Contains NO CBI

RHÔNE-POULENC

TOXICOLOGY DEPARTMENT
P.O. BOX 12014, 2 T.W. ALEXANDER DRIVE
RESEARCH TRIANGLE PARK, NC 27709
(919) 549-2000 TELEFAX (919) 549-8525
INTERNATIONAL TELEX NUMBER 4999378-ANSWERBACK APC RTP

October 27, 1992

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Office of Toxic Substances
US Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

RE: Report Submitted Pursuant to the TSCA Section 8(e) Compliance Audit Program

CAP ID No.: 8ECAP - 0004

Dear Sir/Madam:

On behalf of Rhône-Poulenc Inc. (RPI, CN 5266, Princeton, NJ 08543-5266) and its subsidiary Rhône-Poulenc Ag Company (RPAC), the attached study report is being submitted to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program and the Agreement for a TSCA Section 8(e) Compliance Audit Program (CAP Agreement) executed by RPI and EPA.

The enclosed study report provides information on M&B 46030. Its CAS number and chemical index name are 120068-37-3 and 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile. This chemical is manufactured in Europe and imported by RPAC for pesticide research and development.

No claims of confidentiality are made for this submission. Please note that RPAC released previous confidentiality claims for the subject chemical on September 8, 1992. The title of the enclosed report is "M&B 46030: Toxicity Study by Dietary Administration to CD Rats for 13 Weeks". The following is a summary of the adverse effects observed in this study.

This study is being submitted under Section 8(e) because of dose-related increased liver and thyroid weights, and associated histological findings in both organs. Groups of ten male and ten female CD rats received test material via dietary admixture at levels of 0, 1, 5, 30, or 300 ppm for 13 weeks. Absolute liver weight was statistically increased in females at 5, 30 and 300 ppm and in males at 300 ppm. An increased incidence of panacinar hepatocytic fatty vacuolation was observed in males at 300 ppm. Absolute thyroid weight was statistically increased in females at 30 and 300 ppm and in males at 300 ppm. In the thyroid, higher incidences of hypertrophy of follicular epithelium were noted in males at 30 and 300 ppm and in females at 300 ppm. In addition, a higher incidence of follicular cell hyperplasia was seen at 300 ppm in both sexes.

3/1/95

Seven previous TSCA Section 8(e) notices were submitted on this chemical. The EPA Document Control Numbers for these submissions are 8EHQ-0191-1162S, 8EHQ-0391-1199S, 8EHQ-0591-1232S, 8EHQ-0791-1284S, 8EHQ-0791-1285S and 8EHQ-0891-1315S, and 8EHQ-0392-2540S. Also several Section 8(e) notices will be submitted on this compound under the CAP.

In total, RPI is submitting three copies of the enclosed report and this cover letter: an original and two copies.

Further questions regarding this submission may be directed to the undersigned at 919-549-2222.

Sincerely,

Glenn S. Simon

Glenn S. Simon, PhD, DABT
Director of Toxicology

Contains NO CBI

030-TP-91-1012

LSR Schedule No : RHA/298/46030
LSR Report No : 90/RHA298/0781

M&B 46030: TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR 13 WEEKS

FINAL REPORT

Data requirement

Guideline No 82-1

Study Period Completed on

14 March 1991

Study Director

P. Holmes

To:
Rhône-Poulenc Agrochimie
14-20 rue Pierre Baizet
BP 9163
69263 Lyon Cedex 09
France

From:
Life Science Research Limited
Eye
Suffolk IP23 7PX
England

Draft: 28 September 1990
Final: 9 April 1991

M&B 46030: TOXICITY STUDY BY
DIETARY ADMINISTRATION TO
CD RATS FOR 13 WEEKS

FINAL REPORT

LSR Schedule No : RHA/298/46030
LSR Report No : 90/RHA298/0781

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA 10(d)(1)(A), (B), or (C).

Company Rhône-Poulenc Agrochimie .....

Company Agent: ..... Date: .....

....

LIFE SCIENCE RESEARCH

M&B 46030: TOXICITY STUDY BY
DIETARY ADMINISTRATION TO
CD RATS FOR 13 WEEKS

FINAL REPORT

LSR Schedule No : RHA/298/46030
LSR Report No : 90/RHA298/0781

I declare that the report following constitutes a true and faithful account of the procedures adopted and the results obtained in the performance of this study.

The aspects of the study conducted by Life Science Research were performed in accordance with the principles of Good Laboratory Practice Standards or Guidelines relating to non-clinical studies as follows:

Current OECD Good Laboratory Practice Principles
Current UK DH Principles of Good Laboratory Practice
Current EPA Pesticide Programs Good Laboratory Practice Standards
Current Japanese Good Laboratory Practice Standards on Agricultural Chemicals.

The Study Director fulfilled the responsibilities required by these regulations.

P. Holmes, B.Sc., C.Biol., M.I.Biol.
(Study Director)

P. Holmes
Date: 9 April 1991

.....
Date: .....

(For Submitter)

.....
Date: .....

(For Sponsor)

M&B 46030: TOXICITY STUDY BY
DIETARY ADMINISTRATION TO
CD RATS FOR 13 WEEKS

FINAL REPORT

LSR Schedule No : RHA/298/46030
LSR Report No : 90/RHA298/0781

FLAGGING STATEMENTS

This page is reserved for flagging statements as may be required by EPA in accordance with PR Notice 86-5.

LIFE SCIENCE RESEARCH

M&B 46030: TOXICITY STUDY BY
DIETARY ADMINISTRATION TO
CD RATS FOR 13 WEEKS

FINAL REPORT

LSR Schedule No : RHA/298/46030
LSR Report No : 90/RHA298/0781

I have reviewed this report and concur with its contents.

A.P.A.H. Woolley, B.Sc., M.Sc.,
M.R.C.Path., M.I.Biol.
(Senior Scientist, Office of Research Liaison) Date: 5 April 1991.

We, the undersigned, were responsible for the conduct of the work and reporting of the results in the listed sections; we concur with the views expressed in the Discussion.

T.C. Cowlyn, L.R.S.C.
(Head, Analytical Chemistry)
Section 3
Date: 8 April 1991

L.J. Freeman, B.Sc.
(Staff Toxicologist)
Sections 5.1 to 5.6 and 5.12
Date: 5 April 1991

P. Lee, B.V.Sc., M.R.C.V.S., D.V.S.M.
(Veterinary Officer)
Sections 5.7 and 5.8
Date: 8 April 1991

D.M. Virgo, B.Sc.
(Chief Toxicologist)
Sections 5.9 to 5.11
Date: 8 April 1991.

S. Sparrow, Ph.D., B.Vet.Med., M.R.C.V.S.
(Head, Department of Pathology)
Sections 5.13 and 5.14
Date: 8 April 1991

M&B 46030: TOXICITY STUDY BY
DIETARY ADMINISTRATION TO
CD RATS FOR 13 WEEKS

FINAL REPORT

LSR Schedule No : RHA/298/46030
LSR Report No : 90/RHA298/0781

QUALITY ASSURANCE INSPECTIONS

	Dates (Day.Month.Year)		
	Inspection	Report to Study Director	Report to Management
PROTOCOL			
Inspection of protocol was made in accordance with LSR Standard Operating Procedure QAU/020. Dates for inspection of any protocol amendments, in accordance with this SOP, are not quoted.	02.11.89	02.11.89	02.11.89
DATA			
Inspection of data generated on this study was made in accordance with LSR Standard Operating Procedure QAU/050.	12.12.90	12.12.90	12.12.90
PROCEDURES			
Inspection of procedures on this study was made in accordance with LSR Standard Operating Procedure QAU/040.	20.11.89 20.11.89 11.12.89 11.12.89 11.01.90 13.02.90 20.02.90	20.11.89 21.11.89 12.12.89 12.12.89 11.01.90 13.02.90 20.02.90	20.11.89 21.11.89 12.12.89 12.12.89 11.01.90 13.02.90 20.02.90

LIFE SCIENCE RESEARCH

M&B 46030: TOXICITY STUDY BY
DIETARY ADMINISTRATION TO
CD RATS FOR 13 WEEKS

FINAL REPORT

LSR Schedule No : RHA/298/46030
LSR Report No : 90/RHA298/0781

QUALITY ASSURANCE INSPECTIONS

Other routine procedures used in this type of study were inspected regularly and reports made in accordance with LSR Standard Operating Procedure QAU/040.

This report has been reviewed by the LSR Quality Assurance Unit employing methods laid down in LSR Standard Operating Procedure QAU/060. The reported methods and procedures were found to describe those used and the results to constitute an accurate representation of the data recorded.

This review was completed on: 3 April 1991

D.L.M. Weller, B.Sc.
(Head of Quality Assurance Unit)

.....

Date: 9 April 1991

CONTENTS

		Page
	Title page	1
	Confidentiality statement	2
	GLP compliance statement	3
	Flagging statement	4
	Signature page	5
	Quality assurance statement	6
	Contents	8
1.	SUMMARY	11
2.	INTRODUCTION	13
3.	TEST SUBSTANCE AND DOSAGE FORM	14
4.	METHODS	15
5.	RESULTS	30
6.	DISCUSSION	34
7.	CONCLUSION	35

FIGURES

1.	Group, cage and animal distribution	36
2A.	Group mean bodyweight versus period of treatment - males	37
2B.	Group mean bodyweight versus period of treatment - females	38

TABLES

1.	Food consumption - group mean values	39
2.	Bodyweight - group mean values	40
3.	Food conversion ratio - group mean values	42
4.	Achieved dosges - group mean values	43
5A.	Haematology - background data for CD rats between 17 and 18 weeks of age	44
5B.	Haematology - group mean values after 12 weeks of treatment	45
6.	Blood chemistry - group mean values after 12 weeks of treatment	47

CONTENTS - continued

Page

TABLES - continued

7. Urinalysis - group mean values after 12 weeks of treatment..... 49

8A. Absolute organ weights - group mean values for animals killed after 13 weeks of the treatment period..... 50

8B. Organ weights relative to bodyweight - group mean values for animals killed after 13 weeks of the treatment period..... 54

9. Macropathology - group distribution of findings for animals killed after 13 weeks of the treatment period..... 58

10. Histopathology - group distribution of findings for animals killed after 13 weeks of the treatment period..... 63

APPENDICES

1. Analysis of M&B 46030 - certificate from the Sponsor..... 65

2A. Determination of M&B 46030 in rodent diet mixes..... 76

2B. Homogeneity of M&B 46030 in rodent diet..... 79

2C. Stability of M&B 46030 in rodent diet..... 80

2D. Analysis of treatment mixes for M&B 46030 content..... 81

3. Fate of individual animals and signs observed at routine *in vivo* inspection..... 82

4. Food consumption - individual values..... 92

5. Bodyweight - individual values..... 94

6A. Ophthalmoscopy - individual observations before commencement of treatment..... 100

6B. Ophthalmoscopy - individual observations after 12 weeks of treatment..... 102

7. Haematology - individual values after 12 weeks of treatment..... 104

8. Blood chemistry - individual values after 12 weeks of treatment.. 110

9. Urinalysis - individual values after 12 weeks of treatment..... 116

10A. Absolute organ weights - individual values for animals killed after 13 weeks of the treatment period..... 122

10B. Organ weights relative to bodyweight - individual values for animals killed after 13 weeks of the treatment period..... 142

CONTENTS - continued

Page

APPENDICES - continued

11. Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period..... 162

PROTOCOL

Final protocol..... 262

First amendment to protocol..... 283

Second amendment to protocol..... 289

Third amendment to protocol..... 291

In the livers of males there was a higher incidence of fat than in their controls, with a tendancy to panacinar rather than centriacinar vacuolation.

30 ppm

During the first week of treatment, slightly lower bodyweight gain and food intake were noted in males.

Lower prothrombin times were noted in females.

A higher plasma protein level was noted with an associated change in protein profile in males and females. In addition, in males higher urea level and in females higher plasma glucose level and lower alanine and aspartate amino-transferase activities were noted.

Higher absolute and bodyweight-relative liver weight of females and bodyweight-relative liver weight of males were noted. Slightly higher absolute thyroid weights were also noted in females.

Histopathological examination revealed no treatment-related changes.

5 ppm

Higher plasma protein levels were noted in males and females. Higher plasma urea level was also noted in males while in females a higher plasma glucose level and a lower aspartate amino-transferase activity were noted.

Slightly higher absolute liver weight was noted in females.

1 ppm

In males, a higher urea level and in females lower aspartate amino-transferase activity were noted.

Analysis of organ weight data revealed no changes considered to be attributable to treatment.

1.3 Conclusion

Treatment of CD rats with M&B 46030 at dietary inclusion levels of 5 or 30 ppm resulted in minor, probably adaptive responses.

Treatment at 300 ppm was generally tolerated, although a degree of toxicity was noted involving the liver and thyroid glands.

The maximum-tolerated-level of M&B 46030 in dietary administration to CD rats was considered to be close to, but above, 300 ppm. It was considered that the dietary concentration of 1 ppm represented a no-effect-level in this study and 30 ppm a no-toxic-effect-level.

1. SUMMARY

1.1 Groups of ten male and ten female CD rats received M&B 46030 continuously via the diet at dietary concentrations of 1, 5, 30 or 300 ppm for 13 weeks. A similarly constituted group received untreated diet and served to generate contemporaneous control data.

1.2 The following changes in comparison with the controls were noted:

300 ppm

The appearance and behaviour of the animals were considered to be unaffected by treatment.

There were no deaths.

Food intake was markedly lower than controls during the first two weeks of treatment, in males, and during the first week, in females.

Bodyweight gain in both sexes was significantly lower than that of controls during the first week of treatment. Subsequently, the weight gain and food utilisation efficiency of males were superior and those of females were similar to control values.

During Week 1 of treatment the efficiency of food utilisation of males and females was slightly lower.

Neurological and ophthalmoscopic examination, performed after 12 weeks of treatment, revealed no treatment-related changes.

Haematological investigations after 12 weeks of treatment revealed lower haemoglobin concentrations in males and lower packed cell volume, mean cell volume, mean cell haemoglobin and prothrombin time and higher platelet count, in females.

Blood chemistry investigations after 12 weeks of treatment revealed higher total protein concentrations and lower albumin/globulin ratio with associated changes in plasma protein profile in males and females. Higher urea in males, and slightly higher plasma glucose level and lower alanine and aspartate amino-transferase activities, in females, were noted when compared with their controls.

There were no treatment-related changes noted at the urinalysis investigations performed after 12 weeks of treatment.

Higher liver and thyroid weights were noted for males and females.

Macroscopic *post mortem* examination revealed no evidence of treatment-related effects.

Histopathological examination revealed an increase in follicular epithelial hypertrophy and follicular cell hyperplasia in the thyroids of males and females, when compared with their controls.

2. INTRODUCTION

The purpose of this study was to aid the assessment of the toxic effects of M&B 46030, a trifluoromethyl pyrazole insecticide, and to assist in the selection of dietary concentrations for a proposed combined oncogenicity and toxicity study in CD rats.

The rat was used because of its acceptance as a predictor of neoplastic and toxic change in man and the general requirement by regulatory agencies for a rodent species. The CD strain was used because of the availability of background data relating to this strain. The animals were obtained from Charles River (France) to allow comparison with data from previous studies held by the Sponsor. The dietary route was selected to accord with the potential major route of exposure in manufacture and use. The dietary concentrations of 1, 5, 30 and 300 ppm and the scheduled duration of treatment of 13 weeks were selected by the Sponsor.

Treatment commenced on 20 November 1989 and terminal necropsies were completed, following 13 weeks of treatment, on 22 February 1990.

3. TEST SUBSTANCE AND DOSAGE FORM

A 50 g sample of M&B 46030, Lot No. PGS963, was received on 16 October 1989. The test substance, a fine white powder, was received in amber glass jars and stored at ambient temperature, protected from light.

The stability and homogeneity of distribution of test material achieved by the mixing process was assessed before commencement of treatment as detailed in Section 4.2.3. The concentrations of test material in mixes prepared for Weeks 1 and 13 of treatment were determined and results expressed in terms of the material as received. The analytical procedure (Appendix 2A) was developed from information provided by the Sponsor.

Acceptable homogeneity (Appendix 2B) and stability of M&B 46030 in diet at room temperature (Appendix 2C) were demonstrated in the trial mixes. The concentrations in the mixes analysed during the treatment period (Appendix 2D) averaged 93%, 97%, 105% and 96% of the intended concentration for the lowest to highest dosage levels respectively. The achieved concentrations were considered satisfactory.

4. METHODS

4.1 Design conditions

4.1.1 Animals

Fifty five male and fifty six female CD rats were obtained from Charles River (France), St Aubin-les-Elbeuf, France. They were approximately three to four weeks of age and weighed between 69 and 103 g three days after arrival.

4.1.2 Identification

After random allocation to groups each rat was assigned a number, unique within the study, and identified by a tail tattoo.

4.1.3 Acclimatisation

The rats were allowed to acclimatise to the management conditions described below for 13 days before commencement of treatment, during which their health status was assessed by daily observation.

4.1.4 Environmental control

The animals were housed in one room, inside a barriered, limited-access, rodent facility. Personnel entering the facility were required to shower and change into protective clothing. A further overall, plastic overshoes and mask were put on before entering the room and gloves were worn when handling animals.

Before delivery of the animals the room was cleaned and fogged with an iodophore bactericide. All diet bags and equipment entering the facility were passed through a chamber in which their external surfaces were similarly treated.

The room was kept at positive pressure with respect to the outside and had its own supply of filtered, fresh air which was passed to atmosphere and not recirculated. Ventilation equipment was designed to provide approximately 20 air changes per hour and a 12-hour light : 12-hour dark cycle operated. Target values for temperature and humidity were 21°C and 55% RH respectively.

Maximum and minimum temperature and relative humidity were recorded daily; these records indicate no significant variations from target values.

