphorus (P) |
| Albumin | Aspartate aminotransferase (ASAT) |
| Albumin/Globulin (A/G) | Alanine aminotransferase (ALAT) |
| ratio (by calculation) | Alkaline phosphatase (AP) |
| Sodium (Na ⁺) | Creatinine (Creat) |
| Potassium (K ⁺) | Total cholesterol (Chol) |
| | Total bilirubin (Bili) |

3.3.7 Pathology

On completion of the dosing period all animals (excluding animal number 58 which was killed by intraperitoneal injection) were killed by intravenous overdose of sodium pentobarbitone (Sagatal, 60 mg/ml; May and Baker Limited, Dagenham, Essex, UK) followed by exsanguination.

All animals were subjected to a full external and internal examination, and any macroscopic abnormalities were recorded.

3.3.7.1 Organ Weights

The following organs, removed from animals that were killed at the end of the study, were dissected free from fat and weighed before fixation:

Adrenals	Brain	Epididymides	Heart	Kidneys
Liver	Ovaries	Spleen	Testes	

Normal ranges for these organ weights are given in Appendix XV.

3.3.7.2 Histopathology

Samples of the following tissues were removed from all animals and preserved in buffered 10% formalin:

Adrenals	Oesophagus
Aorta (thoracic)	Ovaries
Bone & bone marrow (femur including stifle joint)	Pancreas
Bone & bone marrow (sternum)	Pituitary
Brain (at three levels)	Prostate
Caecum	Rectum
Colon	Salivary glands (submaxillary)
Duodenum	Sciatic nerve
Eyes*	Seminal vesicles
	Skin (hind limb)

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Epididymides	Spinal cord (cervical)
Gross lesions	Spleen
Heart	Stomach
Ileum	Testes
Jejunum	Thymus
Kidneys	Thyroid/parathyroid
Liver	Tongue
Lungs (with bronchi)	Trachea
Lymph nodes (cervical and mesenteric)	Urinary bladder
Mammary gland	Uterus
Muscle (skeletal)	

* eyes were preserved in Davidson's fluid

All tissues were despatched to Propath UK Ltd, Willow Court, Netherwood Road, Rotherwas, Hereford, UK. for processing. All preserved tissues from control and 1000 mg/kg/day dose group animals were prepared as paraffin blocks, sectioned at nominal thickness of 5 μ m and stained with haematoxylin and eosin for subsequent microscopic examination.

Since there were indications of treatment-related changes in the liver, kidneys, thyroids, lungs and mesenteric lymph nodes, examination was subsequently extended to include similarly prepared sections of these tissues from all animals in the other treatment groups.

Microscopic examination was conducted by the Study Pathologist. All findings were entered into the ROELEE 84 pathology computerisation system for tabulation and report production.

3.4 Evaluation of Data

Data were processed to give group mean values and standard deviations where appropriate.

Haematological, blood chemical, organ weight (absolute and relative to terminal bodyweight) and weekly bodyweight gain data were assessed for dose response relationships by linear regression analysis followed by one way analysis of variance (ANOVA) incorporating Levene's test for homogeneity of variance. Where variances were shown to be homogenous, pairwise comparisons were conducted using Dunnett's test. Where Levene's test showed unequal variances the data were analysed using non-parametric methods: Kruskal-Wallis ANOVA and Mann-Whitney "U" Test.

Following statistical analysis of MCHC among control and test animals, statistical significance was assigned to females from the 50 mg/kg/day treatment group in comparison with controls. The difference in mean and standard deviation between these two groups was negligible and the results of this analysis were rejected for contravening the function of Dunnett's pairwise comparison test. A single t-test was performed to compare the control female MCHC values with those of each treatment group in turn and the results of this test were reported accordingly.

The haematology variable basophils was not analysed since consistently greater than 30% of the data were recorded as the same value.

Probability values (p) are presented as follows:

$p < 0.001$ ***

$p < 0.01$ **

$p < 0.05$ *

$p \geq 0.05$ (not significant)

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Histopathology data were analysed using the following methods to determine significant differences between control and treatment groups for the individual sexes:

1. Chi squared analysis for differences in the incidence of lesions occurring with an overall frequency of 1 or greater.
2. Kruskal-Wallis one way non-parametric analysis of variance for the comparison of severity grades for the more frequently observed graded conditions.

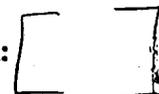
Probability values (p) are presented as follows:

$p < 0.001$	+++	---	***
$p < 0.01$	++	--	**
$p < 0.05$	+	-	*
$p < 0.1$	(+)	(-)	(*)
$p \geq 0.1$	N.S. (not significant)		

With plus signs indicating positive differences from the control group and minus signs indicating negative differences. Asterisks refer to overall group variation which is non-directional.

4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Safepharm archives for a period of five years. After this period, the Sponsor's instructions will be sought.



5. RESULTS

5.1 Mortality

There were no deaths during the study.

5.2 Clinical Observations

A summary incidence of daily clinical observations is given in Tables 1 and 2.

The clinically observable signs detected throughout the study were considered to be without toxicological importance.

Animals of either sex treated with 1000 mg/kg/day showed increased salivation approximately two minutes after dosing from Day 3 onwards; one incident was also noted for a 250 mg/kg/day male on Day 31. Accompanying observations at the high dose included increased salivation up to one hour after dosing, red/brown staining of the external body surface, wet fur and occasional, sporadic incidents of noisy respiration, the latter observation seen in one male and one female only. Such observations are commonly reported when a test material formulation has an unpleasant taste or is slightly irritant and, in isolation are considered not to be indicative of test material toxicity.

The remaining findings observed for both treated and control animals included fur loss, occasional fur staining, facial scabs, a swollen right ear or blue discoloration of the tail. All were considered to be normal observations seen in group housed laboratory maintained rats and were regarded as incidental and of no toxicological significance.

5.3 Bodyweight

Group mean weekly bodyweights and standard deviations are given in Tables 3 and 4 and are presented graphically in Figures I and II. Group mean weekly bodyweight gains and standard deviations are given in Tables 5 and 6 (statistically significant differences are indicated). Individual data are given in Appendices I and II.

A statistically significant reduction in bodyweight gain was detected for 1000 mg/kg/day males during Weeks 2 and 10 when compared with that of controls. Bodyweight development in these animals was unaffected throughout the rest of the study period.

No adverse effect on bodyweight gain was detected for 1000 mg/kg/day females or for animals of either sex treated with 250 or 50 mg/kg/day.

5.4 Food Consumption

Group mean weekly food consumptions are given in Tables 7 and 8 and are presented graphically in Figures III and IV. Weekly food efficiencies are given in Tables 9 and 10.

A slight reduction in dietary intake was detected for 1000 mg/kg/day males over the first three weeks of treatment. Food efficiency was also slightly reduced during Week 10, corresponding to the bodyweight reduction seen at this time.

No adverse effect on food consumption or efficiency was detected for 1000 mg/kg/day females or for animals of either sex treated with 250 or 50 mg/kg/day throughout the study period.

5.5 Water Consumption

Daily visual inspection of water bottles revealed no intergroup differences.

5.6 Ophthalmoscopic Examination

Individual ophthalmoscopic examination findings are given in Appendix III.

There were no treatment-related ocular effects.

The incidental abnormalities recorded for two control males were consistent with occasionally encountered findings in laboratory maintained rats of the strain and age employed.

5.7 Laboratory Investigations

5.7.1 Haematology

Group mean values and standard deviations for test and control group animals are given in Tables 11 and 12 (statistically significant differences are indicated). Individual data are given in Appendix IV.

Statistically significant reductions in haemoglobin, haematocrit, mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration were detected for 1000 mg/kg/day females when compared with controls.

No such changes were detected for 1000 mg/kg/day males or for animals of either sex treated at the remaining dose levels.

The statistically significant reductions in haemoglobin and MCH in 1000 and/or 250 mg/kg/day males were probably attributable to slightly higher than normal control values and, in the absence of effects on erythrocyte numbers and the fact that the majority of individual values were within the respective normal ranges, the intergroup differences were considered to be of no toxicological significance.

5.7.2 Blood Chemistry

Group mean values and standard deviations for test and control group animals are given in Tables 13 and 14 (statistically significant differences are indicated). Individual data are given in Appendix V.

A statistically significant reduction in plasma cholesterol was detected for both males and females treated with 1000 mg/kg/day when compared with controls. Many values from this and the other dose groups, including controls, were outside the respective normal ranges and, in the absence of any other changes in the blood chemical parameters measured, this finding was considered to be of dubious toxicological significance.



There were no other toxicologically significant changes in the blood chemical parameters measured.

The statistically significant increases in plasma albumin, albumin/globulin ratio and plasma calcium and sodium concentration all involved individual values within the respective normal ranges and, in isolation, all were regarded as incidental. The remaining intergroup differences were confined to a reduction in male 50 and 250 mg/kg/day alkaline phosphatase and female 1000 mg/kg/day alanine aminotransferase but reductions in these parameters cannot be regarded as toxicologically significant.

5.8 Pathology

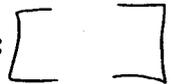
5.8.1 Organ Weights

Group mean absolute and relative organ weights and standard deviations for test and control group animals are given in Tables 15 to 18 (statistically significant differences are indicated). Individual data are given in Appendix VI.

Females treated with 1000 mg/kg/day showed a statistically significant increase in liver and kidney weight, both absolute and relative to bodyweight, when compared with controls. All individual relative liver weights and three kidney weights were outside the respective normal ranges for rats of the strain and age used. The effect extended to 250 mg/kg/day females with increases in relative liver and kidney weight detected although statistical significance was only achieved for liver weight at this dose level.

No adverse organ weight changes were detected for 1000 mg/kg/day males or for animals of either sex treated with 250 or 50 mg/kg/day.

An increase in male 1000 mg/kg/day relative brain weight was detected but, in view of the reduced terminal bodyweight seen in these animals and the absence of any histopathological correlates, the increase was considered to be incidental. Relative adrenal and ovary weights were statistically significantly elevated in 1000 mg/kg/day females compared to those of controls. The level of significance was minimal ($p < 0.05$) and, in the absence of any



histopathological evidence to suggest an adverse effect in these organs, the increases were considered to be without toxicological importance.

The remaining statistically significant intergroup differences detected for the male treatment groups were confined to absolute weights and, in the absence of any similar changes in the respective relative weights, were considered to be fortuitous.

5.8.2 Necropsy

A summary incidence of necropsy findings is given in Tables 19 and 20. Individual data are given in Appendix VII.

No treatment-related macroscopic abnormalities were detected.

One male treated with 1000 mg/kg/day showed speckled kidneys at terminal kill but, in the absence of histopathological changes in this organ or any other finding suggestive of an adverse effect on male renal function, this finding was considered to be of no toxicological importance. The remaining incidental finding recorded for one 1000 mg/kg/day female, identified as dark areas on the lungs, was consistent with a normally expected, low incidence finding in laboratory maintained rats and was, therefore, of no toxicological importance.

5.8.3 Histopathology

A summary incidence of histopathological findings is given in Tables 21 and 22. Details of the grading system used and all individual data are given in Appendix VIII.

The following treatment-related changes were observed:

Liver: Five females treated with 1000 mg/kg/day showed centrilobular hepatocyte enlargement in relation to treatment ($p < 0.05$). Hepatocyte enlargement is commonly observed in the rodent liver following the administration of xenobiotics and, in the absence of associated inflammatory or degenerative changes, is generally considered to be adaptive in nature. The

condition was not observed amongst males, or amongst females from the remaining dose levels.

Kidneys: Five females dosed at 1000 mg/kg/day and one control female exhibited epithelial hypertrophy of inner cortical tubules. Although not quite attaining statistical significance, this minimal change was considered to be related to treatment at 1000 mg/kg/day for females, but was not associated with any degenerative changes. Such an effect of treatment was not observed for males or for females from the 250 or 50 mg/kg/day dose groups.

Thyroids: An increased incidence of follicular cell hypertrophy ($p < 0.05$), occasionally with associated colloid depletion, was observed in relation to treatment for females dosed at 1000 mg/kg/day. A similar effect was not observed for males or amongst females from the remaining treatment levels.

Lungs: The incidence of groups of alveolar macrophages was increased in relation to treatment for females treated with 1000 mg/kg/day ($p < 0.01$). A similar effect was not observed amongst males or for females from 250 or 50 mg/kg/day dose groups.

Mesenteric lymph nodes: Sinus histiocytosis was observed for animals of either sex treated with 1000 mg/kg/day ($p < 0.001$). Histiocytes were generally foamy in appearance. Other lymphoid tissues including spleen, thymus, cervical lymph nodes, and Peyer's patches were not affected and the condition did not involve animals from the remaining treatment groups.

Uterus: Although the incidence of uterine dilatation was increased for females dosed at 1000 mg/kg/day ($p < 0.05$), this was considered to be unrelated to treatment with the test material. Such changes occur frequently in laboratory maintained rats as a spontaneous entity and are associated with normal cyclical uterine changes.

All remaining morphological changes were those commonly observed in laboratory maintained rats of the age and strain employed and, since there were no differences in incidence or severity between control and treatment groups, all were considered to be without toxicological significance.

6. DISCUSSION

The administration of [] [] by oral gavage for a period of ninety consecutive days resulted in treatment-related changes at dose levels of 1000 and 250 mg/kg/day.

A slight reduction in bodyweight development and food consumption and efficiency were observed for 1000 mg/kg/day males during the study but these were transient changes and did not persist past Week 10. No adverse effect on bodyweight gain or dietary intake was detected for 1000 mg/kg/day females, but haematological investigations revealed a mild hypochromic anaemia in this sex at this dose level. Absolute and relative liver weight were elevated for 1000 mg/kg/day females and microscopic examination of liver sections revealed changes identified as centrilobular hepatocyte enlargement for five out of the ten females treated at this dose level. This morphological change is often seen in the rodent liver following treatment with xenobiotics and is associated with induction of microsomal enzymes. In the absence of any associated degenerative or inflammatory changes, this is considered to be an adaptive response. Microscopic examination of thyroid sections revealed an increased incidence of follicular cell hypertrophy, occasionally with associated colloid depletion, for 1000 mg/kg/day females. One possible explanation for these changes is a secondary response to the changes occurring in the liver. It is possible that glucuronyltransferase may have been induced in response to treatment, thereby increasing thyroxine excretion and stimulating a compensatory thyroid response. There were no convincing changes in the blood chemical parameters measured, although plasma cholesterol was slightly reduced for animals of either sex treated with 1000 mg/kg/day.

Further treatment-related changes were also seen in females with increases in both absolute and relative kidney weight detected at 1000 mg/kg/day. Histopathologically five females exhibited epithelial hypertrophy of inner cortical tubules but there were no other findings indicative of an adverse effect on renal function at this dose level. Microscopic lung changes were also observed, identified as an increased incidence of alveolar macrophages and microscopic examination of mesenteric lymph nodes revealed histiocytosis at 1000 mg/kg/day. It is unclear whether these findings are related

but the histiocytosis was probably a normal physiological consequence of infiltrating macrophages being unable to degrade their phagocytosed contents. There were no similar findings for the other lymphatic tissues examined.

Treatment-related changes extended into the 250 mg/kg/day dose group with females showing a dose-related increase in relative liver and kidney weight. Although statistical significance was either absent or minimal ($p < 0.05$), individual values were raised compared with controls. In the absence of any histopathological correlates, however, this was considered not to represent an adverse health effect.

No treatment-related changes were detected in any of the parameters measured for 250 mg/kg/day males or for animals of either sex treated with 50 mg/kg/day.

7. CONCLUSION

Oral administration of the test material, [] [] to rats for a period of ninety consecutive days at dose levels of up to 1000 mg/kg/day resulted in treatment-related changes at 1000 amongst animals of either sex and at 250 mg/kg/day amongst females only. No such changes were detected in animals treated with 50 mg/kg/day and for this reason the "No Observed Effect Level" (NOEL) was considered to be 50 mg/kg/day.

The effects detected at 250 mg/kg/day, however, were confined to marginal liver and kidney weight increases amongst females only and in the absence of any supporting histopathological correlates, these were considered not to represent an adverse health effect.

SPL PROJECT NUMBER:

[] []

T A B L E S

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 1
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 1 TO DAY 7 - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION															
			DAY: 1		DAY: 2		DAY: 3		DAY: 4		DAY: 5		DAY: 6		DAY: 7			
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
50	10	Red/brown staining of fur	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
		No abnormalities detected	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
		Increased salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Red/brown staining around mouth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Wet fur	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1000	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Pre - immediately before dosing
 1h - one hour after dosing
 5h - five hours after dosing
 * - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 4 to 7 inclusive

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 1 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 8 TO DAY 14 - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																					
			DAY: 8		DAY: 9		DAY: 10		DAY: 11		DAY: 12		DAY: 13		DAY: 14									
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h							
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10						
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10						
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10						
1000■	10	Increased salivation Red/brown staining around mouth No abnormalities detected	0	0	0	0	1	0	0	1	0	0	1	0	0	0	2	0	3	0	0	3	0	
			0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	2	0
			10	10	10	10	8	10	10	9	10	10	10	7	10	7	10	7	10	7	10	5	10	10

Pre - immediately before dosing
 1h - one hour after dosing
 5h - five hours after dosing
 * - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 8 to 14 inclusive

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 1 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 15 TO DAY 21 - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																				
			DAY: 15		DAY: 16		DAY: 17		DAY: 18		DAY: 19		DAY: 20		DAY: 21								
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h						
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10				
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10				
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10				
1000■	10	Increased salivation	0	0	0	0	4	0	0	4	0	0	0	0	0	2	*	0	0	0	0		
		Red/brown staining of fur	0	0	0	0	0	0	0	1	2	1	1	*	1	1	*	1	1	1	0	0	
		Red/brown staining around mouth	0	0	0	0	1	0	0	1	0	0	0	*	0	0	*	0	0	0	0	0	0
		Wet fur	0	0	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		No abnormalities detected	10	10	10	10	5	10	10	4	8	9	9	*	9	7	*	9	9	9	10	10	

Pre - immediately before dosing 1h - one hour after dosing 5h - five hours after dosing

* - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 15 to 21 inclusive

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
 TABLE 1 (continued)
 SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 22 TO DAY 28 - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																
			DAY: 22		DAY: 23		DAY: 24		DAY: 25		DAY: 26		DAY: 27		DAY: 28				
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h		
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1000 ■	10	Increased salivation	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		No abnormalities detected	9	10	10	10	10	10	10	2	10	2	10	10	10	10	10	10	10

Pre - immediately before dosing 1h - one hour after dosing 5h - five hours after dosing

* - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 22 to 28 inclusive

SPL PROJECT NUMBER: [] []