Temperature and airflow sensors were connected to an audible and visual alarm, so that immediate action could be taken in the event of a ventilation failure or of temperature fluctuations outside the pre-set limits.

4.1.5 Animal accommodation

The rats were housed five of one sex per cage. Each cage consisted of a high density polypropylene body measuring 56 x 38 x 18 cm with a stainless steel mesh lid and floor (Type RC1 from North Kent Plastics Limited, Dartford, Kent, England). These were suspended above absorbent crêpe paper which was changed three times a week. Cages, cage-trays, food hoppers and water bottles were changed at appropriate intervals.

4.1.6 Diet and water supply

A commercially-available complete powdered rodent diet, ('Laboratory Animal Diet No. 2', Labsure, Manea, Cambridgeshire, England), was fed *ad libitum*. This was an expanded diet which was subsequently ground by the manufacturer. It contained no added antibiotic or other chemotherapeutic or prophylactic agent. Weighed amounts of diet were provided at intervals during each week to each cage.

Drinking water was taken from the public supply, controlled by the East Anglian Water Company, Lowestoft, Suffolk, and offered *ad libitum* to each cage in polyethylene bottles fitted with sipper tubes.

4.1.7 Contaminants control

Each batch of diet was analysed by the supplier for nutritional components and chemical and microbiological contaminants. At approximately six-month intervals the same potential contaminants were also investigated by a laboratory independent of the supplier.

The public water supply meets the European Economic Community and the World Health Organisation International Standards. At approximately six-month intervals water was analysed, by a laboratory independent of the supplier, for selected chlorinated and organophosphorus pesticides, polychlorinated biphenyl, lead and cadmium contaminants; it was also examined for coliform bacteria.

Results of these analyses did not provide evidence of contamination that might have prejudiced the study.

No contaminants of the diet or water supply, other than those covered by the analyses mentioned above, were specifically investigated. None, deemed potentially to interfere with or prejudice the outcome of the study, was considered likely to be present.

4.1.8 Allocation of treatment groups

On arrival the rats were assigned to cages according to a sequence of computer-generated random numbers determining group and cage numbers. All animals were weighed during the acclimatisation period. Four male and four female animals with bodyweights at the extremes of the weight range were discarded and replaced with spare animals from the same batch. In addition, one male was replaced because of a relatively severe ophthalmic lesion detected at the pretreatment examination (see Section 4.3.8). The assignment of cages to the batteries was based on a latin square arrangement. This resulted in a cage distribution designed to minimise the effects of any spatially variable component of the environment. The distribution is presented in Figure 1.

4.1.9 Identity of treatment groups

Group and animal identity numbers related to treatment as follows:

Group	Treatment	Dietary concentration (ppm)	Cage numbers		Animal numbers	
			Male	Female	Male	Female
1	Control	0	1-2	11-12	1-10	51-60
2	M&B 46030	1	3-4	13-14	11-20	61-70
3	M&B 46030	5	5-6	15-16	21-30	71-80
4	M&B 46030	30	7-8	17-18	31-40	81-90
5	M&B 46030	300	9-10	19-20	41-50	91-100

Each cage was provided with a label bearing the LSR Schedule number of this study, the treatment and treatment level (as appropriate), the group number, the cage number, the identity number of the animals therein and their sex.

All remaining spare animals were discarded without necropsy.

4.2 Treatment

4.2.1 Formulation

The M&B 46030 was incorporated into the ground diet at the constant concentration for each group by the preparation of a pre-mix followed by serial dilution with further quantities of untreated diet. Initially the test substance was mixed manually with a small quantity of diet and this pre-mix milled in an ultracentrifugal mill fitted with a 2 mm screen. Further diet was added and mixed for 10 minutes in a Hobart N50 mixer. The final amount of diet required was added to give a final concentration of 300 ppm and mixing was continued for 15 minutes in a Hobart A200 mixer. The diet was divided for treatment of the high treatment level group and for the preparation of diet for the remaining groups by a serial dilution process.

On each occasion of diet preparation, a 100 g aliquot of each treatment diet was taken into sealed aluminimum foil laminated sachets and stored at ambient temperature pending possible future analytical requirements. No such analyses were required and they were discarded after three months.

On those occasions where test diet samples were taken for quality control purposes (Section 4.2.3), additional 100 g aliquots of each test diet were stored in the refrigerator (approximately 4°C) pending possible future analytical requirement.

Batches of test diets were prepared freshly each week. After formulation, diets were sealed in transparent polyethylene bags and labelled to identify the appropriate treatment group.

4.2.2 Test substance balance

On each occasion that quantities of M&B 46030 were weighed out for test diet preparation, the stock container of test compound was weighed before the first and after the last removal of part of its contents. The reduction in the weight of the stock container was documented as an independent check that the correct total weight of the test compound had been used.

4.2.3 Analysis of test diets

Before commencement of treatment, an initial trial preparation was performed to determine the homogeneity of the test mix by analysis of the highest concentration samples taken from six positions in the mixer. However, following clarification, by the Sponsor, of the treatment levels to be employed and an increase in number of treatment groups, a further trial preparation was performed. Only the results from the second trial mix are reported herein.

Samples prepared for the highest and lowest dietary concentration groups were taken from six positions in the mixer and assayed for homogeneity.

Stability was determined for the highest and lowest dietary concentration groups from the trial preparation. Representative samples for stability testing were obtained by pooling the unused portions of the homogeneity samples. Assays were performed after one and two weeks storage at ambient temperature. The mean of the results for the six homogeneity samples was taken as the initial assay for the stability test.

Achieved concentration was assessed for all diet prepared for Weeks 1 and 13 of treatment.

4.2.4 Administration

The M&B 46030 was administered continuously, via the diet, throughout the treatment period. The dietary concentration was maintained at a constant level for each treated group. Control rats received untreated diet of the same batch at the same frequency as treated rats.

A record of the amount of diet required for feeding and the weight actually used was maintained for each group on each occasion of administration. These records did not indicate any significant error of administration.

4.2.5 Duration of treatment

All surviving rats were killed after completing at least 13 weeks of treatment. Necropsies took four days to complete. Treatment and observation of animals continued during this period. Data pertaining to this period were reviewed and, since they did not affect interpretation of the results, are not reported.

4.3 Serial observations

4.3.1 Signs

All rats were inspected at least twice daily throughout the treatment period for evidence of reaction to treatment, ill-health or mortality. Any deviations from normal were recorded at the time in respect of nature and severity, data and time of onset, duration and progress of the observed condition, as appropriate.

Although the various examinations were not confined to specific aspects they were aimed at the particular features listed below:

Twice daily examinations for death, morbidity or evidence of systemic toxicity or ill-health, the first in the morning and the second in the afternoon, on full work days.

A detailed weekly examination including palpation.

Any abnormality on the cage or cage-tray paper was also recorded.

During the acclimatisation period, observations of the animals were recorded at least once per day.

4.3.2 Food consumption

The quantity of food eaten by each cage of rats was calculated weekly by measurement of the amount of food given and that remaining in, or scattered from, the food hoppers.

4.3.3 Water consumption

Water consumption was assessed by visual examination. Quantitative measurements were not carried out.

4.3.4 Bodyweight

Each rat was weighed on the day that treatment commenced, at weekly intervals throughout the treatment period and before necropsy.

4.3.5 Food conversion ratio

Food conversion ratios were calculated for each group at weekly intervals as the amount of food consumed per unit of bodyweight gain.

4.3.6 Achieved dosage

Achieved dosages were calculated weekly and are expressed as mg/kg bodyweight/day.

4.3.7 Neurological examination

After 12 weeks of treatment a full neurological examination was performed on all animals from Groups 1 and 5.

Reflexes tested and observations performed included, but were not necessarily restricted to, the following:

Cranial nerve reflexes

Pupillary light and consensual light
Palpebral - blink
Startle
General examination of the head to assess other cranial nerves

Segmental reflexes

Flexor (withdrawal)

Postural reactions

Placing reactions - visual and tactile
Righting reactions
Grasping

General observations

Behavioural changes, e.g. aggression, sedation
Abnormalities of gait and stance
Presence of tremor or other dyskinesias

The results of this examination, which did not show any evidence of abnormalities, are not presented here, but are held in the archives.

4.3.8 Ophthalmoscopy

Before commencement of treatment both eyes of each rat were examined using a Fisons Binocular Indirect Ophthalmoscope after the instillation of 0.5% tropicamide. One male rat with a relatively severe ophthalmic lesion was replaced with a spare rat with no significant ocular abnormality from the same batch of animals.

The eyes of all rats from Groups 1 and 5 were re-examined after 12 weeks of treatment.

On each occasion the examination included, but was not restricted to, a detailed scrutiny of the following:

Palpebrae and adjacent structures
Conjunctivae including any discharge
Cornea and sclera
Anterior chamber and iris
Lens and vitreous
Ocular fundus.

4.3.9 Haematology

After 12 weeks of treatment blood samples were withdrawn from the retro-orbital sinus of all surviving animals. Samples were taken following overnight deprivation of food, with the rats held under light ether anaesthesia.

Using EDTA as anticoagulant the samples obtained were examined in respect of the characteristics listed below:

Packed cell volume (PCV) - Technicon H1 automated haematology analyser (Technicon Instrument Company Limited, Basingstoke, Hants.).

Haemoglobin concentration (Hb) - Technicon H1 automated haematology analyser (Technicon Instrument Company Limited, Basingstoke, Hants.).

Erythrocyte count (RBC) - Technicon H1 automated haematology analyser (Technicon Instrument Company Limited, Basingstoke, Hants.).

Reticulocyte count - by direct visual count, after suitable staining.

Blood film - Romanowsky stain, examined for abnormal morphology and unusual cell types including normoblasts.

Total leucocyte count (WBC) - Technicon H1 automated haematology analyser (Technicon Instrument Company Limited, Basingstoke, Hants.).

Differential leucocyte count (WBC) - Technicon H1 automated haematology analyser (Technicon Instrument Company Limited, Basingstoke, Hants.), differentiating among neutrophils (N), lymphocytes (L), eosinophils (E), basophils (B), monocyte (M) and large unstained cells (LU).

Platelet count - Technicon H1 automated haematology analyser (Technicon Instrument Company Limited, Basingstoke, Hants.).

Mean cell haemoglobin (MCH) - calculated as Hb multiplied by 10 divided by RBC.

Mean cell volume (MCV) - calculated as PCV multiplied by 10 divided by RBC.

Mean cell haemoglobin concentration (MCHC) - calculated as Hb multiplied by 100 divided by PCV.

Using citrate as anticoagulant, further samples were examined in respect of:

Prothrombin time (PT) - after Quick, 1966 (J. Clin. Pathol. 45, 105).

4.3.10 Blood chemistry

At the same time and for the same animals as for haematology, further blood samples were taken using lithium heparin as anticoagulant. After centrifugation the plasma was examined for the following parameters:

Alkaline phosphatase activity (AP) - after Bessey *et al.*, 1947 (J. Biol. Chem. 164, 321).

Alanine amino-transferase activity (ALT) - by the methodology recommended by the Scandinavian Committe on Enzymes, 1974 (Scand. J. Clin. Lab. Invest. 33, 291).

Aspartate amino-transferase activity (AST) - by the methodology recommended by the Scandinavian Committe on Enzymes, 1974 (Scand. J. Clin. Lab. Invest. 33, 291).

Urea concentration - after Talke and Schubert, 1965 (Klin. Wochenschr. 43, 174).

Creatinine concentration - after Henry, 1974 (in "Clin. Chem. Principles and Technics", 2nd Edition, Harper and Row, Hagerstown Md.).

Glucose concentration - after Bondor and Mead, 1974 (Clin. Chem. 20, 586).

Total bilirubin concentration - after Walters and Gerarde, 1970 (Microchem. J. 15, 231).

Total protein concentration - after Weichselbaum, 1964 (Am. J. Clin. Pathol. Tech. Sect. 10, 40).

Electrophoretic protein fractions - using cellulose acetate strips, staining with Ponceau-S, and densitometric analysis by the Sebia Cello 2 system.

Sodium (Na), Potassium (K), Chloride (Cl), Calcium (Ca) and Inorganic phosphorus (P) concentrations - using the Beckman Astra 4 electrolyte analyser.

4.3.11 Urinalysis

After 12 weeks of treatment overnight urine samples were collected from all rats.

Each animal was placed in an individual metabolism cage and urine collected under conditions of food and water deprivation. The individual samples were examined in respect of the following:

Appearance.

Volume.

pH - by pH meter.

Specific gravity (SG) - using Atago refractometer by comparison with distilled water multiplied by 1000.

Protein - by precipitation with sulphosalicylic acid and comparison with turbidimetric standards.

Total reducing substances (Total Red. Subs.) - by Clinitest*.

Glucose - by N-Multistix*.

Ketone - by N-Multistix*.

Bilirubin - by N-Multistix*.

†Urobilinogen - by N-Multistix*.

Nitrite - by N-Multistix*.

Blood - by N-Multistix*.

Microscopy - the sediment from centrifugation was examined for the epithelial cells (E), polymorphonuclear leucocytes (P), erythrocytes (R), crystals (C), spermatozoa and precursors (S) or other abnormalities (A). Grading of populations was on a four point scale ranging from 0 = none seen to 3 = many in all fields examined.

4.4 Terminal observations

4.4.1 Euthanasia

On completion of the scheduled treatment period, rats were killed by carbon dioxide inhalation.

Each rat was subjected to a detailed necropsy, as described below, with the minimum of delay.

The sequence in which the animals were killed on completion of the treatment period was selected to allow satisfactory inter-group comparison.

4.4.2 Macroscopic pathology

The necropsy procedure included a review of the history of each animal and a detailed examination of the external features and orifices, the neck and associated tissues and the cranial, thoracic, abdominal and pelvic cavities and their viscera. The external and cut surfaces of the tissues and organs were examined as appropriate. Abnormalities, interactions and changes were noted, the requisite organs weighed and the required tissue samples preserved in fixative.

* Reagents prepared by Ames Company, Slough, England. Results are reported on a four point scale ranging from 0 = no reaction to 3 = strongly positive reaction except nitrite which is reported as present (1) or absent (0).

† Urobilin changed to Urobilinogen - this was referred to incorrectly in the protocol.

Before disposal of the carcase the retained tissues were checked against the protocol and a senior prosector reviewed the necropsy report in detail.

4.4.3 Organ weight analysis

After removal of adjacent fat and other contiguous tissue, the weights of the following organs were recorded for each animal:

Adrenals*	Prostate
Brain	Salivary glands - submandibular*
Heart	Spleen
Kidneys*	Testes*
Liver	Thymus
Lungs with mainstem bronchi	Thyroids with parathyroids*
Ovaries*	Uterus with cervix.
Pituitary	

* Recorded separately for left and right organs.

The organ weight relative to bodyweight (recorded immediately before necropsy) was also calculated.

4.4.4 Tissues preserved for histopathology

Samples of the tissues listed below, together with any abnormalities, were preserved in buffered 4% formaldehyde saline, except eyes which were placed in Davidson's fluid and subsequently retained in 70% industrial methylated spirits.

Adrenals	Pancreas
Aorta	Pituitary
Brain	Prostate
Caecum	Rectum
Colon	Salivary glands - submandibular - left
Duodenum	Sciatic nerve - left
Epididymides	Seminal vesicles
Eye and optic nerve - left	Skeletal muscle - thigh
Femoral bone and articular surface	Skin
Heart	Spinal cord
Ileum	Spleen
Jejunum	Sternum with marrow
Kidneys	Stomach - keratinised and glandular
Liver	Testes
Lungs with mainstem bronchi	Thymus
Lymph nodes - mandibular and mesenteric	Thyroids with parathyroids
Mammary gland - caudal	Trachea
Oesophagus	Urinary bladder
Ovaries	Uterus with cervix
	Vagina.

4.4.5 Other tissues preserved

Samples of the following tissues, taken from all rats, were not processed histologically but were preserved as above, against possible future requirements for microscopic evaluation:

Eye and optic nerve - right*	Salivary gland - submandibular - right
Harderian glands*	Sciatic nerve - right
Mammary glands - cranial	Tongue.

* Fixed in Davidson's fluid and subsequently retained in 70% industrial methylated spirits.

In addition, femoral bone marrow smears were taken from each rat, air-dried, fixed in methanol and stained using a May-Grünwald-Giemsa procedure.

4.4.6 Histology

All tissues listed in Section 4.4.4 above were subjected to histological processing for the animals specified in Section 4.4.7. The tissues were dehydrated and embedded in paraffin wax, sectioned at approximately five micron thickness and stained with haematoxylin and eosin. Auricular and ventricular sections of the heart, thyroid, parathyroids and cervix and body of the uterus were prepared, and sections from two lobes of each of the liver and lungs were similarly processed. The brain was sectioned to include the cerebellum, cerebral cortex and medulla.

Similarly further sections of the liver from all animals of all groups were prepared and stained with Oil-Red-O.

4.4.7 Microscopic examination

Microscopic examination of the tissues specified in Section 4.4.4 was performed as follows:

(i) for all rats of Groups 1 and 5.

(ii) the thyroids, parathyroids, kidneys, livers and lungs from all rats of Groups 2, 3 and 4.

In addition, microscopic examination was performed on the Oil-Red-O stained sections of liver from all animals of all groups.

4.5 Data processing

4.5.1 Definition of study week

For the *in vivo* phase the first experimental week was defined as the time elapsing between completion of the recording of bodyweights on the day treatment commenced (Day 0) and completion of recording of bodyweight on the seventh day following. Subsequent experimental weeks were of the same duration throughout the treatment period.

4.5.2 General data treatment

Group mean values were calculated from the individual values presented in the appendices unless otherwise specified below. Standard deviation (SD) was calculated as appropriate using the sample statistic. Group means and standard deviations are presented to the same level of accuracy as the individual values.

4.5.3 Food consumption

Group mean food consumption values were calculated as the total amount of food consumed by the group divided by the number of rat-days, multiplying the result by seven to provide a weekly value. Rat-days were calculated as the total number of rats alive in the group summed for each day during the week.