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 1 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 29 TO DAY 35 - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																
			DAY: 29		DAY: 30		DAY: 31		DAY: 32		DAY: 33		DAY: 34		DAY: 35				
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h		
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
250 □	10	Facial scab	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
		No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9
1000 ■	10	Increased salivation	0	3	0	0	2	0	1	0	0	0	0	1	0	0	0	3	0
		No abnormalities detected	10	7	10	10	8	10	9	10	10	10	10	9	10	10	7	10	5

Pre - immediately before dosing 1h - one hour after dosing 5h - five hours after dosing

* - five hour observation not performed at weekend
 □ - increased salivation detected approximately two minutes after dosing - Day 31 only
 ■ - increased salivation detected approximately two minutes after dosing - Days 29 to 35 inclusive

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 1 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 36 TO DAY 42 - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																	
			DAY: 36		DAY: 37		DAY: 38		DAY: 39		DAY: 40		DAY: 41		DAY: 42					
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h			
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
250	10	Facial scab	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
		No abnormalities detected	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
		Increased salivation	0	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		Red/brown staining around mouth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		Red/brown staining around snout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		Wet fur	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
1000■	10	No abnormalities detected	10	3	10	10	10	10	10	10	8	10	10	10	10	10	8	10	10	

Pre - immediately before dosing
 1h - one hour after dosing
 5h - five hours after dosing
 * - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 36 to 42 inclusive

SPL PROJECT NUMBER:

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 1 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 57 TO DAY 63 - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																
			DAY: 57		DAY: 58		DAY: 59		DAY: 60		DAY: 61		DAY: 62		DAY: 63				
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h		
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
1000 ■	10	Generalised fur loss	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	
		Increased salivation	0	2	0	0	0	0	5	0	2	1	1	1	0	0	1	8	0
		Red/brown staining around mouth	0	0	0	0	0	0	0	0	1	0	1	1	0	0	1	0	0
		No abnormalities detected	10	8	10	9	9	9	9	5	8	7	7	7	9	9	8	2	9

Pre - immediately before dosing 1h - one hour after dosing 5h - five hours after dosing

* - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 57 to 63 inclusive

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 1 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 64 TO DAY 70 - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																
			DAY: 64		DAY: 65		DAY: 66		DAY: 67		DAY: 68		DAY: 69		DAY: 70				
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h		
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1000■	10	Generalised fur loss	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
		Increased salivation	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
		Wet fur	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
		No abnormalities detected	9	9	9	9	7	9	9	9	9	9	9	9	9	9	9	9	9

Pre - immediately before dosing
 1h - one hour after dosing
 5h - five hours after dosing
 * - five hour observation not performed at weekend or public holiday
 ■ - increased salivation detected approximately two minutes after dosing - Days 64 to 70 inclusive

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
 TABLE 1 (continued)
 SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 78 TO DAY 84 - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION															
			DAY: 78		DAY: 79		DAY: 80		DAY: 81		DAY: 82		DAY: 83		DAY: 84			
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1000■	10	Noisy respiration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Increased salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Red/brown staining around mouth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Pre - immediately before dosing
 1h - one hour after dosing
 5h - five hours after dosing
 6½ - approximately 6½ hours after dosing
 ■ - increased salivation detected approximately two minutes after dosing - Days 78 to 84 inclusive
 * - five hour observation not performed at weekend

SPL PROJECT NUMBER:

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 1 TO DAY 7 - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION														
			DAY: 1		DAY: 2		DAY: 3		DAY: 4		DAY: 5		DAY: 6		DAY: 7		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1000 [■]	10	Increased salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Wet fur	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Pre - immediately before dosing 1h - one hour after dosing 5h - five hours after dosing

* - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 3 to 7 inclusive

SPL PROJECT NUMBER: [] []

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 8 TO DAY 14 - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION														
			DAY: 8		DAY: 9		DAY: 10		DAY: 11		DAY: 12		DAY: 13		DAY: 14		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1000■	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Pre - immediately before dosing
 1h - one hour after dosing
 5h - five hours after dosing
 * - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 8 to 14 inclusive

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 15 TO DAY 21 - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																					
			DAY: 15		DAY: 16		DAY: 17		DAY: 18		DAY: 19		DAY: 20		DAY: 21									
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h							
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10		
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10		
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10		
1000 ■	10	Increased salivation	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		Red/brown staining of fur	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		Red/brown staining around mouth	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		No abnormalities detected	10	9	10	9	9	9	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Pre - immediately before dosing
 1h - one hour after dosing
 5h - five hours after dosing
 * - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 15 to 21 inclusive

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 22 TO DAY 28 - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																		
			DAY: 22		DAY: 23		DAY: 24		DAY: 25		DAY: 26		DAY: 27		DAY: 28						
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h				
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10		
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10		
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10		
1000 ■	10	Increased salivation	0	0	0	0	10	0	0	1	*	0	3	*	0	0	0	0	0	0	
		Red/brown staining of fur	2	2	2	1	1	1	1	1	*	1	1	*	1	1	1	1	1	1	1
		Red/brown staining around mouth	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0	0
		No abnormalities detected	8	8	8	9	0	9	9	8	*	9	7	*	9	9	9	9	9	8	9

Pre - immediately before dosing 1h - one hour after dosing 5h - five hours after dosing
 * - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 22 to 28 inclusive

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 43 TO DAY 49 - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																					
			DAY: 43		DAY: 44		DAY: 45		DAY: 46		DAY: 47		DAY: 48		DAY: 49									
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h							
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10	10	10	10			
50	10	No abnormalities detected	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10	10	10	10	10		
250	10	No abnormalities detected	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10	10	10	10	10		
1000 ■	10	Increased salivation	0	2	0	0	0	0	2	*	0	0	0	0	0	0	0	0	0	0	0	0	0	
		Red/brown staining around eyes	0	1	1	1	1	1	1	*	1	1	*	1	1	*	1	1	1	1	1	1	1	1
		Red/brown staining around mouth	0	2	0	0	0	0	0	*	0	0	*	0	0	*	0	0	0	0	0	0	0	0
		No abnormalities detected	10	5	9	9	9	9	9	7	*	9	9	*	8	8	9	9	8	9	9	8	9	9

Pre - immediately before dosing 1h - one hour after dosing 5h - five hours after dosing

* - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 43 to 49 inclusive

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 50 TO DAY 56 - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																	
			DAY: 50		DAY: 51		DAY: 52		DAY: 53		DAY: 54		DAY: 55		DAY: 56					
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h			
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
1000 ■	10	Generalised fur loss	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
		Increased salivation	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Red/brown staining around eyes	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		No abnormalities detected	8	7	8	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9

Pre - immediately before dosing
 1h - one hour after dosing
 5h - five hours after dosing
 * - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 50 to 56 inclusive

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 57 TO DAY 63 - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																					
			DAY: 57		DAY: 58		DAY: 59		DAY: 60		DAY: 61		DAY: 62		DAY: 63									
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h							
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10						
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10						
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10						
1000■	10	Increased salivation	0	0	0	0	1	0	0	2	0	0	0	0	0	4	0	1	6	0	0	0		
		Generalised fur loss	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
		Red/brown staining around eyes	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Red/brown staining around mouth	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
		No abnormalities detected	9	8	9	9	8	8	9	8	9	8	9	8	9	4	8	8	3	9	9	9	9	

Pre - immediately before dosing
 1h - one hour after dosing
 5h - five hours after dosing
 * - five hour observation not performed at weekend
 ■ - increased salivation detected approximately two minutes after dosing - Days 57 to 63 inclusive

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 64 TO DAY 70 - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																	
			DAY: 64		DAY: 65		DAY: 66		DAY: 67		DAY: 68		DAY: 69		DAY: 70					
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h			
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
1000 ■	10	Generalised fur loss	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	
		Increased salivation	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	
		Red/brown staining around mouth	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	
		No abnormalities detected	9	9	9	9	8	8	7	8	8	7	8	8	8	8	8	8	8	

Pre - immediately before dosing
 1h - one hour after dosing
 5h - five hours after dosing
 * - five hour observation not performed at weekend or public holiday
 ■ - increased salivation detected approximately two minutes after dosing - Days 64 to 70 inclusive

SPL PROJECT NUMBER: [] []

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 71 TO DAY 77 - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																			
			DAY: 71		DAY: 72		DAY: 73		DAY: 74		DAY: 75		DAY: 76		DAY: 77							
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h					
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10	10			
50	10	Generalised fur loss No abnormalities detected	0	0	0	0	0	0	*	0	0	*	0	0	0	1	1	1	1			
250	10	No abnormalities detected	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10	10			
1000 ■	10	Generalised fur loss	2	2	2	2	2	2	*	2	2	*	2	2	2	2	2	2	2			
		Noisy respiration	0	0	0	1	0	0	*	0	0	*	0	0	1	0	0	0	0	0		
		Increased salivation	0	2	0	0	1	0	*	1	0	*	1	0	0	0	0	0	0	0	0	
		Red/brown staining around eyes	0	0	0	0	0	0	*	0	0	*	0	0	0	1	0	0	0	0	0	
		Red/brown staining around mouth	0	2	1	0	2	2	*	0	0	*	0	0	0	0	0	0	0	0	0	0
		Red/brown staining around snout	0	0	0	0	0	0	*	0	0	*	0	0	0	0	1	1	1	1	0	0
No abnormalities detected	8	7	8	8	6	6	*	7	8	*	8	8	*	7	8	7	7	7	10	10		

Pre = immediately before dosing 1h = one hour after dosing 5h = five hours after dosing
 * = five hour observation not performed at weekend
 ■ = increased salivation detected approximately two minutes after dosing - Days 71 to 77 inclusive

SPL PROJECT NUMBER:

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 78 TO DAY 84 - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																	
			DAY: 78		DAY: 79		DAY: 80		DAY: 81		DAY: 82		DAY: 83		DAY: 84					
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	6½h	Pre	1h	5h			
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
50	10	Generalised fur loss	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
		No abnormalities detected	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1000 ■	10	Generalised fur loss	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
		Increased salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Red/brown staining around mouth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Red/brown staining of fur	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
		No abnormalities detected	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	

Pre - immediately before dosing 1h - one hour after dosing 5h - five hours after dosing

6½ - approximately 6½ hours after dosing * - five hour observation not performed at weekend

■ - increased salivation detected approximately two minutes after dosing - Days 78 to 84 inclusive

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 85 TO DAY 90 - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION															
			DAY: 85		DAY: 86		DAY: 87		DAY: 88		DAY: 89		DAY: 90					
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
50	10	Generalised fur loss	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
		No abnormalities detected	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
250	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
		Blue discoloration of tail	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1
		Generalised fur loss	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	10	Increased salivation	0	0	0	2	0	0	0	0	0	0	2	0	0	0	0	0
		Red/brown staining of fur	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
		No abnormalities detected	7	7	7	7	7	7	7	7	7	7	5	7	7	7	7	7

Pre - immediately before dosing

1h - one hour after dosing

5h - five hours after dosing

* - five hour observation not performed at weekend

■ - increased salivation detected approximately two minutes after dosing - Days 85 to 90 inclusive

SPL PROJECT NUMBER: []

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 3
GROUP MEAN WEEKLY BODYWEIGHTS AND
STANDARD DEVIATIONS (SD) - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	BODYWEIGHT (g) AT DAY							
		0	7	14	21	28	35	42	
0 (Control)	10	mean	191	246	307	349	381	407	432
		sd	7	10	12	16	18	19	21
50	10	mean	196	248	299	331	358	382	407
		sd	13	14	17	22	30	38	46
250	10	mean	195	248	303	345	375	398	423
		sd	14	18	22	25	29	30	28
1000	10	mean	188	238	284	317	341	362	384
		sd	16	24	31	37	40	40	43

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	BODYWEIGHT (g) AT DAY							
		49	56	63	70	77	84	90	
0 (Control)	10	mean	450	466	478	496	510	514	530
		sd	25	32	36	37	40	41	44
50	10	mean	421	438	449	462	474	484	497
		sd	48	51	54	59	62	66	65
250	10	mean	443	461	476	492	506	513	526
		sd	27	26	25	25	28	29	30
1000	10	mean	396	411	421	430	442	444	458
		sd	49	51	51	53	56	59	60

SPL PROJECT NUMBER: []

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 4
GROUP MEAN WEEKLY BODYWEIGHTS AND
STANDARD DEVIATIONS (SD) - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		BODYWEIGHT (g) AT DAY						
			0	7	14	21	28	35	42
0 (Control)	10	mean	170	194	215	231	243	256	267
		sd	11	13	14	15	17	20	20
50	10	mean	168	192	210	228	240	252	•259
		sd	13	16	17	20	24	27	28
250	10	mean	166	188	211	229	243	255	267
		sd	12	15	18	18	23	23	24
1000	10	mean	164	190	216	231	240	251	260
		sd	7	11	14	13	14	16	15

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		BODYWEIGHT (g) AT DAY						
			49	56	63	70	77	84	90
0 (Control)	10	mean	273	279	285	292	298	303	304
		sd	21	23	25	27	29	29	30
50	10	mean	269	277	284	289	295	299	301
		sd	31	34	32	33	35	37	36
250	10	mean	272	279	285	289	294	299	303
		sd	23	23	22	23	24	23	21
1000	10	mean	265	268	276	282	285	286	293
		sd	18	17	17	19	20	20	21

• - animal number 35 reweighed Day 43

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 5
GROUP MEAN WEEKLY BODYWEIGHT GAINS AND
STANDARD DEVIATIONS (SD) - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		INCREASE IN BODYWEIGHT (g) DURING WEEK						
			1	2	3	4	5	6	7
0 (Control)	10	mean	56	61	42	32	26	25	18
		sd	5	7	6	5	6	7	8
50	10	mean	53	*51	32	27	24	26	14
		sd	4	7	11	10	11	9	6
250	10	mean	53	55	42	30	23	25	20
		sd	6	5	6	9	4	4	4
1000	10	mean	50	***46	33	24	21	22	13
		sd	11	10	9	7	10	8	7

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		INCREASE IN BODYWEIGHT (g) DURING WEEK					
			8	9	10	11	12	13
0 (Control)	10	mean	16	13	18	14	4	16
		sd	9	6	6	7	3	7
50	10	mean	17	12	13	12	10	13
		sd	7	7	8	5	6	4
250	10	mean	18	15	16	15	7	13
		sd	6	3	7	6	6	6
1000	10	mean	15	9	*9	12	3	14
		sd	8	4	5	4	11	4

* - significantly different from control group p<0.05

*** - significantly different from control group p<0.001

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 6
GROUP MEAN WEEKLY BODYWEIGHT GAINS AND
STANDARD DEVIATIONS (SD) - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		INCREASE IN BODYWEIGHT (g) DURING WEEK						
			1	2	3	4	5	6	7
0 (Control)	10	mean	24	21	16	12	12	11	6
		sd	4	4	3	5	6	4	4
50	10	mean	24	18	18	12	12	•8	9
		sd	4	4	6	5	4	4	5
250	10	mean	23	23	18	15	12	12	5
		sd	8	10	4	6	4	5	4
1000	10	mean	26	26	15	9	12	8	6
		sd	5	5	4	6	5	5	4

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		INCREASE IN BODYWEIGHT (g) DURING WEEK					
			8	9	10	11	12	13
0 (Control)	10	mean	6	6	7	7	4	2
		sd	4	5	3	4	5	5
50	10	mean	8	7	4	6	4	2
		sd	4	5	3	4	4	4
250	10	mean	7	6	4	6	5	4
		sd	4	4	2	4	2	5
1000	10	mean	2	8	6	3	0	7
		sd	4	4	6	5	5	5

• - animal number 35 reweighed Day 43

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 7
GROUP MEAN WEEKLY FOOD CONSUMPTION - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	MEAN FOOD CONSUMPTION (g/rat/week)						
		1	2	3	4	5	6	7
0 (Control)	10	207	227	213	207	201	203	203
50	10	200 (-3)	214 (-6)	198 (-7)	194 (-6)	192 (-4)	193 (-5)	199 (-2)
250	10	200 (-3)	213 (-6)	208 (-2)	199 (-4)	194 (-3)	178 (-12)	198 (-2)
1000	10	190 (-8)	199 (-12)	191 (-10)	189 (-9)	189 (-6)	201 (-1)	199 (-2)

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	MEAN FOOD CONSUMPTION (g/rat/week)					
		8	9	10	11	12	13*
0 (Control)	10	240	204	211	210	207	173
50	10	203 (-15)	202 (-1)	199 (-6)	197 (-6)	203 (-2)	169 (-2)
250	10	207 (-14)	207 (+1)	209 (-1)	210 (0)	210 (+1)	175 (+1)
1000	10	204 (-15)	200 (-2)	200 (-5)	201 (-4)	196 (-5)	174 (+1)

() - % change compared to control group * - Week 13 comprises six days only

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 8

GROUP MEAN WEEKLY FOOD CONSUMPTION - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	MEAN FOOD CONSUMPTION (g/rat/week)						
		1	2	3	4	5	6	7
0 (Control)	10	139	144	148	149	155	152	146
50	10	135 (-3)	140 (-3)	145 (-2)	145 (-3)	147 (-5)	147 (-3)	148 (+1)
250	10	124 (-11)	132 (-8)	143 (-3)	149 (0)	146 (-6)	178 (+17)	153 (+5)
1000	10	128 (-8)	144 (0)	150 (+1)	148 (-1)	152 (-2)	133 (-13)	149 (+2)

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	MEAN FOOD CONSUMPTION (g/rat/week)					
		8	9	10	11	12	13*
0 (Control)	10	155	153	155	150	156	126
50	10	153 (-1)	155 (+1)	156 (+1)	148 (-1)	158 (+1)	125 (-1)
250	10	149 (-4)	149 (-3)	151 (-3)	149 (-1)	155 (-1)	126 (0)
1000	10	157 (+1)	160 (+5)	158 (+2)	157 (+5)	162 (+4)	132 (+5)

() = % change compared to control group * = Week 13 comprises six days only

SPL PROJECT NUMBER: []

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 9
WEEKLY FOOD EFFICIENCY* - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	FOOD EFFICIENCY* DURING WEEK						
		1	2	3	4	5	6	7
0 (Control)	10	0.27	0.27	0.20	0.15	0.13	0.12	0.09
50	10	0.27	0.24	0.16	0.14	0.13	0.13	0.07
250	10	0.27	0.26	0.20	0.15	0.12	0.14	0.10
1000	10	0.26	0.23	0.17	0.13	0.11	0.11	0.07