Total food intake values presented in Table 1 were generated from unrounded weekly values.

4.5.4 Bodyweight

Bodyweight change was calculated from the individual bodyweight changes of rats surviving the period.

4.5.5 Food conversion ratio

Food conversion ratios were calculated for each group from unrounded mean food consumption divided by the difference in unrounded mean bodyweights.

4.5.6 Achieved dosages

The values reported for achieved dosages of the test compound were calculated from the nominal dietary concentration (ppm) multiplied by the unrounded mean daily food consumption divided by the unrounded mean mid-period bodyweight (g). The overall mean achieved dosages were calculated from the rounded weekly values presented in Table 4.

4.5.7 Ophthalmoscopy

Findings that were considered to be ontogenic in nature (i.e. hyaloid remnant and persistent hyaloid artery) and data for the rat replaced before commencement of treatment are not presented. Animals which were considered normal are omitted from the appendix.

4.5.8 Haematology

Group mean values for reticulocytes are not presented as the data are not fully quantitative.

4.5.9 Blood chemistry

Differential proteinalysis was determined by integration from an electrophoretic strip, calculation of the proportion of each protein fraction, and determination of the concentration of each fraction by reference to the total protein concentration. The albumin to globulin (A/G) ratio was calculated from the integral values before conversion to absolute concentrations.

4.5.10 Organ weights

The weights of adrenals, kidneys, gonads, salivary glands and thyroids were separately recorded for left and right sides. For presentation of group mean data in either absolute or bodyweight-relative terms these were summed.

Where the condition of an organ rendered weighing impracticable, this is recorded in the appendix as 'unsuitable'.

4.5.11 Pathology

Tissues which could not be examined are reported in the appendix. The absence from the appendix of a tissue which was scheduled for examination therefore indicates that the tissue was examined and was considered to be unremarkable.

4.5.12 Statistical analysis

The significance of inter-group differences in bodyweight gain, haematology, blood chemistry and urine data (where appropriate) were assessed by Student's t-test using a pooled within-group error variance. The results of this test are not reported for eosinophil, monocyte, basophil, reticulocyte or large unidentified cell counts for which the data are clearly not normally distributed.

For organ weights, homogeneity of variance was tested using Bartlett's test. Whenever this was found to be statistically significant a Behren's-Fisher test was used to perform pairwise comparisons, otherwise a Dunnett's test was used.

The group distribution of macroscopic and histopathological findings, expressed as incidences, were tested for statistical significance, where considered appropriate, using Fisher's exact probability test as a two-tailed test.

Unless otherwise indicated the means were not significantly different from controls, $P < 0.05$.

4.5.13 Background data

Background data for haematology used in preparation of this report were generated by computer from control data for various studies performed at these laboratories.

The normal range was calculated as the mean ± (SD x 't' value) where the 't' value was obtained using the number of values as the degree of freedom.

THe normality test performed on these data used the Chi-squared test to compare the actual and expected number of values within each of eight ranges.

The background data are constantly updated as new studies are added to the system. It is not easily possible therefore to generate an identical set of data at a later time but all source data are retained in the archives and a key identifying the source data used is also retained.

4.6 Archives

All raw data and samples pertaining to this study, except those generated in the course of any supplier's or Sponsor's analysis are stored in the archives of Life Science Research.

5. RESULTS

5.1 Signs (Appendix 3)

There were no signs which were considered to be clearly related to treatment. A greater incidence of signs was recorded for females receiving 300 ppm than for the controls, particularly in respect of tail encrustation or abrasion. However similar change was seen in two control females and therefore this observation could not be confidently attributed to treatment.

5.2 Mortality (Appendix 3)

There were no deaths during the treatment period.

5.3 Food consumption (Table 1; Appendix 4)

Food intake was markedly lower than that of the controls during the first two weeks of treatment, in males receiving 300 ppm, and during the first week of treatment, in females receiving this dosage and in males receiving 30 ppm. However, recovery was subsequently noted such that the total food consumption of males receiving 300 ppm or 30 ppm and of females receiving 300 ppm was considered similar to that of their respective controls.

The food intake of rats receiving 1 or 5 ppm was clearly unaffected by treatment.

The low food intakes noted for all groups for Week 13 of treatment were attributable to the effects of clinical pathology procedures performed during this week.

5.4 Bodyweight (Figure 2; Table 2; Appendix 5)

During the first week of treatment, the bodyweight gain of males receiving 30 ppm was slightly inferior and of males and females receiving 300 ppm was markedly and statistically significantly inferior to that of their respective control groups. During the subsequent eleven weeks the bodyweight gains of males receiving 300 ppm was significantly higher and that of the other treated groups were similar or superior to that of their respective controls.

When considered over the whole treatment period the weight gains of females receiving 300 ppm were lower than those of control females, although this difference was not statistically significant. The overall bodyweight gains of other treated females were superior to those of their controls; there was no relationship to dosage and this difference is probably fortuitous. The overall weight gains in treated males were similar to those of the controls.

The fluctuations in bodyweights recorded during Week 13 are considered to be attributable to the effects of clinical pathology investigations at this time, although it should be noted that the bodyweight of males receiving the high treatment level displayed the most marked depression.

5.5 Food conversion ratio (Table 3)

During the first week of treatment the efficiency of food utilisation, as deduced from the food conversion ratios, in animals receiving 300 ppm was lower than that of their controls. Subsequently, the efficiency of food utilisation of males receiving this treatment level was higher while that of the other treated groups were similar to that of their respective controls.

5.6 Achieved dosages (Table 4)

The overall achieved dosages for animals receiving 1, 5, 30 or 300 ppm were, for males, approximately 0.07, 0.3, 1.9 and 20 mg/kg/day and, for females, 0.07, 0.4, 2.3 and 24 mg/kg/day, respectively.

5.7 Neurological examination

Neurological examination after 12 weeks of treatment for the controls and animals receiving 300 ppm revealed no evidence of any abnormalities for any animal.

5.8 Ophthalmoscopy (Appendices 6A and 6B)

No effects of treatment were noted at the ophthalmic examination after 12 weeks of treatment.

5.9 Haematology (Table 5; Appendix 7)

Haematological investigations after 12 weeks of treatment revealed, in females receiving 300 ppm, low packed cell volume, mean cell volume, mean cell haemoglobin and prothrombin time and high platelet count, when compared with their respective control values; lower prothrombin times were also noted in females receiving 30 or 300 ppm. Lower haemoglobin concentrations than in controls were also noted in males receiving 300 ppm and in females treated at 1, 5 or 30 ppm. Inspection of background data for haemoglobin concentration in female controls aged 17 to 18 weeks indicated a mean of 15.5 g% with a normal range of 14.0 to 17.0 g%. The group mean value for control females was slightly higher and that for those of the high treatment level slightly lower than expected. Group means for other treated female groups were similar to that for background data. In males the group mean for controls was the same as that for background data (mean 15.9 g%, normal range 14.6 to 17.3 g%). In view of the above it was considered that the change in haemoglobin concentration in animals receiving 300 ppm, in conjunction with change in other erythrocytic parameters in females of this group, represented minor treatment-related effects. Other inter-group differences in treated females were not clearly attributable to treatment.

5.10 Blood chemistry (Table 6; Appendix 8)

After 12 weeks of treatment the total protein concentrations in animals receiving 300 ppm were higher than in the controls. This was associated with higher values for $\alpha 1$, $\alpha 2$ and β globulins and with lower albumin/globulin ratios than in the controls. There was evidence of similar, dosage-related variation in rats treated at 5 or 30 ppm although the albumin/globulin ratios were unaffected in these animals. Total protein concentrations and $\alpha 2$ and β globulin concentrations were also higher than in the controls in females receiving 1 ppm. However this difference from controls was not related to dosage and was not considered toxicologically significant. Males treated at 1 ppm were clearly unaffected in this respect.

Other changes noted were, in males, higher urea concentration in all treated groups and, in females, lower aspartate amino-transferase activity in all treated groups and lower alanine amino-transferase activity in those receiving 30 or 300 ppm when compared with their controls. Females receiving 5 ppm or above also had slightly higher plasma glucose concentrations than their controls.

5.11 Urinalysis (Table 7; Appendix 9)

No treatment-related changes were noted at the urinalysis investigations performed after 12 weeks of treatment.

5.12 Organ weights (Tables 8A and 8B; Appendices 10A and 10B)

Analysis of organ weights for animals killed after 13 weeks of treatment revealed, higher absolute and bodyweight-relative thyroid weights in animals which received 300 ppm, when compared with their controls. A similar tendency was noted in animals treated at 30 ppm, although statistical significance was only attained for absolute values in females.

Absolute liver weights for males which received 300 ppm and females which received 5 ppm or above, were higher than that of their controls. When bodyweight-relative values were considered higher liver weights were noted in males and females which received 30 or 300 ppm.

The absolute and bodyweight-relative salivary gland weights of treated females tended to be lower than those of their controls, although statistical significance was not consistently attained. However, as there was no evidence of dosage-relationship and no associated histopathological changes were noted, this was considered to be a chance occurence and toxicological significance was not attached.

Other inter-group differences in organ weight were noted but were considered to be fortuitous or relate to inter-group disparity in bodyweight and were not attributable to treatment.

5.13 Macroscopic pathology (Table 9; Appendix 11)

There were no macroscopic changes which were attributed to treatment.

5.14 Histopathology (Table 10; Appendix 11)

Findings considered to be related to treatment with M&B 46030 were seen in the thyroids and liver.

In the thyroid there was an increased incidence of hypertrophy of the follicular epithelium in male and female rats which had received 300 ppm ($P < 0.001$ for females). There was also a higher incidence of follicular cell hyperplasia in these animals although this was not statistically significant.

In the liver, examination of the haematoxylin and eosin stained sections revealed a low incidence of panacinar fatty vacuolation in males and females which received 300 ppm. Examination of liver sections stained with Oil-Red-O showed a high incidence of fat in the livers of all groups including control animals. However, the incidence in males which received 300 ppm was significantly greater than their controls and the distribution was more widespread (panacinar compared with centriacinar in controls). No real differences were seen with Oil-Red-O staining in the treated females when compared with their controls.

6. DISCUSSION

Evidence of effects of treatment with M&B 46030, a trifluoromethyl pyrazole insecticide, was found at dietary concentrations of 5 ppm or more.

During the first week of treatment, an impairment of growth performance and lowering of food intake and efficiency of food utilisation, was apparent for animals receiving 300 ppm. In addition low food intake was also noted at this level during the second week of treatment. Subsequently, adaptation to treatment was noted, particularly in males for which superior weight gains and utilisation efficiency were noted such that the overall values were similar to that of their controls. It should be noted that, based on bodyweight change values, males receiving 300 ppm appeared to be more affected by the stresses associated with clinical pathology sampling during the final week of treatment. Males receiving 30 ppm also displayed lower weight gain and food intake in Week 1 of treatment. However their food utilisation efficiency was not disturbed and these differences were not considered to be of toxicological importance. Females receiving 5 or 30 ppm displayed an overall higher weight gain and food intake than their controls. This may reflect a change in metabolism in these animals (see below), but in the absence of any significant change in food utilisation efficiency no toxicological significance was attached.

The dosage-related higher liver weights noted in rats receiving 5 ppm or above, together with changes in plasma amino-transferase activity and protein, urea and glucose levels in treated animals, were considered indicative of altered liver function. In animals receiving up to 30 ppm, plasma changes were generally minor and no associated histopathological change was noted and these differences were, therefore, considered to represent an adaptive metabolic response to the administration of a xenobiotic and are unlikely to be of direct toxicological importance. However, at 300 ppm there was evidence that a degree of toxicity was elicited with, in males, an increase in liver fat deposition being noted while, in females, a minor disturbance of red cell parameters was evident.

Further evidence of potentially toxicologically significant effects at 300 ppm comprised follicular epithelial hypertrophy and follicular hyperplasia noted in the thyroids of males and females. Together with the hepatic changes observed, these are indicative of a possible alteration in the hypothalamic-pituitary-thyroid-liver axis. A possible mechanism would be enhanced thyroxine clearance by the liver resulting from an increased metabolic activity, leading to increased thyroid stimulating hormone (TSH) stimulation of the thyroid gland.

Change at the dietary concentration of 1 ppm was confined to minor variation in plasma composition not present in both sexes and which was not considered to be of toxicological significance. These variations and the more marked changes seen in males and females at 5 or 30 ppm were considered to be adaptive in origin and unlikely to be of direct toxicological importance. A number of changes were observed at 300 ppm that were of potential toxicological importance. Nonetheless, this treatment level was generally tolerated by the animals over the course of the 13-week treatment period.

7. CONCLUSION

Treatment of CD rats with M&B 46030 at dietary inclusion levels of 5 or 30 ppm resulted in minor, probably adaptive, responses.

Treatment at 300 ppm was generally tolerated, although a degree of toxicity was noted involving the liver and thyroid gland.

The maximum-tolerated-level of M&B 46030 in dietary administration to CD rats was considered to be close to, but above, 300 ppm. It was considered that the dietary concentration of 1 ppm represented a no-effect-level in this study.

FIGURE 1

Group, cage and animal distribution

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Cage number
Group number
Animal number

MALES

1 1 1-5	7 4 31-35	5 3 21-25
3 2 11-15	9 5 41-45	2 1 6-10
8 4 36-40	6 3 26-30	4 2 16-20
10 5 46-50		

FEMALES

13 2 61-65	11 1 51-55	19 5 91-95
15 3 71-75	17 4 81-85	14 2 66-70
12 1 56-60	20 5 96-100	16 3 76-80
18 4 86-90		

FIGURE 2A

Group mean bodyweight versus period of treatment - males

Group	:	1	2	3	4	5
Compound	:	Control	------	M+B	46030	------
Level (ppm)	:	0	1	5	30	300

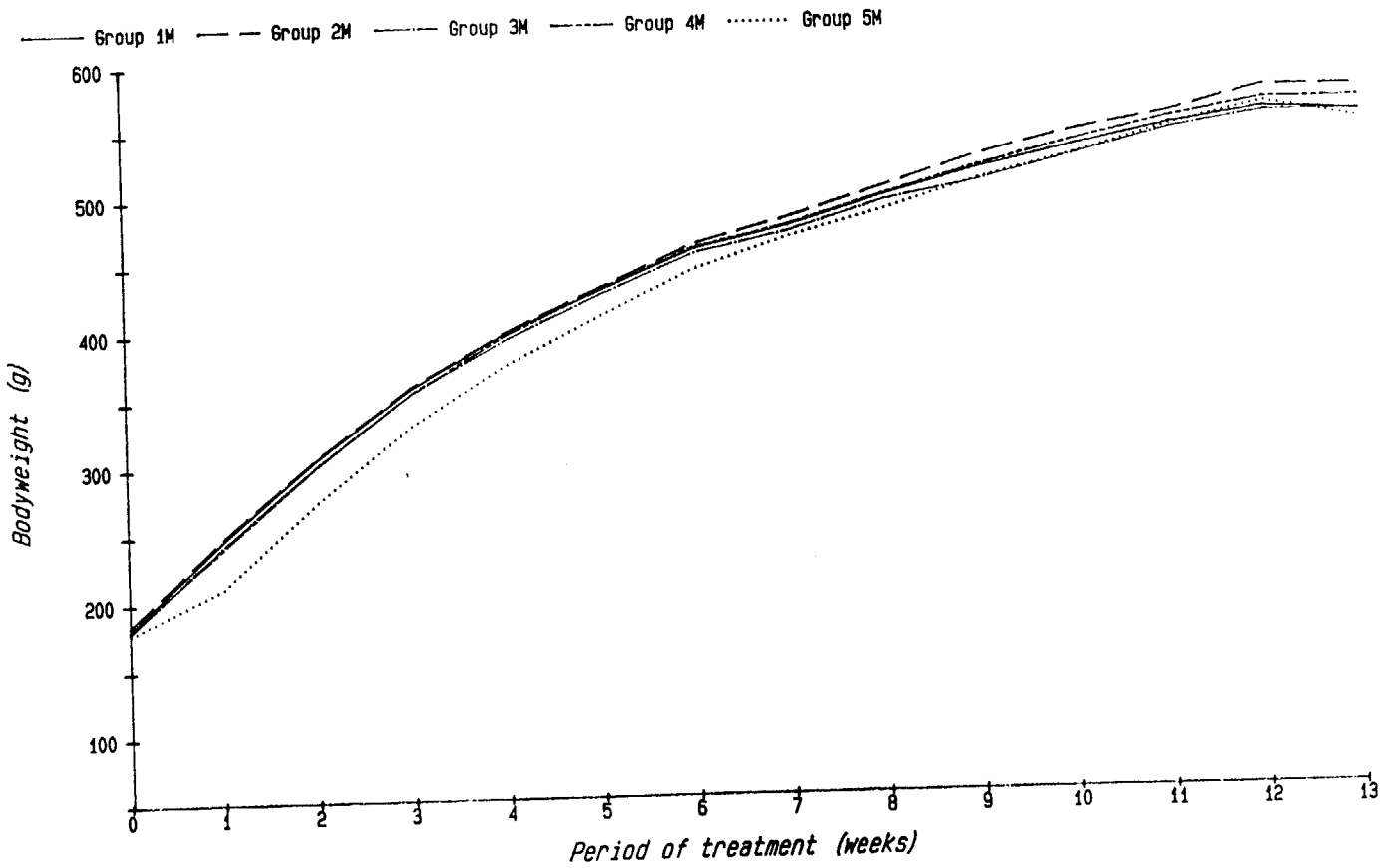

FIGURE 2B

Group mean bodyweight versus period of treatment - females

Group	:	1	2	3	4	5
Compound	:	Control	------	M+B	46030	------
Level (ppm)	:	0	1	5	30	300