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	FOOD EFFICIENCY* DURING WEEK					
		8	9	10	11	12	13#
0 (Control)	10	0.07	0.06	0.09	0.07	0.02	0.09
50	10	0.08	0.06	0.07	0.06	0.05	0.08
250	10	0.09	0.07	0.08	0.07	0.03	0.07
1000	10	0.07	0.05	0.05	0.06	0.02	0.08

- Week 13 comprises six days only

$$*Food\ efficiency = \frac{Group\ mean\ bodyweight\ gain\ (g/rat/week)}{Group\ mean\ food\ consumption\ (g/rat/week)}$$

SPL PROJECT NUMBER:

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 10

WEEKLY FOOD EFFICIENCY* - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	FOOD EFFICIENCY* DURING WEEK						
		1	2	3	4	5	6*	7
0 (Control)	10	0.17	0.15	0.11	0.08	0.08	0.07	0.04
50	10	0.18	0.13	0.12	0.08	0.08	0.05	0.06
250	10	0.19	0.17	0.13	0.10	0.08	0.07	0.03
1000	10	0.20	0.18	0.10	0.06	0.08	0.06	0.04

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	FOOD EFFICIENCY* DURING WEEK					
		8	9	10	11	12	13#
0 (Control)	10	0.04	0.04	0.05	0.05	0.03	0.02
50	10	0.05	0.05	0.03	0.04	0.03	0.02
250	10	0.05	0.04	0.03	0.04	0.03	0.03
1000	10	0.01	0.05	0.04	0.02	0.00	0.05

- Week 13 comprises six days only

* - animal number 35 reweighed Day 43

$$*Food\ efficiency = \frac{Group\ mean\ bodyweight\ gain\ (g/rat/week)}{Group\ mean\ food\ consumption\ (g/rat/week)}$$

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 11
GROUP MEAN HAEMATOLOGICAL VALUES AND
STANDARD DEVIATIONS (SD) - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		Hb (g/dl)	RBC (10 ¹² /l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10 ⁹ /l)	APTT (secs)
0 (Control)	10	mean	16.1	8.58	45.8	18.8	53.4	35.2	10.7	10.1
		sd	0.6	0.25	1.7	0.5	1.4	1.0	1.6	1.0
50	10	mean	16.3	8.96	47.2	18.2	52.7	34.5	10.5	10.8
		sd	0.4	0.39	1.7	0.9	2.3	0.7	3.2	1.7
250	10	mean	15.7	8.72	45.3	*18.1	52.0	34.8	10.5	10.8
		sd	0.8	0.42	2.6	0.6	1.0	1.1	1.9	2.7
1000	10	mean	*15.4	8.66	45.1	**17.7	52.1	34.1	9.3	11.5
		sd	0.6	0.31	2.0	0.5	1.3	0.8	2.3	2.5

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		DIFFERENTIAL (10 ⁹ /l)					CT (secs)	PLT (10 ⁹ /l)
			Neut	Lymph	Mono	Eos	Bas		
0 (Control)	10	mean	1.53	8.88	0.05	0.21	0.00	25.5	906
		sd	0.38	1.57	0.10	0.09	0.00	1.1	72
50	10	mean	1.78	8.51	0.04	0.15	0.00	26.8	857
		sd	2.14	2.65	0.07	0.12	0.00	1.9	70
250	10	mean	1.64	8.74	0.00	0.13	0.00	26.7	927
		sd	0.70	1.62	0.00	0.10	0.00	1.3	83
1000	10	mean	1.44	7.78	0.00	0.11	0.00	27.1	848
		sd	0.67	2.02	0.00	0.10	0.00	1.4	80

* - significantly different from control group p<0.05
** - significantly different from control group p<0.01

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 12
GROUP MEAN HAEMATOLOGICAL VALUES AND
STANDARD DEVIATIONS (SD) - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		Hb (g/dl)	RBC (10 ¹² /l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10 ⁹ /l)	APTT (secs)
0 (Control)	10	mean	15.3	8.04	43.9	19.1	54.7	34.9	6.5	12.2
		sd	0.4	0.42	1.9	0.7	1.5	0.8	1.3	1.9
50	10	mean	15.5	8.24	44.6	18.9	54.1	34.9	6.8	11.2
		sd	0.5	0.39	1.7	0.6	1.2	0.9	1.3	1.8
250	10	mean	14.8	7.91	42.4	18.8	53.7	35.0	6.3	11.7
		sd	0.9	0.62	3.1	0.8	2.3	0.9	1.0	1.4
1000	10	mean	***13.8	7.70	**40.5	**17.9	52.6	*34.0	6.2	13.0
		sd	0.9	0.37	2.1	0.7	1.6	0.6	1.0	2.4

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		DIFFERENTIAL (10 ⁹ /l)					CT (secs)	PLT (10 ⁹ /l)
			Neut	Lymph	Mono	Eos	Bas		
0 (Control)	10	mean	1.12	5.21	0.02	0.12	0.00	23.5	827
		sd	0.40	1.05	0.03	0.09	0.00	1.8	85
50	10	mean	0.79	5.90	0.00	0.08	0.00	22.8	832
		sd	0.34	1.06	0.00	0.10	0.00	1.3	132
250	10	mean	0.78	5.37	0.01	0.11	0.00	23.4	820
		sd	0.36	1.19	0.03	0.06	0.00	1.6	98
1000	10	mean	0.73	5.41	0.01	0.03	0.00	24.2	882
		sd	0.42	0.86	0.02	0.05	0.00	1.2	140

* - significantly different from control group p<0.05
 ** - significantly different from control group p<0.01
 *** - significantly different from control group p<0.001

SPL PROJECT NUMBER: []

[] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 13
GROUP MEAN BLOOD CHEMICAL VALUES AND
STANDARD DEVIATIONS (SD) - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		Urea (mg/dl)	Glucose (mg/dl)	Tot.Prot (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)
0 (Control)	10	mean	31	153	7.15	3.17	0.80	141	5.26	105
		sd	2	10	0.21	0.09	0.06	2	0.89	1
50	10	mean	31	143	7.20	3.26	0.83	143	4.87	105
		sd	5	12	0.29	0.07	0.05	1	0.29	1
250	10	mean	30	152	7.17	3.18	0.80	142	4.60	106
		sd	3	21	0.34	0.11	0.03	1	0.39	1
1000	10	mean	35	142	7.25	**3.35	*0.86	*143	4.95	106
		sd	3	11	0.31	0.16	0.05	1	0.24	1

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		Ca+ + (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
0 (Control)	10	mean	2.45	2.10	87	59	575	0.58	74	0.09
		sd	0.37	0.15	8	5	104	0.04	15	0.02
50	10	mean	2.63	2.10	87	58	*471	0.57	69	0.09
		sd	0.14	0.27	6	4	75	0.04	15	0.03
250	10	mean	2.68	1.89	87	54	**422	0.58	67	0.10
		sd	0.06	0.13	14	10	111	0.04	15	0.03
1000	10	mean	**2.76	1.86	92	55	487	0.60	**51	0.11
		sd	0.04	0.33	6	3	83	0.02	8	0.02

* - significantly different from control group p<0.05

** - significantly different from control group p<0.01

SPL PROJECT NUMBER:

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 14
GROUP MEAN BLOOD CHEMICAL VALUES AND
STANDARD DEVIATIONS (SD) - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		Urea (mg/dl)	Glucose (mg/dl)	Tot.Prot (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)
0 (Control)	10	mean	44	134	7.93	3.85	0.95	143	4.88	106
		sd	11	10	0.49	0.19	0.04	1	1.00	1
50	10	mean	43	135	8.09	3.88	0.92	143	4.72	107
		sd	7	11	0.35	0.21	0.05	1	0.68	1
250	10	mean	47	135	8.02	3.95	0.97	142	5.54	106
		sd	33	9	0.82	0.38	0.05	2	2.81	2
1000	10	mean	40	134	8.22	4.03	0.96	144	4.86	107
		sd	6	10	0.74	0.37	0.05	1	0.42	2

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS		Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
0 (Control)	10	mean	2.84	1.59	86	65	260	0.71	86	0.09
		sd	0.07	0.28	10	12	63	0.11	19	0.02
50	10	mean	2.87	1.41	94	60	295	0.67	88	0.09
		sd	0.06	0.31	24	19	89	0.05	17	0.01
250	10	mean	2.86	1.47	106	55	271	0.78	74	0.08
		sd	0.15	0.35	38	16	59	0.37	14	0.03
1000	10	mean	2.92	1.57	86	**42	291	0.65	***58	0.11
		sd	0.11	0.35	22	9	83	0.03	9	0.02

** - significantly different from control group p<0.01
 *** - significantly different from control group p<0.001

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 15
GROUP MEAN ORGAN WEIGHTS AND
STANDARD DEVIATIONS (SD) - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	BODY- WEIGHT (g) AT TERMINAL KILL	ORGAN WEIGHT (g)								
			Adrenals	Brain	Epididy- mides	Heart	Kidneys	Liver	Spleen	Testes	
0 (Control)	10	mean	522	0.0566	2.0906	2.0748	1.7626	2.9412	15.7660	0.7972	3.5551
		sd	43	0.0058	0.0689	0.2889	0.3664	0.3009	1.7291	0.0973	0.3092
50	10	mean	490	0.0608	2.0765	*1.7101	1.6194	2.9040	14.4589	0.7405	3.7377
		sd	66	0.0102	0.0861	0.1401	0.1669	0.2413	1.9260	0.0937	0.3155
250	10	mean	520	0.0620	2.1282	**1.6691	1.7635	3.1011	15.5553	0.7670	3.9041
		sd	30	0.0085	0.1215	0.2597	0.2376	0.3590	1.7291	0.1023	0.5206
1000	10	mean	449	0.0581	2.0352	**1.6915	**1.3943	2.7614	13.7709	**0.6495	3.6157
		sd	58	0.0083	0.1516	0.3240	0.1886	0.3585	2.0753	0.1024	0.3757

* - significantly different from control group $p < 0.05$
** - significantly different from control group $p < 0.01$

SPL PROJECT NUMBER: []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 16
GROUP MEAN ORGAN WEIGHTS AND
STANDARD DEVIATIONS (SD) - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	BODYWEIGHT (g) AT TERMINAL KILL	ORGAN WEIGHT (g)							
			Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	
0 (Control)	10	mean	301	0.0675	1.7869	1.0964	1.7064	9.4548	0.1482	0.5170
		sd	31	0.0105	0.0849	0.1246	0.1542	1.2741	0.0155	0.0663
50	10	mean	298	0.0619	1.7409	1.0425	1.7464	9.5041	0.1498	0.5194
		sd	38	0.0109	0.0991	0.0718	0.1969	1.2089	0.0169	0.0946
250	10	mean	300	0.0747	1.7495	1.0929	1.8601	9.9485	0.1630	0.5426
		sd	21	0.0091	0.1176	0.1837	0.1963	0.6066	0.0205	0.0635
1000	10	mean	287	0.0757	1.8766	0.9663	**2.0522	***11.6788	0.1719	0.4877
		sd	22	0.0064	0.0818	0.0479	0.2589	1.3822	0.0309	0.0686

** - significantly different from control group p<0.01
*** - significantly different from control group p<0.001

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 17
GROUP MEAN RELATIVE ORGAN WEIGHTS (% OF BODYWEIGHT) AND
STANDARD DEVIATIONS (SD) - MALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	BODY- WEIGHT (g) AT TERMINAL KILL	RELATIVE ORGAN WEIGHT (%)								
			Adrenals	Brain	Epididy- mides	Heart	Kidneys	Liver	Spleen	Testes	
0 (Control)	10	mean	522	0.0109	0.4022	0.3985	0.3433	0.5644	3.0128	0.1528	0.6878
		sd	43	0.0015	0.0284	0.0551	0.0977	0.0532	0.0925	0.0164	0.1062
50	10	mean	490	0.0125	0.4285	0.3522	0.3342	0.5996	2.9577	0.1522	0.7721
		sd	66	0.0021	0.0418	0.0354	0.0475	0.0737	0.1916	0.0188	0.0994
250	10	mean	520	0.0120	0.4093	0.3210	0.3394	0.5965	2.9887	0.1470	0.7513
		sd	30	0.0018	0.0169	0.0485	0.0465	0.0670	0.2801	0.0130	0.0997
1000	10	mean	449	0.0130	**0.4570	0.3754	0.3109	0.6170	3.0639	0.1447	0.8159
		sd	58	0.0020	0.0429	0.0379	0.0247	0.0627	0.2029	0.0142	0.1291

** - significantly different from control group p<0.01

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 18
GROUP MEAN RELATIVE ORGAN WEIGHTS (% OF BODYWEIGHT) AND
STANDARD DEVIATIONS (SD) - FEMALES

DOSE LEVEL (mg/kg/day)	NUMBER OF ANIMALS	BODYWEIGHT (g) AT TERMINAL KILL	RELATIVE ORGAN WEIGHT (%)							
			Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	
0 (Control)	10	mean	301	0.0225	0.5985	0.3676	0.5683	3.1313	0.0493	0.1716
		sd	31	0.0033	0.0664	0.0610	0.0419	0.1873	0.0029	0.0141
50	10	mean	298	0.0209	0.5916	0.3542	0.5888	3.1937	0.0509	0.1760
		sd	38	0.0032	0.0716	0.0443	0.0493	0.1787	0.0079	0.0331
250	10	mean	300	0.0251	0.5846	0.3645	0.6221	*3.3235	0.0544	0.1813
		sd	21	0.0042	0.0375	0.0533	0.0699	0.1787	0.0058	0.0206
1000	10	mean	287	*0.0265	0.6577	0.3385	***0.7151	***4.0730	*0.0598	0.1701
		sd	22	0.0025	0.0475	0.0235	0.0609	0.3306	0.0085	0.0197

* - significantly different from control group p<0.05
*** - significantly different from control group p<0.001

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 19
SUMMARY INCIDENCE OF NECROPSY FINDINGS - MALES

	DOSE LEVEL (mg/kg/day)			
	0 (Control)	50	250	1000
Number of animals examined at terminal kill	10	10	10	10
No abnormalities detected	10	10	10	9
Kidneys: speckled	0	0	0	1

SPL PROJECT NUMBER:

] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 20
SUMMARY INCIDENCE OF NECROPSY FINDINGS - FEMALES

	DOSE LEVEL (mg/kg/day)			
	0 (Control)	50	250	1000
Number of animals examined at terminal kill	10	10	10	10
No abnormalities detected	10	10	10	9
Lungs: dark areas - intermediate lobe	0	0	0	1

SPL PROJECT NUMBER:

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 21
SUMMARY INCIDENCE OF
HISTOPATHOLOGICAL FINDINGS - MALES

	DOSE LEVEL (mg/kg/day)			
	0 (Control)	50	250	1000
number of animals	10	10	10	10
Heart				
Focal myocarditis				
no data				
absent	0	10	10	0
(minimal)	1	0	0	4
(slight)	8	0	0	6
	1	0	0	0
Kidneys				
Groups of basophilic tubules				
absent				
(minimal)	7	6	7	10
	3	4	3	0
Globular accumulations of eosinophilic material				
absent				
(minimal)	7	3	6	9
(slight)	0	3	2	0
(moderate)	2	2	1	0
(marked)	1	2	0	1
	0	0	1	0
Hydronephrosis				
absent				
(minimal)	10	10	10	9
	0	0	0	1
Liver				
Mononuclear cell foci				
(minimal)				
(slight)	10	8	9	10
	0	2	1	0
Lungs				
Perivascular/peribronchiolar lymphoid aggregations				
(minimal)				
(slight)	10	10	9	10
	0	0	1	0

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 21 (continued)
SUMMARY INCIDENCE OF
HISTOPATHOLOGICAL FINDINGS - MALES

	DOSE LEVEL (mg/kg/day)			
	0 (Control)	50	250	1000
number of animals	10	10	10	10
Lungs				
Focal pneumonitis				
absent	9	10	9	9
(minimal)	1	0	0	0
(slight)	0	0	1	1
Groups of alveolar macrophages				
absent	3	6	2	4
(minimal)	6	3	7	5
(slight)	1	1	1	1
Artefactual haemorrhage				
absent	10	10	10	9
present	0	0	0	1
Mesenteric lymph nodes				
Sinus histiocytosis				
absent	10	10	10	1
(minimal)	0	0	0	5
(slight)	0	0	0	2
(moderate)	0	0	0	2
Oesophagus				
Peripheral inflammatory cell infiltrates				
no data	0	10	10	0
absent	8	0	0	8
present	2	0	0	2

SPL PROJECT NUMBER:

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 21 (continued)
SUMMARY INCIDENCE OF
HISTOPATHOLOGICAL FINDINGS - MALES

	DOSE LEVEL (mg/kg/day)			
	0 (Control)	50	250	1000
number of animals	10	10	10	10
Prostate				
Epithelial and subepithelial inflammatory cells				
no data				
absent	0	10	10	0
(minimal)	7	0	0	8
	3	0	0	2
Thymus				
Multifocal haemorrhage				
no data				
absent	0	10	10	0
present	10	0	0	9
	0	0	0	1
Thyroids				
Follicular cell hypertrophy				
absent				
(minimal)	6	8	4	4
(slight)	3	2	5	3
	1	0	1	3
Depletion of colloid				
absent				
(minimal)	7	9	4	7
	3	1	6	3
Tongue				
Mononuclear cell foci				
no data				
absent	0	10	10	0
(minimal)	9	0	0	10
	1	0	0	0
Statistical Information				
Mode of death				
Terminal kill	10	10	10	10

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 21 (continued)
SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS
(CHI-SQUARED ANALYSIS) - MALES

		DOSE LEVEL (mg/kg/day)				Total
		0 (Control)	50	250	1000	
Heart						
Focal myocarditis						
n	9	0	0	6	15	
E	7.50	0.00	0.00	7.50	15.00	
E(2)		0.00	0.00	7.50		
N	10	0	0	10	20	
ChiSq		0.00	0.00	2.28	2.28	
P				N.S.	N.S.	
Kidneys						
Groups of basophilic tubules						
n	3	4	3	0	10	
E	2.50	2.50	2.50	2.50	10.00	
E(2)		3.50	3.00	1.50		
N	10	10	10	10	40	
ChiSq		0.21	0.00	3.35	4.68	
P		N.S.	N.S.	(-)	N.S.	
Kidneys						
Globular accumulations of eosinophilic material						
n	3	7	4	1	15	
E	3.75	3.75	3.75	3.75	15.00	
E(2)		5.00	3.50	2.00		
N	10	10	10	10	40	
ChiSq		3.04	0.21	1.19	7.80	
P		(+)	N.S.	N.S.	(*)	
Kidneys						
Hydronephrosis						
n	0	0	0	1	1	
E	0.25	0.25	0.25	0.25	1.00	
E(2)		0.00	0.00	0.50		
N	10	10	10	10	40	
ChiSq		0.00	0.00	1.00	3.00	
P				N.S.	N.S.	
Lungs						
Focal pneumonitis						
n	1	0	1	1	3	
E	0.75	0.75	0.75	0.75	3.00	
E(2)		0.50	1.00	1.00		
N	10	10	10	10	40	
ChiSq		1.00	0.00	0.00	1.05	
P		N.S.	N.S.	N.S.	N.S.	