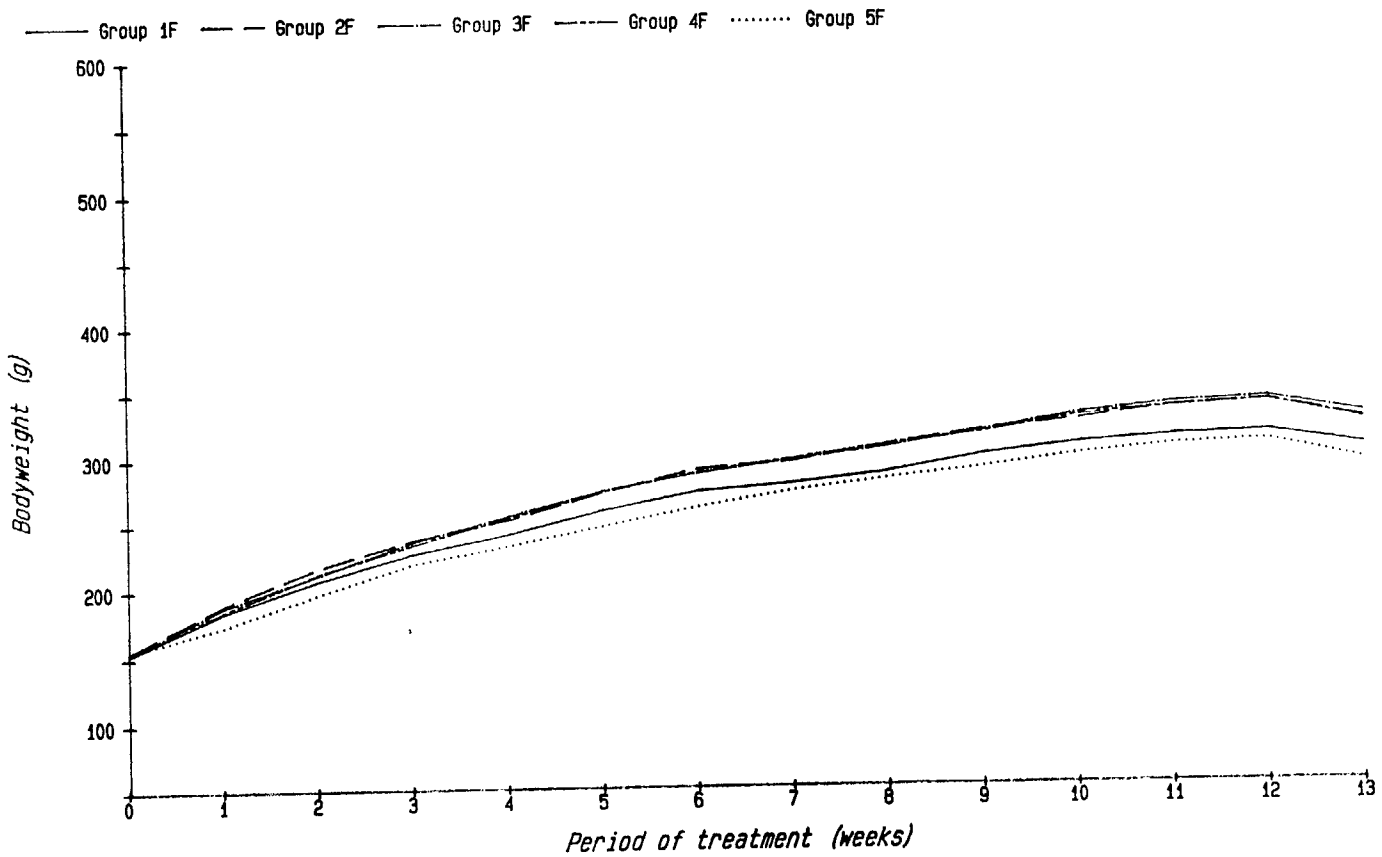

TABLE 1

Food consumption - group mean values (g/rat/week)

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Week number	Group and sex 1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
1	187	189	183	175	138	142	147	142	147	122
2	193	195	182	183	174	140	142	144	149	144
3	200	198	194	188	194	137	140	135	148	147
4	200	194	195	191	193	138	137	144	145	146
5	188	189	188	180	180	135	137	139	143	143
6	188	193	191	186	187	121	138	142	147	143
7	191	190	192	184	191	133	137	133	146	150
8	185	185	180	178	185	137	136	136	139	142
9	186	187	178	183	187	140	132	142	139	139
10	186	187	181	182	188	142	123	145	144	140
11	185	189	193	186	189	138	134	142	138	137
12	183	190	187	183	191	134	131	138	133	136
13	150	152	154	153	145	104	104	101	104	100
Total 2-12	2084	2097	2060	2023	2057	1496	1486	1539	1572	1565
1-13	2421	2438	2397	2351	2340	1742	1737	1782	1823	1787
As % of control		101	99	97	97		100	102	105	103

TABLE 2

Bodyweight - group mean values (g)

Group	:	1	2	3	4	5
Compound	:	Control	------ M&B 46030 ------			
Level (ppm)	:	0	1	5	30	300

	Group and sex									
Week	1M		2M		3M		4M		5M	
number	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	182	8	185	8	180	12	181	11	178	12
1	247	9	248	13	243	17	241	11	211	12
2	306	12	307	17	301	24	301	14	274	16
3	357	15	359	20	354	27	354	19	330	19
4	398	19	398	22	393	30	396	21	374	22
5	428	25	430	26	425	31	429	25	409	24
6	458	24	462	30	455	35	459	28	443	26
7	474	25	480	29	470	35	475	27	466	29
8	495	25	502	31	492	37	496	29	485	29
9	514	28	524	32	505	41	516	29	506	30
10	530	28	541	35	523	43	534	32	523	31
11	545	30	554	34	541	48	550	33	543	36
12	555	30	571	38	552	46	562	32	559	40
13	552	30	571	42	552	45	562	34	546	47
Change										
0-1	65	3	64	6	63	9	60[a]	5	33[c]	4
1-12	309	25	323	34	310	37	321	27	348[b]	38
12-13	-4	2	-1	5	0	5	0	4	-13	11
1-13	305	25	322	37	310	36	322	29	335	45
0-13	370	25	386	39	372	41	381	32	368	48
As % of control			104		101		103		99	

SD Standard deviation
a Significantly different from controls, $P < 0.05$
b Significantly different from controls, $P < 0.01$
c Significantly different from controls, $P < 0.001$

TABLE 2 - continued

Bodyweight - group mean values (g)

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Week number	Group and sex 1F Mean	1F SD	2F Mean	2F SD	3F Mean	3F SD	4F Mean	4F SD	5F Mean	5F SD
0	153	13	155	12	153	10	153	12	155	6
1	184	17	190	12	188	8	185	11	174	5
2	207	15	217	12	212	10	213	13	197	6
3	227	17	237	18	236	12	234	15	220	9
4	241	21	252	17	256	16	254	20	233	11
5	259	20	272	19	274	21	273	21	247	13
6	273	18	290	25	287	22	288	23	261	12
7	279	18	295	24	297	24	297	27	273	13
8	286	21	307	27	305	27	307	28	282	15
9	299	20	317	27	317	25	315	29	289	15
10	307	19	324	28	329	34	327	27	298	15
11	312	23	333	30	336	37	333	30	305	16
12	314	20	337	29	339	49	337	30	307	19
13	303	22	322	29	327	43	322	30	292	16
Change										
0-1	31	9	35	3	35	5	32	5	19[c]	4
1-12	130	17	147	23	151	47	152	25	133	18
12-13	-11	8	-15	6	-12	9	-15	6	-16	7
1-13	119	19	132	23	138	41	136	24	118	15
0-13	150	21	167	24	173	41	168	27	136	16
As % of control			111		115		112		91	

SD Standard deviation
c Significantly different from controls, $P < 0.001$

TABLE 3

Food conversion ratio - group mean values

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Week number	Group and sex 1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
1	2.9	3.0	2.9	2.9	4.2	4.6	4.2	4.0	4.6	6.5
2	3.2	3.3	3.1	3.0	2.8	6.0	5.2	6.1	5.4	6.2
3	3.9	3.8	3.7	3.5	3.5	6.9	6.8	5.5	6.9	6.6
4	4.9	4.9	5.0	4.5	4.4	9.7	9.4	7.5	7.3	11.2
5	6.2	5.9	5.9	5.5	5.1	7.5	6.7	7.5	7.4	9.8
6	6.3	6.1	6.4	6.1	5.5	8.9	7.9	11.3	10.4	10.2
7	11.8	10.2	12.6	11.6	8.3	23.8	25.8	13.6	15.4	12.8
8	8.7	8.5	8.3	8.3	9.8	17.6	11.7	15.6	13.8	16.1
9	9.8	8.5	13.2	9.2	8.6	11.3	12.7	12.4	16.8	18.7
10	12.2	11.1	10.3	10.4	11.1	18.0	17.8	12.0	12.2	15.2
11	12.3	14.8	10.7	11.5	9.4	28.2	15.0	19.4	23.4	21.4
12	17.1	10.7	16.3	14.7	11.9	63.8	36.4	47.4	36.9	54.2
13	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞
2-12	6.8	6.5	6.7	6.3	5.9	11.5	10.1	10.2	10.4	11.7
1-13	6.5	6.3	6.4	6.2	6.4	11.6	10.4	10.3	10.8	13.1

∞ Bodyweight loss or stasis, no value calculable

TABLE 4

Achieved dosages - group mean values (mg/kg/day)

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Week number	Group and sex 1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
1	-	0.12	0.62	3.56	30.25	-	0.12	0.59	3.73	31.64
2	-	0.10	0.48	2.89	30.77	-	0.10	0.51	3.21	33.33
3	-	0.08	0.42	2.46	27.59	-	0.09	0.43	2.84	30.25
4	-	0.07	0.37	2.18	23.51	-	0.08	0.42	2.55	27.64
5	-	0.07	0.33	1.88	19.66	-	0.07	0.38	2.32	25.51
6	-	0.06	0.31	1.79	18.81	-	0.07	0.36	2.25	24.09
7	-	0.06	0.30	1.69	18.04	-	0.07	0.33	2.14	24.02
8	-	0.05	0.27	1.57	16.64	-	0.06	0.32	1.98	21.96
9	-	0.05	0.26	1.55	16.14	-	0.06	0.33	1.92	20.83
10	-	0.05	0.25	1.48	15.67	-	0.05	0.32	1.91	20.36
11	-	0.05	0.26	1.47	15.15	-	0.06	0.30	1.79	19.50
12	-	0.05	0.24	1.41	14.81	-	0.06	0.29	1.70	18.99
13	-	0.04	0.20	1.17	11.24	-	0.04	0.22	1.36	14.29
Mean	-	0.07	0.33	1.93	19.87	-	0.07	0.37	2.28	24.03

TABLE 5A

Haematology - background data for CD rats between 17 and 18 weeks of age

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Parameter	Sex	N	Average age (weeks)	Mean	SD	Normal range$^{\Delta}$ Min	Max	Actual range Min	Max
Hb	M	499	17	15.9	0.7	14.6	17.3	14.0	18.3
Hb	F	500	17	15.5	0.8	14.0	17.0	11.9	17.4

SD Standard deviation
N Number of animals
Δ 95% confidence limits

TABLE 5B

Haematology - group mean values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	PCV %	Hb g%	RBC mil/cmm	MCHC %	MCV cμ	MCH pg	WBC 1000/cmm Total	N	L	E	B	M	LU	Platelets 1000/cmm	PT secs
1M	46	15.9	8.91	35	52	18	14.6	1.8	11.6	0.2	0.1	0.4	0.5	852	15.0
SD	1	0.4	0.22	1	2	1	2.8	0.7	2.0	0.1	0.0	0.2	0.2	99	0.8
2M	46	16.0	9.03	35	51	18	14.0	1.6	11.2	0.1	0.1	0.4	0.5	858	15.8[a]
SD	1	0.3	0.27	1	2	1	1.9	0.5	1.4	0.0	0.0	0.2	0.2	89	1.4
3M	46	16.2	8.80	35[b]	52	19[a]	13.3	1.8	10.5	0.1	0.1	0.3	0.4	911	14.7
SD	1	0.4	0.28	1	1	1	1.7	0.5	1.7	0.0	0.1	0.1	0.1	73	0.6
4M	45	15.9	8.77	35[a]	52	18	11.9[a]	1.5	9.5[a]	0.1	0.0	0.3	0.4	948[a]	15.2
SD	1	0.6	0.30	1	1	0	2.2	0.4	1.7	0.0	0.1	0.1	0.2	72	0.7
5M	45	15.3[b]	8.68	34	52	18	14.0	1.8	11.0	0.2	0.1	0.4	0.6	926	14.7
SD	2	0.6	0.40	1	2	1	3.7	0.7	3.0	0.1	0.1	0.2	0.2	118	0.7

SD Standard deviation
a Significantly different from controls, $P < 0.05$
b Significantly different from controls, $P < 0.01$

TABLE 5B - continued

Haematology - group mean values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	PCV %	Hb g%	RBC mil/cmm	MCHC %	MCV cμ	MCH pg	WBC 1000/cmm Total	N	L	E	B	M	LU	Platelets 1000/cmm	PT secs
1F	45	15.9	8.31	36	54	19	8.9	1.0	7.2	0.1	0.0	0.3	0.3	913	14.2
SD	1	0.5	0.18	0	1	0	2.0	0.3	1.8	0.1	0.0	0.1	0.1	102	0.4
2F	44	15.6[a]	8.22	36	53	19	10.1	1.3	8.0	0.1	0.0	0.3	0.3	937	14.4
SD	1	0.2	0.14	1	1	0	2.3	0.4	1.9	0.0	0.0	0.1	0.1	113	0.3
3F	44	15.5[a]	8.14	35	54	19	8.1	0.9	6.7	0.1	0.0	0.2	0.2	933	14.0
SD	1	0.4	0.18	1	1	0	1.4	0.4	1.4	0.1	0.0	0.1	0.1	93	0.5
4F	44[a]	15.4[b]	8.18	36	53	19	6.7[a]	0.9	5.4[a]	0.1	0.0	0.2	0.2	993	13.7[a]
SD	1	0.4	0.23	1	2	1	1.6	0.4	1.4	0.0	0.0	0.1	0.1	104	0.6
5F	43[c]	15.3[c]	8.35	36	51[c]	18[b]	9.1	1.2	7.2	0.1	0.0	0.3	0.3	1028[a]	13.5[b]
SD	1	0.3	0.29	1	2	1	1.9	0.6	1.6	0.0	0.0	0.1	0.1	68	0.2

SD Standard deviation
a Significantly different from controls, $P < 0.05$
b Significantly different from controls, $P < 0.01$
c Significantly different from controls, $P < 0.001$

TABLE 6

Blood chemistry - group mean values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	AP iu/l	ALT iu/l	AST iu/l	Urea mg%	Creat-inine mg%	Glu-cose mg%	Total Bili-rubin mg%	Plasma Proteins g% Total	Alb-umin	Globulins α1	α2	β	γ	A/G ratio -:1	Electrolytes mMol/l Na	K	Cl	Ca	P
1M	87	34	73	25	0.7	140	0.1	6.8	3.0	1.3	0.4	1.7	0.4	0.8	144	3.8	105	2.6	2.0
SD	17	13	14	4	0.1	25	0.0	0.3	0.3	0.2	0.0	0.1	0.1	0.1	1	0.3	1	0.1	0.2
2M	98	31	63	29[a]	0.7	132	0.1	6.9	3.3	1.3	0.4	1.6	0.4	0.9	144	3.7	105	2.6	2.1
SD	17	4	8	2	0.1	20	0.0	0.2	0.2	0.1	0.1	0.2	0.1	0.1	1	0.1	2	0.1	0.1
3M	84	30	63	30[b]	0.7	127	0.1	7.1[b]	3.0	1.5[a]	0.4	1.8	0.5	0.7	144	3.8	106[a]	2.6	2.0
SD	21	3	6	4	0.1	13	0.0	0.3	0.3	0.2	0.1	0.4	0.2	0.1	1	0.3	2	0.1	0.2
4M	92	28	61[a]	31[c]	0.7	135	0.1	7.1[b]	3.2	1.5[b]	0.4	1.6	0.3	0.8	144	3.7	103	2.7[b]	2.0
SD	9	5	10	3	0.0	23	0.0	0.3	0.1	0.2	0.0	0.1	0.1	0.1	1	0.1	1	0.1	0.2
5M	104	32	71	31[b]	0.7	146	0.1	7.4[c]	2.9	1.7[c]	0.5[c]	2.0[b]	0.3	0.6[b]	144	4.0	104	2.7[b]	2.0
SD	29	5	15	4	0.0	22	0.0	0.3	0.4	0.1	0.1	0.3	0.1	0.1	1	0.3	1	0.1	0.2

SD Standard deviation
a Significantly different from controls, $P < 0.05$
b Significantly different from controls, $P < 0.01$
c Significantly different from controls, $P < 0.001$