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 21 (continued)
SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS
(CHI-SQUARED ANALYSIS) - MALES

		DOSE LEVEL (mg/kg/day)				Total
		0 (Control)	50	250	1000	
Lungs Groups of alveolar macrophages	n	7	4	8	6	25
	E	6.25	6.25	6.25	6.25	25.00
	E(2)		5.50	7.50	6.50	
	N	10	10	10	10	40
	ChiSq P		1.73 N.S.	0.25 N.S.	0.21 N.S.	3.64 N.S.
Lungs Artefactual haemorrhage	n	0	0	0	1	1
	E	0.25	0.25	0.25	0.25	1.00
	E(2)		0.00	0.00	0.50	
	N	10	10	10	10	40
	ChiSq P		0.00	0.00	1.00 N.S.	3.00 N.S.
Mesenteric lymph nodes Sinus histiocytosis	n	0	0	0	9	9
	E	2.25	2.25	2.25	2.25	9.00
	E(2)		0.00	0.00	4.50	
	N	10	10	10	10	40
	ChiSq P		0.00	0.00	15.55 +++	33.97 ***
Oesophagus Peripheral inflammatory cell infiltrates	n	2	0	0	2	4
	E	2.00	0.00	0.00	2.00	4.00
	E(2)		0.00	0.00	2.00	
	N	10	0	0	10	20
	ChiSq P		0.00	0.00	0.00 N.S.	0.00 N.S.
Prostate Epithelial and subepithelial inflammatory cells	n	3	0	0	2	5
	E	2.50	0.00	0.00	2.50	5.00
	E(2)		0.00	0.00	2.50	
	N	10	0	0	10	20
	ChiSq P		0.00	0.00	0.25 N.S.	0.25 N.S.

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 21 (continued)
SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS
(CHI-SQUARED ANALYSIS) - MALES

		DOSE LEVEL (mg/kg/day)				Total
		0 (Control)	50	250	1000	
Thymus						
Multifocal haemorrhage	n	0	0	0	1	1
	E	0.50	0.00	0.00	0.50	1.00
	E(2)		0.00	0.00	0.50	
	N	10	0	0	10	20
	ChiSq		0.00	0.00	1.00	1.00
	P				N.S.	N.S.
Thyroids						
Follicular cell hypertrophy	n	4	2	6	6	18
	E	4.50	4.50	4.50	4.50	18.00
	E(2)		3.00	5.00	5.00	
	N	10	10	10	10	40
	ChiSq		0.90	0.76	0.76	4.33
	P		N.S.	N.S.	N.S.	N.S.
Thyroids						
Depletion of colloid	n	3	1	6	3	13
	E	3.25	3.25	3.25	3.25	13.00
	E(2)		2.00	4.50	3.00	
	N	10	10	10	10	40
	ChiSq		1.19	1.73	0.00	5.67
	P		N.S.	N.S.	N.S.	N.S.
Tongue						
Mononuclear cell foci	n	1	0	0	0	1
	E	0.50	0.00	0.00	0.50	1.00
	E(2)		0.00	0.00	0.50	
	N	10	0	0	10	20
	ChiSq		0.00	0.00	1.00	1.00
	P				N.S.	N.S.

SPL PROJECT NUMBER:

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 21 (continued)
SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS
(KRUSKAL-WALLIS ANALYSIS) - MALES

		DOSE LEVEL (mg/kg/day)				Total
		0 (Control)	50	250	1000	
Kidneys						
Epithelial hypertrophy inner cortical tubules	N	10	10	10	10	40
	Mrank	20.50	20.50	20.50	20.50	20.50
	Median	0.00	0.00	0.00	0.00	0.00
	Min	0	0	0	0	0
	Max	0	0	0	0	0
	ChiSq		0.00	0.00	0.00	0.00
	P		N.S.	N.S.	N.S.	
Liver						
Mononuclear cell foci	N	10	10	10	10	40
	Mrank	19.00	23.00	21.00	19.00	20.50
	Median	1.00	1.00	1.00	1.00	1.00
	Min	1	1	1	1	1
	Max	1	2	2	1	2
	ChiSq		2.11	1.00	0.00	3.86
	P		N.S.	N.S.	N.S.	N.S.
Liver						
Centrilobular hepatocyte enlargement	N	10	10	10	10	40
	Mrank	20.50	20.50	20.50	20.50	20.50
	Median	0.00	0.00	0.00	0.00	0.00
	Min	0	0	0	0	0
	Max	0	0	0	0	0
	ChiSq		0.00	0.00	0.00	0.00
	P		N.S.	N.S.	N.S.	
Lungs						
Perivascular/ peribronchiolar lymphoid aggregations	N	10	10	10	10	40
	Mrank	20.00	20.00	22.00	20.00	20.50
	Median	1.00	1.00	1.00	1.00	1.00
	Min	1	1	1	1	1
	Max	1	1	2	1	2
	ChiSq		0.00	1.00	0.00	3.00
	P		N.S.	N.S.	N.S.	N.S.
Lungs						
Groups of alveolar macrophages	N	10	10	10	10	40
	Mrank	21.85	16.45	23.65	20.05	20.50
	Median	1.00	0.00	1.00	1.00	1.00
	Min	0	0	0	0	0
	Max	2	2	2	2	2
	ChiSq		1.27	0.16	0.15	2.59
	P		N.S.	N.S.	N.S.	N.S.

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 21 (continued)
SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS
(KRUSKAL-WALLIS ANALYSIS) - MALES

		DOSE LEVEL (mg/kg/day)				Total
		0 (Control)	50	250	1000	
Mesenteric lymph nodes Sinus histiocytosis	N	10	10	10	10	40
	Mrank	16.00	16.00	16.00	34.00	20.50
	Median	0.00	0.00	0.00	1.00	0.00
	Min	0	0	0	0	0
	Max	0	0	0	3	3
	ChiSq		0.00	0.00	14.15	33.38
	P		N.S.	N.S.	+++	***
Thyroids Follicular cell hypertrophy	N	10	10	10	10	40
	Mrank	19.40	15.00	22.90	24.70	20.50
	Median	0.00	0.00	1.00	1.00	0.00
	Min	0	0	0	0	0
	Max	2	1	2	2	2
	ChiSq		1.08	0.57	1.15	5.03
	P		N.S.	N.S.	N.S.	N.S.
Thyroids Depletion of colloid	N	10	10	10	10	40
	Mrank	20.00	16.00	26.00	20.00	20.50
	Median	0.00	0.00	1.00	0.00	0.00
	Min	0	0	0	0	0
	Max	1	1	1	1	1
	ChiSq		1.19	1.73	0.00	5.67
	P		N.S.	N.S.	N.S.	N.S.

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 22
SUMMARY INCIDENCE OF
HISTOPATHOLOGICAL FINDINGS - FEMALES

	DOSE LEVEL (mg/kg/day)			
	0 (Control)	50	250	1000
number of animals	10	10	10	10
Heart				
Focal myocarditis				
no data				
absent	0	10	10	0
(minimal)	4	0	0	5
	6	0	0	5
Kidneys				
Groups of basophilic tubules				
absent	10	10	10	9
(minimal)	0	0	0	1
Epithelial hypertrophy inner cortical tubules				
absent	9	10	10	5
(minimal)	1	0	0	5
Pelvic mineralisation				
absent	10	9	10	10
present	0	1	0	0
Liver				
Mononuclear cell foci (minimal)	10	10	10	10
Centrilobular hepatocyte enlargement				
absent	10	10	10	5
(minimal)	0	0	0	4
(slight)	0	0	0	1
Lungs				
Perivascular/peribronchiolar lymphoid aggregations				
absent	0	1	0	0
(minimal)	10	9	10	10

SPL PROJECT NUMBER:

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 22 (continued)
SUMMARY INCIDENCE OF
HISTOPATHOLOGICAL FINDINGS - FEMALES

	DOSE LEVEL (mg/kg/day)			
	0 (Control)	50	250	1000
number of animals	10	10	10	10
Lungs				
Groups of alveolar macrophages				
absent	7	9	6	1
(minimal)	3	1	4	8
(slight)	0	0	0	1
Artefactual haemorrhage				
absent	9	8	9	9
present	1	2	1	1
Mesenteric lymph nodes				
Sinus histiocytosis				
absent	10	10	10	2
(minimal)	0	0	0	2
(slight)	0	0	0	5
(moderate)	0	0	0	1
Oesophagus				
Peripheral inflammatory cell infiltrates				
no data	0	10	10	0
absent	9	0	0	8
present	1	0	0	2
Thyroids				
Follicular cell hypertrophy				
absent	9	10	8	4
(minimal)	1	0	2	5
(slight)	0	0	0	1
Depletion of colloid				
absent	9	10	9	6
(minimal)	1	0	1	4

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 22 (continued)
SUMMARY INCIDENCE OF
HISTOPATHOLOGICAL FINDINGS - FEMALES

	DOSE LEVEL (mg/kg/day)			
	0 (Control)	50	250	1000
number of animals	10	10	10	10
	Tongue			
Mononuclear cell foci				
no data	0	10	10	0
absent	10	0	0	9
(minimal)	0	0	0	1
	Uterus/cervix			
Dilatation horn1				
no data	0	10	10	0
absent	8	0	0	3
(minimal)	1	0	0	3
(slight)	1	0	0	3
(moderate)	0	0	0	1
Dilatation horn2				
no data	0	10	10	0
absent	8	0	0	4
(minimal)	1	0	0	4
(slight)	1	0	0	2
	Statistical Information			
Mode of death				
Terminal kill	10	10	10	10

SPL PROJECT NUMBER: [] []

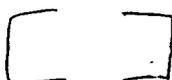
[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 22 (continued)
SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS
(CHI-SQUARED ANALYSIS) - FEMALES

		DOSE LEVEL (mg/kg/day)				Total
		0 (Control)	50	250	1000	
Heart						
Focal myocarditis	n	6	0	0	5	11
	E	5.50	0.00	0.00	5.50	11.00
	E(2)		0.00	0.00	5.50	
	N	10	0	0	10	20
	ChiSq		0.00	0.00	0.19	0.19
	P				N.S.	N.S.
Kidneys						
Groups of basophilic tubules	n	0	0	0	1	1
	E	0.25	0.25	0.25	0.25	1.00
	E(2)		0.00	0.00	0.50	
	N	10	10	10	10	40
	ChiSq		0.00	0.00	1.00	3.00
	P				N.S.	N.S.
Kidneys						
Epithelial hypertrophy inner cortical tubules	n	1	0	0	5	6
	E	1.50	1.50	1.50	1.50	6.00
	E(2)		0.50	0.50	3.00	
	N	10	10	10	10	40
	ChiSq		1.00	1.00	3.62	13.00
	P		N.S.	N.S.	(+)	**
Kidneys						
Pelvic mineralisation	n	0	1	0	0	1
	E	0.25	0.25	0.25	0.25	1.00
	E(2)		0.50	0.00	0.00	
	N	10	10	10	10	40
	ChiSq		1.00	0.00	0.00	3.00
	P		N.S.			N.S.
Liver						
Centrilobular hepatocyte enlargement	n	0	0	0	5	5
	E	1.25	1.25	1.25	1.25	5.00
	E(2)		0.00	0.00	2.50	
	N	10	10	10	10	40
	ChiSq		0.00	0.00	6.33	16.71
	P				+	***

SPL PROJECT NUMBER:

NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 22 (continued)
SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS
(CHI-SQUARED ANALYSIS) - FEMALES

		DOSE LEVEL (mg/kg/day)				Total
		0 (Control)	50	250	1000	
Lungs Perivascular/ peribronchiolar lymphoid aggregations	n	10	9	10	10	39
	E	9.75	9.75	9.75	9.75	39.00
	E(2)		9.50	10.00	10.00	
	N	10	10	10	10	40
	ChiSq P		1.00 N.S.	0.00	0.00	3.00 N.S.
Lungs Groups of alveolar macrophages	n	3	1	4	9	17
	E	4.25	4.25	4.25	4.25	17.00
	E(2)		2.00	3.50	6.00	
	N	10	10	10	10	40
	ChiSq P		1.19 N.S.	0.21 N.S.	7.13 ++	13.86 **
Lungs Artefactual haemorrhage	n	1	2	1	1	5
	E	1.25	1.25	1.25	1.25	5.00
	E(2)		1.50	1.00	1.00	
	N	10	10	10	10	40
	ChiSq P		0.37 N.S.	0.00 N.S.	0.00 N.S.	0.67 N.S.
Mesenteric lymph nodes Sinus histiocytosis	n	0	0	0	8	8
	E	2.00	2.00	2.00	2.00	8.00
	E(2)		0.00	0.00	4.00	
	N	10	10	10	10	40
	ChiSq P		0.00	0.00	12.67 +++	29.25 ***
Oesophagus Peripheral inflammatory cell infiltrates	n	1	0	0	2	3
	E	1.50	0.00	0.00	1.50	3.00
	E(2)		0.00	0.00	1.50	
	N	10	0	0	10	20
	ChiSq P		0.00	0.00	0.37 N.S.	0.37 N.S.



NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 22 (continued)

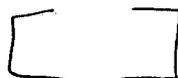
SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS
(CHI-SQUARED ANALYSIS) - FEMALES

		DOSE LEVEL (mg/kg/day)				Total
		0 (Control)	50	250	1000	
Thyroids						
Follicular cell hypertrophy						
n	1	0	2	6	9	
E	2.25	2.25	2.25	2.25	9.00	
E(2)		0.50	1.50	3.50		
N	10	10	10	10	40	
ChiSq		1.00	0.37	5.22	11.60	
P		N.S.	N.S.	+	**	
Thyroids						
Depletion of colloid						
n	1	0	1	4	6	
E	1.50	1.50	1.50	1.50	6.00	
E(2)		0.50	1.00	2.50		
N	10	10	10	10	40	
ChiSq		1.00	0.00	2.28	6.88	
P		N.S.	N.S.	N.S.	(*)	
Tongue						
Mononuclear cell foci						
n	0	0	0	1	1	
E	0.50	0.00	0.00	0.50	1.00	
E(2)		0.00	0.00	0.50		
N	10	0	0	10	20	
ChiSq		0.00	0.00	1.00	1.00	
P				N.S.	N.S.	
Uterus/cervix						
Dilatation horn1						
n	2	0	0	7	9	
E	4.50	0.00	0.00	4.50	9.00	
E(2)		0.00	0.00	4.50		
N	10	0	0	10	20	
ChiSq		0.00	0.00	4.80	4.80	
P				+	*	
Uterus/cervix						
Dilatation horn2						
n	2	0	0	6	8	
E	4.00	0.00	0.00	4.00	8.00	
E(2)		0.00	0.00	4.00		
N	10	0	0	10	20	
ChiSq		0.00	0.00	3.17	3.17	
P				(+)	(*)	

SPL PROJECT NUMBER: [] []

[] [] NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TABLE 22 (continued)
SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS
(KRUSKAL-WALLIS ANALYSIS) - FEMALES

		DOSE LEVEL (mg/kg/day)				Total
		0 (Control)	50	250	1000	
Kidneys						
Epithelial hypertrophy inner cortical tubules	N	10	10	10	10	40
	Mrank	19.50	17.50	17.50	27.50	20.50
	Median	0.00	0.00	0.00	0.50	0.00
	Min	0	0	0	0	0
	Max	1	0	0	1	1
	ChiSq		1.00	1.00	3.62	13.00
	P		N.S.	N.S.	(+)	**
Liver						
Mononuclear cell foci	N	10	10	10	10	40
	Mrank	20.50	20.50	20.50	20.50	20.50
	Median	1.00	1.00	1.00	1.00	1.00
	Min	1	1	1	1	1
	Max	1	1	1	1	1
	ChiSq		0.00	0.00	0.00	0.00
	P		N.S.	N.S.	N.S.	
Liver						
Centrilobular hepatocyte enlargement	N	10	10	10	10	40
	Mrank	18.00	18.00	18.00	28.00	20.50
	Median	0.00	0.00	0.00	0.50	0.00
	Min	0	0	0	0	0
	Max	0	0	0	2	2
	ChiSq		0.00	0.00	6.25	16.67
	P		N.S.	N.S.	+	***
Lungs						
Perivascular/ peribronchiolar lymphoid aggregations	N	10	10	10	10	40
	Mrank	21.00	19.00	21.00	21.00	20.50
	Median	1.00	1.00	1.00	1.00	1.00
	Min	1	0	1	1	0
	Max	1	1	1	1	1
	ChiSq		1.00	0.00	0.00	3.00
	P		N.S.	N.S.	N.S.	N.S.
Lungs						
Groups of alveolar macrophages	N	10	10	10	10	40
	Mrank	17.85	13.95	19.80	30.40	20.50
	Median	0.00	0.00	0.00	1.00	0.00
	Min	0	0	0	0	0
	Max	1	1	1	2	2
	ChiSq		1.19	0.21	7.35	14.55
	P		N.S.	N.S.	++	**



NINETY DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 22 (continued)

SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS
(KRUSKAL-WALLIS ANALYSIS) - FEMALES

		DOSE LEVEL (mg/kg/day)				Total
		0 (Control)	50	250	1000	
Mesenteric lymph nodes						
Sinus histiocytosis						
	N	10	10	10	10	40
	Mrank	16.50	16.50	16.50	32.50	20.50
	Median	0.00	0.00	0.00	2.00	0.00
	Min	0	0	0	0	0
	Max	0	0	0	3	3
	ChiSq		0.00	0.00	11.89	28.89
	P		N.S.	N.S.	+++	***
Thyroids						
Follicular cell hypertrophy						
	N	10	10	10	10	40
	Mrank	17.95	16.00	19.90	28.15	20.50
	Median	0.00	0.00	0.00	1.00	0.00
	Min	0	0	0	0	0
	Max	1	0	1	2	2
	ChiSq		1.00	0.37	5.31	11.89
	P		N.S.	N.S.	+	**
Thyroids						
Depletion of colloid						
	N	10	10	10	10	40
	Mrank	19.50	17.50	19.50	25.50	20.50
	Median	0.00	0.00	0.00	0.00	0.00
	Min	0	0	0	0	0
	Max	1	0	1	1	1
	ChiSq		1.00	0.00	2.28	6.88
	P		N.S.	N.S.	N.S.	(*)