TABLE 6 - continued

Blood chemistry - group mean values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	AP iu/l	ALT iu/l	AST iu/l	Urea mg%	Creat-inine mg%	Glu-cose mg%	Total Bili-rubin mg%	Plasma Proteins g% Total	Alb-umin	Globulins α1	α2	β	γ	A/G ratio -:1	Electrolytes mMol/l Na	K	Cl	Ca	P
1F	49	30	74	34	0.7	125	0.1	7.2	3.8	1.1	0.4	1.4	0.6	1.1	143	3.4	106	2.6	1.9
SD	15	6	15	9	0.1	16	0.0	0.3	0.3	0.1	0.0	0.2	0.2	0.1	1	0.2	2	0.1	0.3
2F	51	28	59[a]	38	0.8	136	0.1	7.8[a]	4.0	1.1	0.5[b]	1.6[a]	0.6	1.0	140[c]	3.4	104[b]	2.6	1.9
SD	14	7	18	5	0.1	11	0.0	0.5	0.5	0.1	0.1	0.3	0.2	0.2	1	0.3	1	0.1	0.1
3F	63[a]	27	53[c]	33	0.7	140[a]	0.1	7.6[a]	4.0	1.2	0.4[a]	1.6	0.5	1.1	141[c]	3.3	105	2.6	1.9
SD	9	5	8	6	0.1	14	0.0	0.6	0.4	0.2	0.0	0.2	0.0	0.1	1	0.2	2	0.1	0.2
4F	53	24[a]	40[c]	37	0.8	151[c]	0.1	7.8[b]	3.9	1.3[a]	0.5[b]	1.7[b]	0.5	1.0	141[b]	3.3	104[a]	2.6	1.8
SD	14	3	7	8	0.1	14	0.0	0.5	0.3	0.2	0.1	0.2	0.1	0.1	1	0.2	1	0.1	0.1
5F	53	24[a]	48[c]	32	0.7	144[b]	0.1	7.9[b]	3.7	1.4[c]	0.6[c]	1.8[c]	0.5	0.9[c]	143	3.4	105	2.7	1.9
SD	18	4	15	5	0.1	10	0.0	0.5	0.3	0.2	0.0	0.1	0.1	0.1	1	0.3	2	0.1	0.2

SD Standard deviation
a Significantly different from controls, $P < 0.05$
b Significantly different from controls, $P < 0.01$
c Significantly different from controls, $P < 0.001$

TABLE 7

Urinalysis - group mean values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Volume ml	pH	SG	Group / sex	Volume ml	pH	SG
1M	4.0	6.7	1070	1F	6.5	7.1	1046
SD	1.0	0.2	6	SD	2.5	0.9	8
2M	4.5	6.6	1071	2F	5.0[a]	6.7	1056[a]
SD	1.0	0.1	7	SD	2.0	0.6	10
3M	4.5	6.7	1062[a]	3F	6.5	7.0	1041
SD	1.5	0.3	9	SD	1.5	0.9	8
4M	4.5	6.7	1064	4F	5.0	6.8	1054
SD	1.5	0.3	8	SD	1.5	0.7	13
5M	4.5	6.6	1067	5F	6.0	6.7	1046
SD	1.0	0.2	7	SD	1.0	0.7	4

SD Standard deviation
a Significantly different from controls, $P < 0.05$

TABLE 8A

Absolute organ weights - group mean values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030	------	
Level (ppm)	0	1	5	30	300

SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER:	10	10	10	10	10	10	10	10	10	10
TERMINAL BODY WEIGHT (g)										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	10	10	10	10	10
MEAN	540.5	563.9	540.3	546.8	539.1	304.9	324.6	330.6	325.8	298.0
sd	28.5	42.3	44.9	34.9	46.8	26.8	29.2	42.9	27.7	17.5
BRAIN										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	10	10	10	10	10
MEAN	2.12	2.20	2.19	2.15	2.15	2.07	2.01	2.04	2.08	2.07
sd	0.15	0.10	0.12	0.07	0.10	0.10	0.09	0.09	0.10	0.11
PITUITARY										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	9	10	10	10	10	10	10
MEAN	0.010	0.011	0.010	0.011	0.010	0.012	0.011	0.015	0.012	0.011
sd	0.002	0.003	0.003	0.003	0.002	0.004	0.002	0.002	0.002	0.003
ADRENALS (L&R)										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	10	10	10	10	10
MEAN	0.051	0.053	0.052	0.052	0.056	0.067	0.065	0.074	0.073	0.076
sd	0.010	0.006	0.012	0.009	0.006	0.011	0.011	0.010	0.015	0.015
HEART										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	10	10	10	10	10
MEAN	1.61	1.66	1.62	1.62	1.58	1.09	1.07	1.10	1.18	1.04
sd	0.16	0.18	0.13	0.09	0.17	0.11	0.15	0.11	0.08	0.08

Significant when compared with Group 1: a - $p<0.05$; b - $p<0.01$

TABLE 8A - continued.

Absolute organ weights - group mean values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030	------	
Level (ppm)	0	1	5	30	300

SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER:	10	10	10	10	10	10	10	10	10	10
KIDNEYS (L&R)										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	10	10	10	10	10
MEAN	3.91	4.02	4.09	3.90	4.04	2.43	2.39	2.59	2.55	2.35
sd	0.24	0.35	0.36	0.23	0.34	0.25	0.18	0.24	0.24	0.17
LIVER										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	10	10	10	10	10
MEAN	19.1	21.0	19.4	21.8	27.2 b	10.8	11.3	12.7 a	13.4 b	16.6 b
sd	2.5	2.1	2.4	2.6	3.3	1.5	1.1	1.8	0.9	1.9
LUNGS										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	10	10	10	10	10
MEAN	2.02	2.04	2.05	2.05	1.98	1.62	1.57	1.66	1.68	1.43
sd	0.24	0.28	0.29	0.21	0.18	0.29	0.12	0.26	0.23	0.16
OVARIES (L&R)										
						DUNNETT'S TEST				
N	0	0	0	0	0	10	10	10	10	10
MEAN						0.099	0.090	0.104	0.100	0.095
sd						0.024	0.018	0.024	0.019	0.026
PROSTATE										
	DUNNETT'S TEST									
N	10	10	10	10	10	0	0	0	0	0
MEAN	0.685	0.691	0.675	0.658	0.628					
sd	0.120	0.102	0.226	0.147	0.215					

Significant when compared with Group 1: a - $p<0.05$; b - $p<0.01$

TABLE 8A - continued.

Absolute organ weights - group mean values (g) for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER:	10	10	10	10	10	10	10	10	10	10
SALIVARY G. L&R										
	DUNNETT'S TEST					DUNNETT'S TEST				
N :	10	10	10	10	10	10	10	10	10	10
MEAN :	0.637	0.654	0.660	0.684	0.624	0.427	0.384	0.397	0.423	0.365 a
sd :	0.082	0.090	0.107	0.090	0.043	0.055	0.043	0.036	0.066	0.028
SPLEEN										
	DUNNETT'S TEST					DUNNETT'S TEST				
N :	10	10	10	10	10	10	10	10	10	10
MEAN :	0.786	0.855	0.853	0.850	0.872	0.595	0.534	0.562	0.566	0.538
sd :	0.099	0.139	0.119	0.133	0.141	0.100	0.083	0.059	0.099	0.082
TESTES (L&R)										
	DUNNETT'S TEST									
N :	10	10	10	10	10	0	0	0	0	0
MEAN :	3.54	3.56	3.68	3.68	3.63					
sd :	0.31	0.29	0.20	0.34	0.35					
THYMUS										
	DUNNETT'S TEST					DUNNETT'S TEST				
N :	10	10	10	10	10	10	10	10	10	10
MEAN :	0.504	0.512	0.476	0.562	0.529	0.389	0.374	0.449	0.381	0.364
sd :	0.104	0.106	0.050	0.096	0.120	0.061	0.091	0.095	0.078	0.073
UTERUS+CERVIX										
						BEHREN'S - FISHER'S TEST				
N :	0	0	0	0	0	10	10	10	10	10
MEAN :						0.71	0.65	0.54	0.60	0.54
sd :						0.29	0.22	0.14	0.19	0.11

Significant when compared with Group 1: a $p<0.05$; b - $p<0.01$

TABLE 8A - continued.

Absolute organ weights - group mean values (g) for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER:	10	10	10	10	10	10	10	10	10	10
THYROIDS (L&R)										
	DUNNETT'S TEST					BEHREN'S - FISHER'S TEST				
N :	10	9	10	10	10	10	10	10	10	10
MEAN :	0.024	0.024	0.025	0.030	0.048 b	0.019	0.019	0.021	0.023 a	0.032 b
sd :	0.005	0.007	0.007	0.007	0.009	0.004	0.003	0.003	0.005	0.007

Significant when compared with Group 1: a - $p<0.05$; b - $p<0.01$

TABLE 8B

Organ weights relative to bodyweight - group mean values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	M&B 46030			
Level (ppm)	0	1	5	30	300

SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER:	10	10	10	10	10	10	10	10	10	10
TERMINAL BODY WEIGHT (g)										
		DUNNETT'S TEST					DUNNETT'S TEST			
N	10	10	10	10	10	10	10	10	10	10
MEAN	540.5	563.9	540.3	546.8	539.1	**304.9**	324.6	330.6	325.8	298.0
sd	28.5	42.3	44.9	34.9	46.8	**26.8**	29.2	42.9	27.7	17.5
BRAIN										
		DUNNETT'S TEST					DUNNETT'S TEST			
N	10	10	10	10	10	10	10	10	10	10
MEAN	0.394	0.391	0.406	0.395	0.401	**0.682**	0.624	0.626	0.641	0.696
sd	0.039	0.032	0.026	0.034	0.038	**0.056**	0.058	0.067	0.041	0.044
PITUITARY										
		DUNNETT'S TEST					DUNNETT'S TEST			
N	10	10	10	9	10	10	10	10	10	10
MEAN	0.0018	0.0019	0.0018	0.0020	0.0018	**0.0041**	0.0035	0.0046	0.0038	0.0036
sd	0.0004	0.0005	0.0006	0.0006	0.0003	**0.0012**	0.0006	0.0010	0.0006	0.0009
ADRENALS (L&R)										
		BEHREN'S - FISHER'S TEST					DUNNETT'S TEST			
N	10	10	10	10	10	10	10	10	10	10
MEAN	0.0093	0.0094	0.0098	0.0096	0.0105	**0.0218**	0.0202	0.0225	0.0224	0.0253
sd	0.0016	0.0006	0.0024	0.0019	0.0017	**0.0026**	0.0037	0.0033	0.0034	0.0048
HEART										
		DUNNETT'S TEST					DUNNETT'S TEST			
N	10	10	10	10	10	10	10	10	10	10
MEAN	0.298	0.294	0.301	0.298	0.293	**0.359**	0.330	0.336	0.364	0.350
sd	0.035	0.017	0.020	0.021	0.026	**0.034**	0.033	0.030	0.023	0.025

Significant when compared with Group 1: a - $p<0.05$; b - $p<0.01$

TABLE 8B - continued.

Organ weights relative to bodyweight - group mean values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER:	10	10	10	10	10	10	10	10	10	10
KIDNEYS (L&R)										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	10	10	10	10	10
MEAN	0.726	0.714	0.760	0.715	0.750	0.798	0.740	0.786	0.783	0.790
sd	0.055	0.059	0.059	0.046	0.039	0.055	0.054	0.042	0.052	0.059
LIVER										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	10	10	10	10	10
MEAN	3.54	3.72	3.59	3.99 a	5.05 b	3.52	3.48	3.86	4.13 b	5.57 b
sd	0.39	0.26	0.32	0.46	0.35	0.22	0.27	0.25	0.26	0.50
LUNGS										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	10	10	10	10	10
MEAN	0.375	0.361	0.379	0.375	0.369	0.532	0.488	0.509	0.519	0.479
sd	0.055	0.038	0.041	0.035	0.033	0.094	0.065	0.098	0.091	0.043
OVARIES (L&R)										
						DUNNETT'S TEST				
N	0	0	0	0	0	10	10	10	10	10
MEAN						0.0325	0.0278	0.0321	0.0307	0.0317
sd						0.0073	0.0050	0.0094	0.0055	0.0081
PROSTATE										
	DUNNETT'S TEST									
N	10	10	10	10	10	0	0	0	0	0
MEAN	0.1270	0.1227	0.1241	0.1214	0.1161					
sd	0.0223	0.0180	0.0357	0.0314	0.0354					

Significant when compared with Group 1: a - $p<0.05$; b - $p<0.01$

TABLE 8B - continued.

Organ weights relative to bodyweight - group mean values (%) for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030	------	
Level (ppm)	0	1	5	30	300

SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER:	10	10	10	10	10	10	10	10	10	10
SALIVARY G. L&R										
	DUNNETT'S TEST					BEHREN'S - FISHER'S TEST				
N	10	10	10	10	10	10	10	10	10	10
MEAN	0.1179	0.1157	0.1225	0.1256	0.1167	**0.1409**	0.1184b	0.1214a	0.1298	0.1227a
sd	0.0144	0.0102	0.0189	0.0205	0.0141	**0.0198**	0.0068	0.0148	0.0184	0.0106
SPLEEN										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	**10**	10	10	10	10
MEAN	0.1455	0.1512	0.1585	0.1550	0.1623	**0.1952**	0.1639a	0.1723	0.1732	0.1804
sd	0.0177	0.0171	0.0228	0.0199	0.0281	**0.0305**	0.0158	0.0282	0.0193	0.0230
TESTES (L&R)										
	DUNNETT'S TEST									
N	10	10	10	10	10	**0**	0	0	0	0
MEAN	0.656	0.632	0.684	0.674	0.679					
sd	0.065	0.042	0.047	0.061	0.091					
THYMUS										
	DUNNETT'S TEST					DUNNETT'S TEST				
N	10	10	10	10	10	**10**	10	10	10	10
MEAN	0.0935	0.0906	0.0885	0.1025	0.0977	**0.1275**	0.1152	0.1363	0.1167	0.1223
sd	0.0200	0.0152	0.0113	0.0148	0.0180	**0.0163**	0.0248	0.0266	0.0211	0.0252
UTERUS+CERVIX										
						BEHREN'S - FISHER'S TEST				
N	0	0	0	0	0	10	10	10	10	10
MEAN						**0.236**	0.206	0.168	0.184	0.180
sd						**0.098**	0.078	0.055	0.066	0.034

Significant when compared with Group 1: a - $p<0.05$; b - $p<0.01$

TABLE 8B - continued.

Organ weights relative to bodyweight - group mean values (%) for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER:	10	10	10	10	10	10	10	10	10	10
THYROIDS (L&R)										
	BEHREN'S - FISHER'S TEST					BEHREN'S - FISHER'S TEST				
N :	10	9	10	10	10	10	10	10	10	10
MEAN :	0.0044	0.0042	0.0046	0.0054	0.0091b	0.0061	0.0059	0.0063	0.0071	0.0107b
sd :	0.0009	0.0012	0.0012	0.0013	0.0023	0.0013	0.0009	0.0011	0.0013	0.0024

Significant when compared with Group 1: a - $p<0.05$; b - $p<0.01$

TABLE 9

Macropathology - group distribution of findings for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

--- NUMBER OF ANIMALS AFFECTED ---

ORGAN AND KEYWORD(S) OR PHRASE	SEX:	MALE					FEMALE				
	GROUP:	1	2	3	4	5	1	2	3	4	5
	NUMBER:	10	10	10	10	10	10	10	10	10	10
** TOP OF LIST **											
ADRENALS (L&R)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
APPEARS LARGE		0	0	0	0	0	0	0	0	0	1
AREA(S) OF CHANGE		0	0	0	0	0	0	0	0	0	1
AORTA	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
BRAIN X 3	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
BRONCHI	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
CAECUM	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
COLON	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
DUODENUM	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
EPIDIDYMIDES L&R	NUMBER EXAMINED:	10	10	10	10	10	0	0	0	0	0
EYES (L&R)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
ABNORMAL SHAPE		1	0	0	0	1	0	0	0	0	0
DARK		1	0	0	0	0	0	0	0	0	1
OPAQUE		0	0	0	0	1	0	0	0	0	1
EXOPHTHALMIC		0	0	0	0	1	0	0	0	0	0
FEMUR INC. JTX2	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
HEART, AURICLE	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
HEART, VENTRICLE	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
ILEUM	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10

TABLE 9 - continued.

Macropathology - group distribution of findings for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

ORGAN AND KEYWORD(S) OR PHRASE		--- NUMBER OF ANIMALS AFFECTED ---									
	SEX:	MALE					FEMALE				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	10	10	10	10	10	10	10	10	10	10
JEJUNUM	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
ABNORMAL CONTENTS		0	0	0	0	0	1	0	1	0	0
DISTENDED		0	0	0	0	0	0	0	1	0	0
KIDNEYS (L&R)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
HYDRONEPHROSIS		0	0	0	1	0	0	0	0	0	0
CYSTIC		0	0	0	1	0	0	0	0	0	0
L N MANDIBULAR	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
APPEAR LARGE		1	0	0	0	1	0	0	0	0	0
DARK		2	1	1	1	1	0	1	0	0	1
L N MESENTERIC	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
LIVER X 2	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
LUNGS X 2	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
DARK		0	0	0	0	0	0	0	0	2	0
MAMMARY A. CAUD	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
OESOPHAGUS	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
LEFT OPTIC NERVE	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
OVARIES (L&R)	NUMBER EXAMINED:	0	0	0	0	0	10	10	10	10	10
PANCREAS	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
PARATHYROIDS L&R	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10

TABLE 9 - continued.

Macropathology - group distribution of findings for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

--- NUMBER OF ANIMALS AFFECTED ---

ORGAN AND KEYWORD(S) OR PHRASE		MALE 1	MALE 2	MALE 3	MALE 4	MALE 5	FEMALE 1	FEMALE 2	FEMALE 3	FEMALE 4	FEMALE 5
	NUMBER:	10	10	10	10	10	10	10	10	10	10
PITUITARY	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
MASS(ES)		0	0	0	1	0	0	0	0	0	0
PROSTATE	NUMBER EXAMINED:	10	10	10	10	10	0	0	0	0	0
RECTUM	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
SCIATIC N. LT	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
SEMINAL VESICLES	NUMBER EXAMINED:	10	10	10	10	10	0	0	0	0	0
SK. MUSCLE THIGH	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
SKIN	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
HAIRLOSS MODERATE		2	2	2	1	2	0	2	0	1	1
FACIAL STAINING		1	0	1	0	3	0	1	0	4	0
NON-SPECIFIC STAINING		4	0	1	0	0	0	1	2	0	0
TRAUMA		0	0	1	0	0	0	0	0	0	0
ENCRUSTATION(S)		1	0	0	0	0	0	0	0	0	0
SPINAL C. CERV	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
SPINAL C. LUMB	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
SPINAL C. THOR	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
SPLEEN	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
STERNUM/MAR X 2	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10

TABLE 9 - continued.

Macropathology - group distribution of findings for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	.....	M&B 46030		.....
Level (ppm)	0	1	5	30	300

--- NUMBER OF ANIMALS AFFECTED ---

ORGAN AND KEYWORD(S) OR PHRASE	SEX:	MALE					FEMALE				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	10	10	10	10	10	10	10	10	10	10
STOMACH X 2	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
THICKENED WALL		0	1	0	0	0	0	0	0	0	0
LEFT SUBMANDIB SL.GL.	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
TESTES (L&R)	NUMBER EXAMINED:	10	10	10	10	10	0	0	0	0	0
THYMUS	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
AREA(S) OF CHANGE		0	0	1	0	0	0	0	0	2	0
THYROIDS (L&R)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
TRACHEA	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
URINARY BLADDER	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
UTERINE CERVIX	NUMBER EXAMINED:	0	0	0	0	0	10	10	10	10	10
UTERUS	NUMBER EXAMINED:	0	0	0	0	0	10	10	10	10	10
FLUID DISTENSION		0	0	0	0	0	3	1	1	0	0
VAGINA	NUMBER EXAMINED:	0	0	0	0	0	10	10	10	10	10
FOOT/FEET	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
ABNORMAL SHAPE		0	0	0	0	0	0	0	1	0	0
RIGHT HARDERIAN GLAND	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
EXCESS FLUID		0	0	0	0	1	0	0	0	0	0
L N POPLITEAL	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
DARK		0	0	0	0	0	1	0	0	0	0

TABLE 9 - continued.

Macropathology - group distribution of findings for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

		NUMBER OF ANIMALS AFFECTED									
	SEX:	MALE					FEMALE				
	GROUP:	1	2	3	4	5	1	2	3	4	5
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	10	10	10	10	10	10	10	10	10	10
LIVER OIL RED O	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
TAIL	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
AREA(S) OF CHANGE		0	0	0	4	0	0	0	0	0	3
ENCRUSTATION(S)		0	0	0	1	0	0	0	0	0	5a
TRAUMA		0	0	0	0	0	1	0	0	0	0

** END OF LIST **

a Significantly different from controls, P < 0.05

TABLE 10

Histopathology - group distribution of findings for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-91
Page: 1

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

ORGAN AND FINDING DESCRIPTION		NUMBER OF ANIMALS AFFECTED									
	SEX:	MALE					FEMALE				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	10	10	10	10	10	10	10	10	10	10
** TOP OF LIST **											
BRAIN X 3	NUMBER EXAMINED:	10	0	0	0	10	10	0	0	0	10
..MICROCAVITATION OF WHITE MATTER		0	0	0	0	0	1	0	0	0	3
CAECUM	NUMBER EXAMINED:	10	0	0	0	10	10	0	0	0	10
..LYMPHOID HYPERPLASIA		0	0	0	0	0	1	0	0	0	0
HEART, VENTRICLE	NUMBER EXAMINED:	10	0	0	0	10	10	0	0	0	10
..CHRONIC MYOCARDITIS		0	0	0	0	1	0	0	0	0	0
KIDNEYS (L&R)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
..CORTICAL MINERALISATION		0	0	0	0	0	1	3	2	0	0
..PAPILLARY CYST(S)		0	0	0	1	0	0	0	0	1	0
..MEDULLARY CYST(S)		0	0	0	1	1	0	0	0	0	0
..CORTICO-MEDULLARY MINERALISATION		0	0	0	0	0	0	0	1	0	0
..CORTICAL CYST(S)		0	0	0	1	0	0	0	0	0	0
..HYDRONEPHROSIS		0	0	0	1	0	0	0	0	0	0
..DILATED CORTICAL TUBULES		1	0	0	0	0	0	0	0	0	0
L N MANDIBULAR	NUMBER EXAMINED:	10	1	1	1	10	10	1	0	0	9
..FOLLICULAR HYPERPLASIA		0	1	1	0	0	0	1	0	0	0
..HAEMORRHAGE		1	0	0	0	1	0	0	0	0	0
..PARAFOLLICULAR HYPERPLASIA		1	0	0	0	2	0	0	0	0	0
L N MESENTERIC	NUMBER EXAMINED:	10	0	0	0	10	10	0	0	0	10
..FOLLICULAR HYPERPLASIA		1	0	0	0	0	0	0	0	0	0
LIVER X 2	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
..PANACINAR HEPATOCYTIC FATTY VACUOLATION		0	0	0	0	2	0	0	0	0	2
..CONGESTION		4	2	3	3	6	2	0	1	0	5
..FOCI OF LEUCOCYTES WITHIN SINUSOIDS		1	0	0	1	2	0	0	1	0	0
..ARTERITIS		2	0	3	0	1	0	0	0	0	0

TABLE 10 - continued.

Histopathology - group distribution of findings for animals killed after 13 weeks of the treatment period.

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030	------	
Level (ppm)	0	1	5	30	300

Printed: 21-MAR-91
Page: 2

Schedule number: RHA 298

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
	SEX:	MALE					FEMALE				
	GROUP:	1	2	3	4	5	1	2	3	4	5
	NUMBER:	10	10	10	10	10	10	10	10	10	10
LUNGS X 2	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
--INTERSTITIAL PNEUMONITIS		1	3	2	2	2	2	3	2	3	0
--FOCAL ALVEOLAR WALL EPITHELIALISATION		0	1	0	0	0	0	0	1	0	0
PANCREAS	NUMBER EXAMINED:	10	0	0	0	10	10	0	0	0	10
--ACINAR ATROPHY WITH CHRONIC INFLAMMATION		0	0	0	0	1	0	0	0	0	0
PROSTATE	NUMBER EXAMINED:	10	0	0	0	10	0	0	0	0	0
--CHRONIC INFLAMMATION		2	0	0	0	0	0	0	0	0	0
RECTUM	NUMBER EXAMINED:	10	0	0	0	10	10	0	0	0	10
--LYMPHOID HYPERPLASIA		0	0	0	0	2	0	0	0	0	0
STOMACH X 2	NUMBER EXAMINED:	10	1	0	0	10	10	0	0	0	10
--GLANDULAR REGION: CHRONIC INFLAMMATION		0	0	0	0	1	0	0	0	0	0
THYROIDS (L&R)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
--LYMPHOCYTIC INFILTRATION		1	0	0	0	0	0	0	0	0	0
--HYPERTROPHY OF FOLLICULAR EPITHELIUM		3	1	0	5	8	1	0	0	0	10 c
--FOLLICULAR CELL HYPERPLASIA		2	0	0	1	6	0	0	1	1	2
UTERUS	NUMBER EXAMINED:	0	0	0	0	0	10	1	1	1	10
--POLYLUMINAL DILATATION		0	0	0	0	0	1	1	1	0	0
EYE RT	NUMBER EXAMINED:	1	0	0	0	1	0	0	0	0	1
--DISRUPTION/FIBROSIS		1	0	0	0	1	0	0	0	0	1
LIVER OIL RED O	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
--PANACINAR HEPATOCYTIC FATTY VACUOLATION		0	2	0	1	7 b	0	0	0	0	1
--CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION		4	3	2	6	3	7	9	6	10	7

** END OF LIST **

b Significantly different from controls, P < 0.01
c Significantly different from controls, P < 0.001

APPENDIX 1

Analysis of M&B 46030 - certificate from the Sponsor

The certificate of analysis for the batch of test compound used on this study is presented on the following pages.

CONFIDENTIAL

Copy No. 1527

D.Ag. No 5.

PHENYLPYRAZOLES: M&B 46,030:

Analysis of batch PGS 963 ex St. Fons, Lyon, France.

A Scientific Report from the Analytical Chemistry Laboratories

of

Rhône-Poulenc Agriculture Limited

by

G.C. Buddle, M.Sc., C.Chem., F.R.S.C.

and

W.Z. Jablonski

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October, 1990

Rhône-Poulenc Agriculture Limited,
Fyfield Road,
Ongar,
Essex,
CM5 OHW,
England.

SUMMARY

1. A pilot scale batch of M&B 46,030, batch no. PGS 963 (ex St. Fons, France) has been examined by hplc, capillary g.c. and loss on drying.

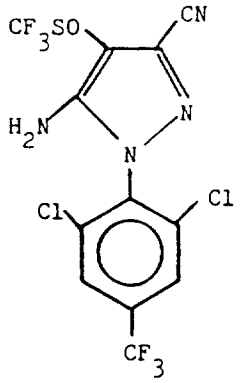
2. The assay of the material is 95.4% w/w. Impurities detected included:

M&B 45,950	=	0.23% w/w
M&B 46,136	=	3.03% w/w
3 unidentifieds	=	0.4% by peak area (total).

On the basis of present knowledge, the expiry date for this batch is set as November, 1992. However, this may be updated as the results of future retests become available.

1. INTRODUCTION

A pilot scale batch of M&B 46,030 has been prepared at St. Fons. An analysis of this was required to allow its use in Toxicology studies.



M&B 46,030

2. METHODS OF ANALYSIS

An hplc procedure has been developed for the assay of M&B 46,030[1]. This also allows the determination of 3 possible manufacturing impurities M&B 45,897, M&B 45,950 and M&B 46,136 (see Appendix I).

Additionally, this batch has been examined using a capillary g.c. procedure (see Appendix II) and for its loss on drying at 105°C.

3. RESULTS

3.1. Appearance — Creamy-yellow crystalline powder.

3.2. Assay — M&B 46,030, % w/w = 95.4.

3.3. Impurities

M&B 45,950, % w/w = 0.23.
M&B 46,136, % w/w = 3.03.
M&B 45,897, % w/w = none detected.

Other impurities, % peak area

RT	=	3.2	=	0.23
RT	=	4.08	=	0.16
RT	=	4.75	=	0.03

Chromatogram of sample and standard solutions are shown in Figure 1.

3.4. Loss on Drying — % w/w = 0.02

3.5. Capillary g.c.

A capillary g.c. trace is shown in Figure 2. Area percentages are generally similar to figures calculated for % w/w for known impurities by hplc.

M&B 46,030	=	96.1%	peak area
M&B 45,950	=	0.35%	peak area
M&B 46,136	=	2.77%	peak area.

Two unidentifieds are also observed.

4. **CONCLUSION**

This batch of M&B 46,030, batch PGS 963, has been characterised for toxicology studies. A mass balance of ~99.2% has been achieved, which is considered acceptable.

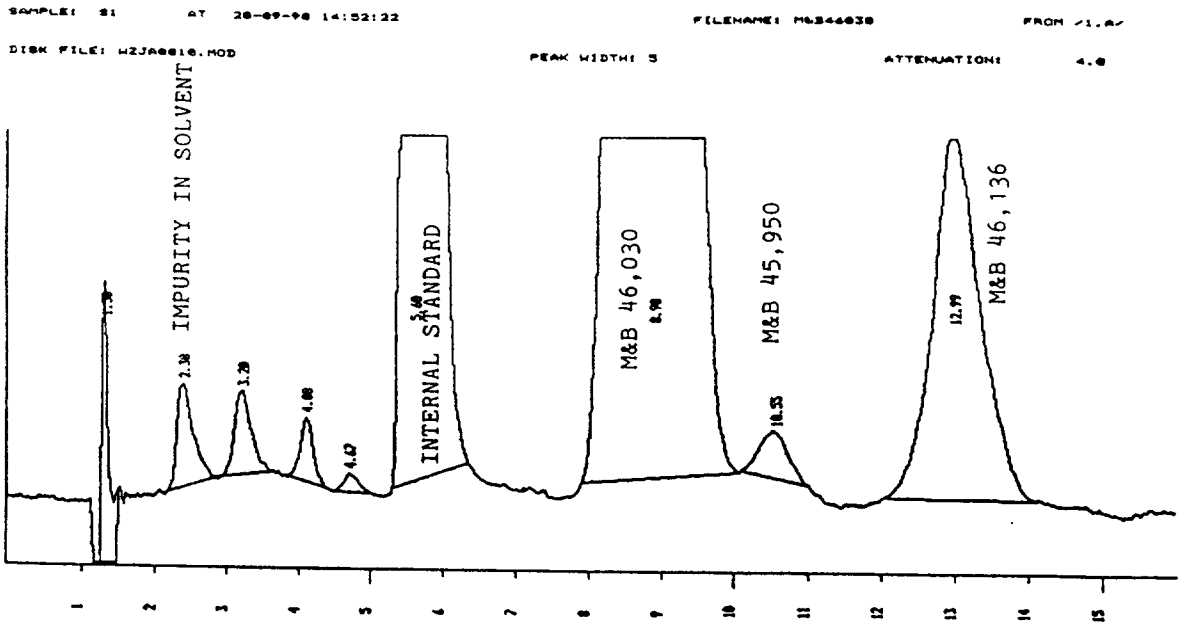
On the basis of current knowledge on this compound, an expiry date of November, 1992 is recommended for this batch stored at 20°C in the dark. This may be revised on the results of future retests of material.

5. **REFERENCE**

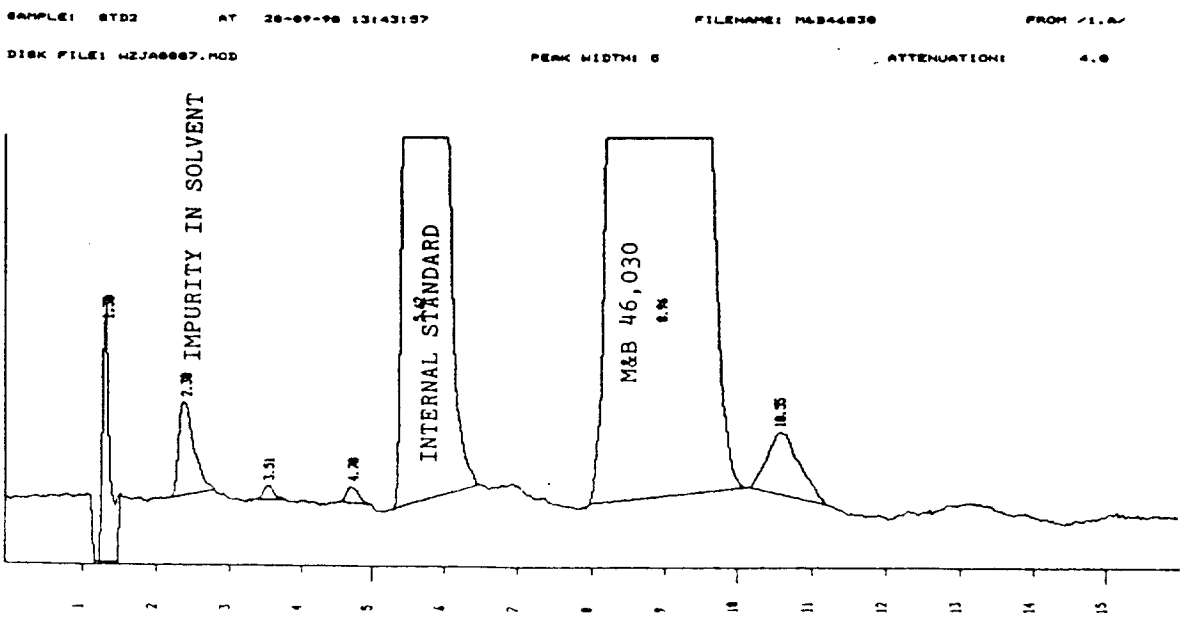
1. PHENYLPYRAZOLES: M&B 46,030: Hplc procedure for assay and impurities in the technical material. D.Ag. 1495, E.A.M. Mills, and G.C. Buddle, issued 16/8/90.

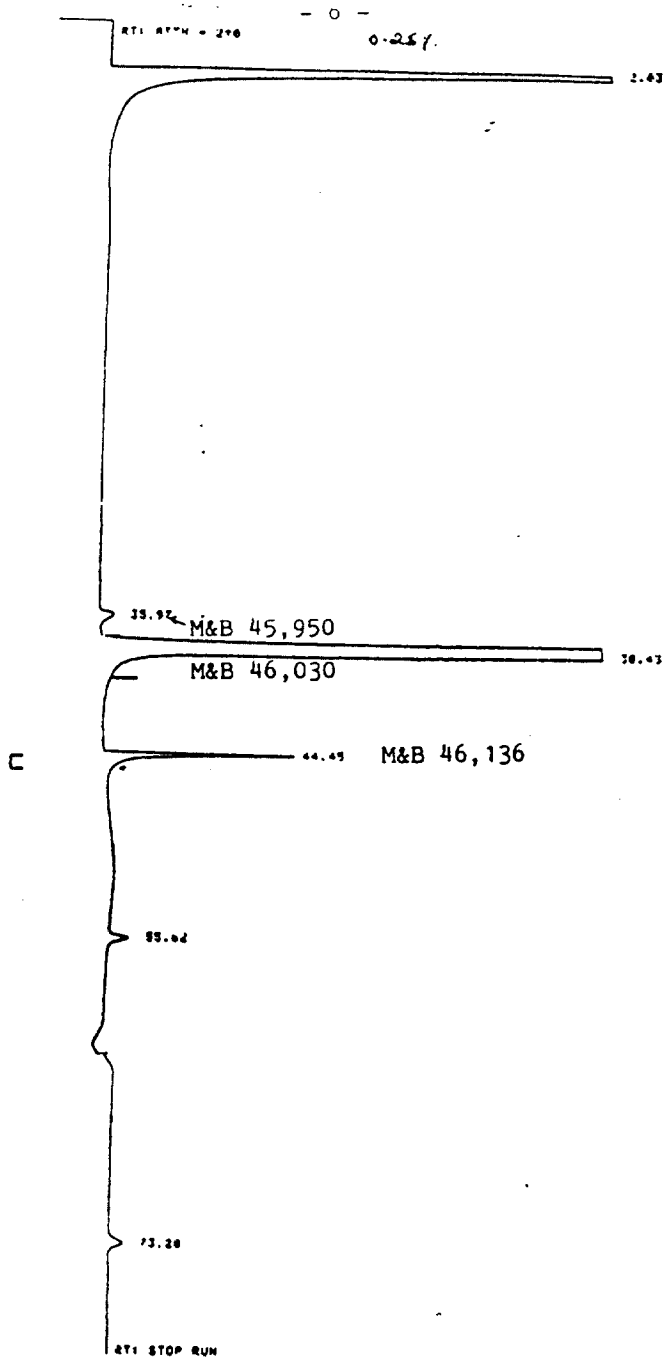
FIGURE 1 - Hplc Chromatograms of M&B 46,030

a) Batch PGS 963 (+ internal standard)



b) Reference sample (AJK 232) + internal standard





EMD 3688A SAMPLER INJECTION @ 08:24 OCT 3, 1990
SAMPLE # : ID CODE :
: PCS 963
AREA % COMPENSATED ANALYSIS

RT	AREA	TYPE	WIDTH	HEIGHT	BASELINE	AREA %
0.30			BASELINE @ START RUN = 10.97			
0.00			THRESHOLD @ START RUN = -2			
0.00			PEAK WIDTH @ START RUN = 0.32			
0.10			RPI REJECT = 9E+09			
4.00			RPI REJECT = 0			
35.97	9.61	BB	------	0.38	10.99	0.349
38.43	2652.36	BB	------	109.04	11.24	96.072
44.45	76.47	BV	0.23	5.25	11.39	2.770
55.62	11.21	BB	------	0.55	11.36	0.406
73.28	11.16	BB	------	0.39	11.06	0.404

FIGURE 2 - Capillary Chromatogram of M&B 46,030, batch 'S 963

Work carried out by:

9.10.90.

W.Z. Jablonski
(Analytical Development Chemist)

Work directed by:

9/10/90

G.C. Buddle, M.Sc., C.Chem., F.R.S.C.
(Section Head, Formulations Analysis)

Report prepared by:

9/10/90

G.C. Buddle, M.Sc., C.Chem., F.R.S.C.
(Section Head, Formulations Analysis)

Report approved by:

10/10/90

Dr. J.R. Outram, B.Sc., Ph.D., D.I.C.
(Analytical Chemistry Manager)

Date of Work:	September-October, 1990.
Notebook Number:	5818
Project Number:	P-90-320
Raw Data Storage:	Rhône-Poulenc GLP Archive, Ongar, Esssex.

QUALITY ASSURANCE COMPLIANCE

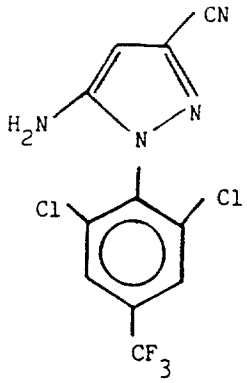
In an audit which was completed on 9/10/90 this report was found to describe accurately the methods and S.O.P.s used and to reflect accurately the results recorded in the raw data.

Signed: A Brentnall

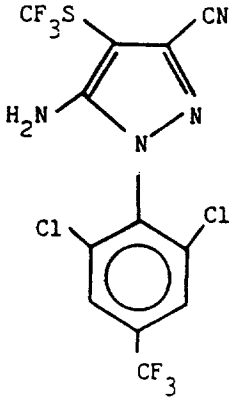
Quality Assurance (G.L.P.)

Dated: 10/10/90

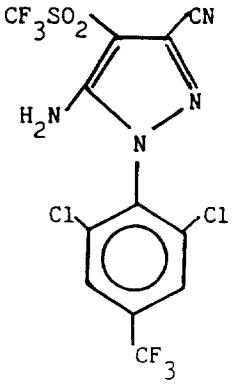
Appendix I - Structures of Manufacturing Impurities of M&B 46,030



M&B 45,897



M&B 45,950



M&B 46,136

Appendix II - Capillary g.c. Procedure for Impurity Profile

The following procedure has been developed to profile samples of M&B 46,030 technical. It is in the process of being fully validated for quantitative use and will be reported in due course.

G.C. Condition

Column:	Methyl silicone cross linked fused silica 50m x 0.3mm i.d., 0.52µ phase thickness.
Temperature programme:	150°C for 5 minutes, then 8°C/min to 190°C. Hold for 27 minutes, then 6°C/min to 270°C.
Detector temperature:	290°C.
Injector:	Cold on-column.
Carrier gas:	Helium, 2 ml/min.
Injection volume:	1µl.

Sample Solution

0.25% (or 0.1%) w/v in methanol.

APPENDIX 2A

Determination of M&B 46030 in rodent diet mixes

1. Introduction

A method provided by the Sponsor (Ref 1) was modified to comply with LSR standard procedures and instrumentation.

2. Outline

M&B 46030 was extracted from diet mixes with acetonitrile. The extract was filtered and the concentration of M&B 46030 in the filtrate adjusted to within a nominal range before quantitative analysis by gas chromatography using an electron capture detector.

3. Standard

M&B 46030 : The analytical standard was taken from the batch used to prepare the diet mix under examination. Results are consequently expressed in terms of the test material as supplied.

4. Reagents

Acetonitrile (HPLC grade).

5. Instrumentation

The following instrumentation was found to be suitable:

Auto-injector	: Philips Analytical PU 4700
Gas chromatograph	: PU 4550
Computing integrator	: PU 4850

Ref 1 : SAVAGE, E.A.
'Rat Feed Analysis : M&B 46030'.
Ref ACD/EAS/6287. 25 August 1989.
Rhône-Poulenc Agriculture, Fyfield Road, Ongar, Essex CM5 OHW.

Determination of M&B 46030 in rodent diet mixes

6. Extraction

M&B 46030 was extracted from a sample (10 g) of diet mix by sonicating with acetonitrile (40 ml) for 10 minutes. The mixture was filtered and the extraction process repeated with a further portion of acetonitrile (40 ml). The filtrates were combined by washing into a volumetric flask (100 ml) and were made to volume. This extract was then further diluted with acetonitrile to give an expected concentration of M&B 46030 within the range 10 to 20 ng/ml in the final solution.

7. Gas Liquid Chromatography

The following conditions was found to be suitable. Minor modifications to these conditions may have been applied if required to improve sensitivity or resolution.

Column	: 5% SE-30 on Supelcoport 100-200 mesh (2 m x 2 mm i.d.)
Injector temperature	: 220°C
Oven temperature	: 200°C
Carrier gas	: 5% Methane in argon
Carrier flow	: 30 ml/min
Detector	: Electron capture
Purge	: 10 psi
Detector temperature	: 300°C
Injection volume	: 5 μl
Retention time	: Approximately 5 minutes

8. Calibration

Five accurate standard solutions of M&B 46030 in acetonitrile containing approximately 5, 10, 15, 20 and 25 ng/ml were prepared and chromatographed. A graph of M&B 46030 concentration (ng/ml) versus peak area measured by computing integrator was prepared to confirm linearity. The data were regressed linearly and the regression line plotted on the graph. A chemical standard of intermediate concentration was injected at intervals throughout the run to monitor chromatographic performance and update the response factor for computation.

9. Recovery

Samples of blank diet were fortified with M&B 46030 to provide concentrations spanning the range of treatment mixes. Normally duplicates at the highest, lowest and an intermediate concentration were prepared and analysed to determine the recovery of M&B 46030.

Determination of M&B 46030 in rodent diet mixes

10. Calculations

Concentration of M&B 46030 in diet was computed by the integrator from the response factor and the following equations :

Recovery from fortified diet samples R(%)

$$= C_a \times D \times \frac{100}{C_f}$$

Concentration in sample (ppm)

$$= C_a \times D \times \frac{100}{R}$$

Where C_a = concentration in final solution (μg/ml)
D = dilution (ml/g)
C_f = concentration of fortified diet (ppm)

11. Validation

11.1 Calibration under the conditions described was found to be linear over the range 5 to 25 ng/ml.

M&B 46030 was efficiently extracted from fortified diet and recovery values and precision of 91 ± 2.9% at 1 ppm, 82 ± 3.7% at 300 ppm and 82 ± 8.9% at 800 ppm were obtained.

11.2 Limit of Analysis

Rodent diet analysed by these procedures gave no chromatographic peak close to the retention time of M&B 46030. The lowest level of fortification examined was 0.1 ppm which was considered to be the limit of assay.

APPENDIX 2B

Homogeneity of M&B 46030 in rodent diet

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Sample designation	Intended concentration (ppm)	Found concentration (ppm) Individual values	Mean ± SD	Mean concentration (as % of intended concentration)	Coefficient of variation (%)
2MF	1.0	0.916 0.936 1.00 0.991 0.946 0.947	0.956 ± 0.033	96	3.4
5MF	300	275 269 268 269 265 287	272 ± 8.0	91	2.9

SD Standard deviation

APPENDIX 2C

Stability of M&B 46030 in rodent diet

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Intended concentration (ppm)	Storage temperature (°C)	Found concentration (ppm) Initial*	Mean	7 days	14 days
		0.916			
		0.936			
1.0	21	1.00	0.956	0.995	1.01
		0.991		0.963	0.931
		0.946			
		0.947			

Apparent first order rate constant is not significantly different from zero. Estimated shelf life = 14 days+

		275			
		269			
300	21	268	272	265	276
		269		259	269
		265			
		287			

Apparent first order rate constant = 5.8×10^{-4}/day. Estimated shelf life = 14 days+

* Results of homogeneity assays (Appendix 2B)
\+ Conventional limit, defined by duration of test

APPENDIX 2D

Analysis of treatment mixes for M&B 46030 content

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Concentration (ppm) of M&B 46030

Group	Week 1 Individual values	Week 1 Mean	Week 1 Percent of intended	Week 13 Individual values	Week 13 Mean	Week 13 Percent of intended
1MF	ND, ND	-	-	ND, ND	-	-
2MF	0.920, 0.862	0.891	89	0.937, 0.988	0.963	96
3MF	5.05, 4.96	5.01	100	4.67, 4.64	4.66	93
4MF	29.9, 33.9	31.9	106	30.5, 31.7	31.1	104
5MF	288, 311	300	100	262, 284	273	91

ND None detected

APPENDIX 3

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 1M : Control

Animal number	Death Week	Death Date	Death Mode	Signs and Weeks observed
1	14	19.02.90	Terminal kill	
2	14	19.02.90	Terminal kill	
3	14	19.02.90	Terminal kill	
4	14	19.02.90	Terminal kill	Staining dorsal 14.
5	14	19.02.90	Terminal kill	Eye dull, dry and misshapen 13-14. Hair-loss and staining head 13.
6	14	19.02.90	Terminal kill	Ear cut and swollen 11. Ear encrustation 11. Ear red 11-14. Ear scar tissue 12-14.
7	14	19.02.90	Terminal kill	Hair-loss head 7.
8	14	19.02.90	Terminal kill	Hair-loss head 10-14. Encrustations head 10.
9	14	19.02.90	Terminal kill	Staining dorsal 9. Staining dorsal and head 11-14.
10	14	19.02.90	Terminal kill	Staining dorsal 14. Encrustations and hair-loss head 14.

APPENDIX 3 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 2M : M&B 46030 : 1 ppm

Animal number	Death Week	Death Date	Death Mode	Signs and Weeks observed
11	14	19.02.90	Terminal kill	
12	14	19.02.90	Terminal kill	Staining dorsal 5-14. Hair-loss head 14.
13	14	19.02.90	Terminal kill	Staining head 8. Encrustation head 11.
14	14	19.02.90	Terminal kill	
15	14	19.02.90	Terminal kill	
16	14	20.02.90	Terminal kill	
17	14	20.02.90	Terminal kill	
18	14	20.02.90	Terminal kill	Hair-loss limb(s) 1-14. Encrustation limbs 1, 11. Annulated ridges on tail 1-6. Reddening limbs 11. Swollen limbs 11-12.
19	14	20.02.90	Terminal kill	Annulated ridges on tail 1-4.
20	14	20.02.90	Terminal kill	

APPENDIX 3 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 3M : M&B 46030 : 5 ppm

Animal number	Death Week	Death Date	Death Mode	Signs and Weeks observed
21	14	19.02.90	Terminal kill	Hair-loss limbs 7-14. Staining head 14.
22	14	19.02.90	Terminal kill	
23	14	19.02.90	Terminal kill	Staining dorsal 9-14.
24	14	19.02.90	Terminal kill	Staining orbital 14.
25	14	19.02.90	Terminal kill	Staining dorsal 8-14.
26	14	19.02.90	Terminal kill	Staining head 6.
27	14	19.02.90	Terminal kill	
28	14	19.02.90	Terminal kill	
29	14	19.02.90	Terminal kill	Annulated ridges on tail 1-3. Encrustation head 7. Staining head 7-14.
30	14	19.02.90	Terminal kill	Annulated ridges on tail 1-3. Hair-loss and scar tissue head 8-14.

APPENDIX 3 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 4M : M&B 46030 : 30 ppm

Animal number	Death Week	Death Date	Death Mode	Signs and Weeks observed
31	14	19.02.90	Terminal kill	Annulated ridges on tail 1-4. Orbital staining 12-13.
32	14	19.02.90	Terminal kill	
33	14	19.02.90	Terminal kill	
34	14	19.02.90	Terminal kill	
35	14	19.02.90	Terminal kill	Annulated ridges on tail 2-4. Reddening tail 10-14.
36	14	19.02.90	Terminal kill	Annulated ridges on tail 1-4. Exfoliation tail 7-14. Reddening tail 7-14. Encrustations tail 7. Hair-loss limb 11-14.
37	14	19.02.90	Terminal kill	Exfoliation tail 7-14. Reddening tail 7.
38	14	19.02.90	Terminal kill	Reddening tail 9-14. Exfoliation tail 9-14. Abrasion tail 9.
39	14	19.02.90	Terminal kill	Encrustation tail 10-14. Encrustation dorsal 10.
40	14	19.02.90	Terminal kill	Salivation 2. Reddening tail 9-14. Exfoliation tail 9-10. Hair-loss head 9-10.

APPENDIX 3 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 5M : M&B 46030 : 300 ppm

Animal number	Death Week	Death Date	Death Mode	Signs and Weeks observed
41	14	19.02.90	Terminal kill	Hair-loss limbs 8-14.
42	14	19.02.90	Terminal kill	Hair-loss limbs 11-14. Hair-loss head 14.
43	14	19.02.90	Terminal kill	Annulated ridges on tail 2-4. Encrustations head 2-4. Staining ventral 9. Clonic convulsion 9. Salivation 9. Head cut 10. Hair-loss head 10-14.
44	14	19.02.90	Terminal kill	Hair-loss dorsal 1. Staining head and orbital 14.
45	14	19.02.90	Terminal kill	Hair-loss dorsal 1-2. Annulated ridges on tail 1-4. Staining head 14.
46	14	20.02.90	Terminal kill	
47	14	20.02.90	Terminal kill	
48	14	20.02.90	Terminal kill	Annulated ridges on tail 2-5. Staining head and dorsal 11-14.
49	14	20.02.90	Terminal kill	Encrustation head 12-14. Exfoliation limbs 12. Hair-loss head and limbs 12-14. Eye dry, prominent and dark 13-14. Staining head and dorsal 13. Swollen head 13-14. Slow, deep and noisy respiration 13-14. Discharge orbital 13.
50	14	20.02.90	Terminal kill	

APPENDIX 3 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 1F : Control

Animal number	Death Week	Death Date	Death Mode	Signs and Weeks observed
51	14	20.02.90	Terminal kill	
52	14	20.02.90	Terminal kill	Exfoliation tail 5-14. Eye partially closed 8-10. Staining orbital 9-10.
53	14	20.02.90	Terminal kill	Staining dorsal 6. Encrustation head 7-8. Staining head 12.
54	14	20.02.90	Terminal kill	
55	14	20.02.90	Terminal kill	Staining head 13.
56	14	20.02.90	Terminal kill	
57	14	20.02.90	Terminal kill	Hair-loss dorsal 9-10.
58	14	20.02.90	Terminal kill	
59	14	20.02.90	Terminal kill	
60	14	20.02.90	Terminal kill	Annulated ridges on tail 4. Exfoliation tail 4-14. Tail red 4-11. Encrustation tail 7-13. Reddening tail 4-10. Tip of tail absent 8-14. Tail black 7-10.

APPENDIX 3 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 2F : M&B 46030 : 1 ppm

Animal number	Death Week	Death Date	Death Mode	Signs and Weeks observed
61	14	20.02.90	Terminal kill	Hair-loss head 8-14. Staining dorsal 10-14. Encrustation head 11-14. Staining head 13-14.
62	14	20.02.90	Terminal kill	
63	14	20.02.90	Terminal kill	Staining head 10-12.
64	14	20.02.90	Terminal kill	Encrustation head 12. Hair-loss dorsal 12-13.
65	14	20.02.90	Terminal kill	Eye dark 13.
66	14	20.02.90	Terminal kill	
67	14	20.02.90	Terminal kill	
68	14	20.02.90	Terminal kill	
69	14	20.02.90	Terminal kill	
70	14	20.02.90	Terminal kill	Hair-loss limbs 5-14.

APPENDIX 3 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 3F : M&B 46030 : 5 ppm

Animal number	Death Week	Death Date	Death Mode	Signs and Weeks observed
71	14	20.02.90	Terminal kill	Encrustation head 10.
72	14	20.02.90	Terminal kill	
73	14	20.02.90	Terminal kill	
74	14	20.02.90	Terminal kill	Twisted digit 5-14.
75	14	20.02.90	Terminal kill	
76	14	22.02.90	Terminal kill	Staining head 8-9. Staining dorsal 13-14.
77	14	22.02.90	Terminal kill	Staining head 11-12. Staining dorsal 13-14.
78	14	22.02.90	Terminal kill	Encrustation head 8.
79	14	22.02.90	Terminal kill	Annulated ridges on tail 1-8. Irritable 8. Hair-loss dorsal 11-13. Hair-loss limb 11-12.
80	14	22.02.90	Terminal kill	Staining dorsal 7-14.

APPENDIX 3 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 4F : M&B 46030 : 30 ppm

Animal number	Death Week	Death Date	Death Mode	Signs and Weeks observed
81	14	20.02.90	Terminal kill	Annulated ridges on tail 1-3. Staining head 10-14.
82	14	20.02.90	Terminal kill	Staining head 11-12. Irritable 11.
83	14	20.02.90	Terminal kill	Encrustation head 6. Staining head 13-14.
84	14	20.02.90	Terminal kill	Staining head 11-14.
85	14	20.02.90	Terminal kill	Staining head 10-14.
86	14	22.02.90	Terminal kill	
87	14	22.02.90	Terminal kill	Irritable 8.
88	14	22.02.90	Terminal kill	Annulated ridges on tail 1-3. Salivation 6. Hair-loss limb 8-14. Irritable 10.
89	14	22.02.90	Terminal kill	Irritable 8.
90	14	22.02.90	Terminal kill	

APPENDIX 3 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 5F : M&B 46030 : 300 ppm

Animal number	Death Week	Death Date	Death Mode	Signs and Weeks observed
91	14	20.02.90	Terminal kill	Exfoliation tail 4-14. Reddening tail 4-7. Encrustation tail 4-14. Staining head 8.
92	14	20.02.90	Terminal kill	Reddening tail 5-14. Exfoliation tail 5-14. Encrustation tail 5-14. Abrasion tail 5-6. Irritable 10.
93	14	20.02.90	Terminal kill	Reddening tail 4-14. Exfoliation tail 4-14. Abrasion tail 4-7. Encrustation tail 5-14. Eye dull, prominent and dry 13-14. Swollen head 13-14. Staining head 13. Hair-loss limbs 13-14. Hair-loss head 14.
94	14	20.02.90	Terminal kill	Annulated ridges on tail 4. Reddening tail 4-14. Exfoliation tail 4-14. Abrasion tail 4-7. Encrustation tail 5-10.
95	14	20.02.90	Terminal kill	Reddening tail 4-14. Exfoliation tail 4-14. Abrasion tail 5-6. Exfoliation head 5-6. Abrasion head 5-6. Encrustation tail 5-14. Encrustation head 5-6. Hair-loss head 7-12. Eye dark 13.
96	14	22.02.90	Terminal kill	Staining head 3-5. Encrustations head 6-7. Hair-loss head 7.
97	14	22.02.90	Terminal kill	Staining head 10-14.
98	14	22.02.90	Terminal kill	
99	14	22.02.90	Terminal kill	Hair-loss limb(s) 4-14.
100	14	22.02.90	Terminal kill	Hair-loss limb 7. Hair-loss head 8. Exfoliation tail 8-10. Reddening tail 9.

APPENDIX 4

Food consumption - individual values (g/rat/week)

Group :	1	2	3	4	5
Compound :	Control	------ M&B 46030 ------			
Level (ppm) :	0	1	5	30	300

Group / sex	Cage number	Week of treatment 1	2	3	4	5	6	7	8	9	10	11	12	13
1M	1	193	195	198	197	183	185	193	189	192	189	190	182	148
	2	181	190	202	202	192	191	188	181	179	183	180	184	152
2M	3	186	188	190	189	182	186	186	180	179	176	183	181	149
	4	193	202	205	199	196	201	195	190	196	198	194	198	155
3M	5	181	185	196	197	187	187	184	179	175	178	192	189	156
	6	184	178	192	194	188	194	200	181	181	184	194	185	153
4M	7	167	180	183	185	177	177	180	176	176	170	178	177	148
	8	184	185	193	197	184	194	188	181	189	193	193	188	159
5M	9	133	173	190	191	178	184	192	177	176	181	181	179	144
	10	142	175	199	195	181	190	191	192	197	195	196	202	146

APPENDIX 4 - continued

Food consumption - individual values (g/rat/week)

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Cage number	Week of treatment 1	2	3	4	5	6	7	8	9	10	11	12	13
1F	11	146	145	147	147	141	144	138	145	145	146	145	138	111
	12	138	135	127	129	128	98	128	129	134	138	132	130	98
2F	13	149	146	145	141	143	140	140	136	131	112	131	127	91
	14	144	139	135	133	131	136	133	136	133	134	136	135	116
3F	15	136	140	136	134	129	135	111	128	132	142	131	120	84
	16	149	147	135	153	150	149	154	143	151	148	153	155	118
4F	17	148	149	152	147	144	146	147	138	138	142	133	131	106
	18	147	149	144	144	142	148	145	140	141	145	142	134	103
5F	19	129	150	151	142	141	136	143	139	140	140	135	137	97
	20	114	138	144	149	145	149	156	145	137	139	139	134	102

APPENDIX 5

Bodyweight - individual values (g)

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	Week of treatment 0	1	2	3	4	5	6	7	8	9	10	11	12	13
1M	1	177	239	294	335	362	377	410	431	453	470	486	501	512	507
	2	174	240	305	356	403	437	469	483	507	535	534	566	572	568
	3	184	249	309	364	412	438	473	487	510	538	553	567	581	576
	4	190	263	333	387	426	458	489	511	533	551	562	572	582	578
	5	178	241	296	349	387	414	440	461	495	517	539	558	570	564
	6	174	241	300	351	387	416	447	462	481	494	511	521	536	530
	7	183	249	304	350	386	414	445	460	477	493	505	514	521	521
	8	196	259	319	374	423	463	490	510	529	548	574	589	600	597
	9	186	249	306	360	403	437	463	476	495	510	530	546	553	550
	10	173	236	295	348	389	425	454	461	474	487	502	512	526	524
2M	11	171	231	283	329	363	394	420	444	468	487	501	524	539	538
	12	184	244	300	354	396	429	469	493	520	538	556	562	571	576
	13	178	238	295	342	374	402	421	435	467	483	491	503	510	503
	14	185	249	304	358	398	436	466	478	492	527	530	562	583	587
	15	196	271	334	394	435	475	507	524	555	576	593	608	631	636
	16	188	249	308	359	396	414	454	477	495	512	528	540	559	555
	17	196	269	333	383	427	457	483	500	508	529	539	537	551	547
	18	175	233	292	342	392	421	454	471	485	517	549	554	576	577
	19	184	247	304	352	386	415	442	461	480	499	525	536	559	549
	20	189	253	315	372	414	457	500	519	550	573	597	610	635	637

APPENDIX 5 - continued

Bodyweight - individual values (g)

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	Week of treatment 0	1	2	3	4	5	6	7	8	9	10	11	12	13
3M	21	180	236	297	356	395	423	454	475	494	498	516	535	554	560
	22	178	238	298	346	381	407	430	443	460	462	475	494	503	500
	23	182	230	306	353	391	422	448	462	476	485	507	526	543	547
	24	198	270	337	393	426	453	484	503	526	548	567	589	601	597
	25	188	243	299	338	375	400	430	446	461	472	486	496	512	513
	26	188	261	327	381	423	461	491	510	529	547	563	592	600	603
	27	185	258	317	376	418	458	492	509	531	549	573	591	602	593
	28	179	251	309	367	417	445	480	490	515	542	561	580	578	583
	29	157	215	260	319	371	418	458	461	506	514	527	548	563	556
	30	164	224	264	307	331	362	381	401	419	435	453	458	468	470
4M	31	187	245	307	372	426	462	497	515	539	559	577	599	610	614
	32	188	238	288	330	369	399	422	439	460	475	493	505	513	514
	33	182	235	306	353	388	414	443	456	486	513	522	540	552	547
	34	187	250	318	377	420	460	488	504	530	545	561	578	586	591
	35	184	241	294	346	382	414	439	452	474	491	502	524	534	533
	36	181	239	302	355	386	403	444	460	475	500	523	546	566	565
	37	154	217	271	316	363	401	426	446	462	484	493	502	522	516
	38	170	238	297	358	402	436	466	486	511	528	555	567	577	583
	39	192	256	312	364	410	447	475	491	503	520	539	550	568	566
	40	187	248	311	366	411	452	490	500	523	547	571	586	593	593

APPENDIX 5 - continued

Bodyweight - individual values (g)

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	Week of treatment 0	1	2	3	4	5	6	7	8	9	10	11	12	13
5M	41	179	209	269	322	364	397	433	458	481	500	514	526	539	525
	42	168	206	267	327	374	412	453	479	507	526	549	569	589	582
	43	203	236	307	367	413	450	481	497	523	548	573	589	607	599
	44	178	205	263	314	356	389	420	442	461	478	500	506	508	492
	45	190	228	296	356	405	436	473	504	501	521	542	562	578	564
	46	163	197	256	315	369	411	454	489	509	533	541	577	605	596
	47	174	202	267	321	357	385	416	435	453	475	480	507	520	515
	48	174	205	260	310	355	394	424	439	458	478	498	512	523	509
	49	183	214	270	321	354	382	407	426	442	467	490	503	523	480
	50	171	211	282	343	389	433	468	491	513	538	546	583	602	599

APPENDIX 5 - continued

Bodyweight - individual values (g)

Group :	1	2	3	4	5
Compound :	Control	------ M&B 46030 ------			
Level (ppm) :	0	1	5	30	300

Group / sex	Animal number	Week of treatment 0	1	2	3	4	5	6	7	8	9	10	11	12	13
1F	51	158	199	235	254	283	300	302	309	318	330	332	351	341	349
	52	143	173	195	215	223	245	264	269	272	289	306	313	315	300
	53	142	165	193	213	226	240	255	263	267	271	284	293	290	275
	54	161	204	224	258	269	288	308	303	319	331	344	346	348	327
	55	143	155	200	221	234	248	276	280	295	300	306	302	309	300
	56	180	207	221	231	244	261	272	282	286	296	297	296	309	298
	57	158	191	212	221	238	257	264	272	277	297	302	295	303	291
	58	158	184	200	223	244	255	265	279	286	301	307	317	324	308
	59	150	189	203	231	239	261	253	282	290	299	306	319	314	306
	60	136	172	190	204	213	238	270	246	253	273	282	283	283	274
2F	61	171	202	226	252	265	282	290	291	301	310	314	316	321	309
	62	139	172	199	217	238	253	269	273	285	296	303	301	310	294
	63	151	190	218	240	253	279	299	311	312	327	337	343	339	332
	64	155	195	222	243	256	286	303	309	312	333	341	344	336	322
	65	147	184	206	242	261	280	317	322	333	331	338	349	355	332
	66	170	207	239	258	279	293	328	328	353	359	373	384	383	365
	67	157	188	209	232	248	255	264	281	288	290	293	306	306	285
	68	137	170	215	206	225	243	255	254	270	282	286	289	295	281
	69	156	188	208	221	231	256	267	276	279	294	306	329	344	340
	70	167	200	226	263	264	297	307	307	335	350	350	369	377	360

APPENDIX 5 - continued

Bodyweight - individual values (g)

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	Week of treatment 0	1	2	3	4	5	6	7	8	9	10	11	12	13
3F	71	156	190	219	248	270	289	311	306	324	336	344	352	353	335
	72	150	180	202	230	250	262	267	282	293	309	344	346	331	314
	73	139	182	204	228	248	263	276	285	292	297	302	307	311	295
	74	168	198	224	241	257	268	286	291	304	304	316	326	326	319
	75	140	179	193	217	232	247	261	268	263	278	282	281	277	281
	76	172	202	221	244	259	279	295	300	314	327	336	342	343	332
	77	151	185	219	248	259	288	310	312	311	335	350	353	348	348
	78	152	184	205	233	255	276	289	306	313	323	329	339	342	325
	79	153	193	221	251	287	317	316	348	360	364	396	416	460	432
	80	152	191	210	224	238	252	256	267	278	293	288	298	298	285
4F	81	167	198	218	247	274	294	293	307	313	315	334	340	340	330
	82	161	189	213	233	248	253	273	289	291	295	311	315	315	302
	83	139	168	197	224	246	270	291	299	310	317	330	336	341	322
	84	144	173	203	213	233	251	260	259	277	284	298	290	303	292
	85	162	200	225	261	286	313	327	352	367	376	380	396	403	383
	86	170	198	239	246	278	296	313	308	329	339	345	344	350	343
	87	155	180	199	218	238	259	267	273	289	298	302	320	324	313
	88	135	177	211	228	236	267	288	288	291	321	333	335	336	322
	89	148	181	204	228	236	255	257	273	278	277	293	299	301	276
	90	152	188	218	243	265	276	306	322	326	332	346	356	354	333

APPENDIX 5 - continued

Bodyweight - individual values (g)

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	Week of treatment 0	1	2	3	4	5	6	7	8	9	10	11	12	13
5F	91	156	171	193	221	227	234	248	258	267	268	279	290	293	271
	92	165	183	206	226	234	253	270	274	280	294	301	306	301	286
	93	147	169	194	214	221	226	243	252	256	264	275	283	287	266
	94	149	171	197	210	218	234	254	271	276	287	301	306	302	293
	95	156	176	200	227	245	255	275	291	298	305	321	335	341	319
	96	150	166	189	216	234	250	256	275	282	292	296	302	305	289
	97	154	173	190	201	218	238	253	257	272	277	286	285	285	284
	98	155	176	203	226	246	255	265	279	293	298	301	308	314	299
	99	153	176	197	227	246	268	275	288	308	309	313	323	336	311
	100	167	178	203	228	237	259	273	284	285	297	310	309	308	298

APPENDIX 6A

Ophthalmoscopy - individual observations before commencement of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

		Group and sex									
Structure	Observations	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Cornea	Focal superficial opacity		18R								
Iris	Persistent pupillary membrane					45					
	Free blood vessel loop									86R	
Lens	Nuclear opacity spot		12L								
	Faint nuclear opacity				33L		57L				
	Serum droplet on posterior capsule				34R			61R			
	Anterior polar vacuole		19L				52				97L
	Arcuate opacity						51L	64R			
	Faint focal anterior capsular opacity						55L				
	Haemorrhage on posterior capsule									86R	
Number of animals examined :		10	10	10	10	10	10	10	10	10	10

L Left R Right

APPENDIX 6A - continued

Ophthalmoscopy - individual observations before commencement of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

		Group and sex									
Structure	Observations	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Vitreous	Brown pigment spots					45L					
	Slight haemorrhage						56R	63R			
Ocular fundus	Rosette/rosette cluster		12L 20R					68R			
	Pre-retinal loop									85R	99R
Number of animals examined :		10	10	10	10	10	10	10	10	10	10

L Left R Right

APPENDIX 6B

Ophthalmoscopy - individual observations after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

		Group and sex			
Structure	Observations	1M	5M	1F	5F
Cornea	Slight superficial opacity	8 9		59L	
	Linear opacity				97L
Iris	Persistent pupillary membrane		45		
	Free blood vessel loop				93L
	Haemorrhage spot				95R
Lens	Posterior capsular opacity	3			
	Faint nuclear opacity	5		57L	
	Arcuate opacity			51L	
	Nuclear opacity spot			56R	
	Refractile change				96R
Number of animals examined :		10	10	10	10

L Left R Right

APPENDIX 6B - continued

Ophthalmoscopy - individual observations after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

		Group and sex			
Structure	Observations	1M	5M	1F	5F
Ocular fundus	Pre-retinal loop		41R		99R
Anterior chamber	Aqueous flare		45R		
Number of animals examined :		10	10	10	10

L Left R Right

APPENDIX 7

Haematology - individual values after 12 weeks of treatment

Group :	1	2	3	4	5
Compound :	Control	------ M&B 46030 ------			
Level (ppm) :	0	1	5	30	300

Group / sex	Animal number	PCV %	Hb g%	RBC mil/cmm	Reticulocytes %	MCHC %	MCV cμ	MCH pg	WBC 1000/cmm Total	N	L	E	B	M	LU	Platelets 1000/cmm	PT secs
1M	1	47	16.5	9.12	<2	35	52	18	12.1	1.6	9.7	0.1	0.0	0.2	0.3	968	14.1
	2	49	16.8	9.13	<2	34	54	18	13.7	1.7	11.0	0.2	0.1	0.2	0.5	842	15.1
	3	46	15.9	8.66	<2	35	53	18	14.8	2.4	11.5	0.2	0.1	0.3	0.4	700	14.5
	4	45	15.7	9.10	<2	35	49	17	19.2	3.2	13.7	0.4	0.1	0.8	1.0	745	15.9
	5	45	15.5	8.81	<2	34	51	18	12.6	1.8	10.1	0.1	0.0	0.3	0.3	877	14.8
	6	46	15.7	8.81	<2	34	52	18	14.7	1.2	12.8	0.1	0.1	0.2	0.3	842	14.5
	7	46	15.7	9.07	<2	34	51	17	10.4	1.1	8.6	0.1	0.0	0.3	0.4	1023	15.7
	8	45	15.9	8.53	<2	35	53	19	13.0	1.1	10.6	0.2	0.1	0.4	0.5	919	14.8
	9	47	15.8	8.77	<2	34	54	18	17.0	1.7	14.1	0.2	0.1	0.4	0.6	792	14.2
	10	46	15.9	9.05	<2	35	51	18	18.1	2.1	14.2	0.2	0.1	0.7	0.9	810	16.4
2M	11	46	16.2	8.86	<2	35	52	18	12.1	0.9	10.4	0.1	0.0	0.3	0.3	877	14.6
	12	44	15.5	8.71	<2	35	51	18	12.3	1.3	9.9	0.2	0.1	0.4	0.4	946	15.5
	13	47	16.0	9.20	<2	34	51	17	13.1	1.4	10.8	0.1	0.0	0.3	0.3	976	15.4
	14	45	15.5	8.66	<2	34	52	18	17.8	2.2	13.6	0.2	0.1	0.7	1.0	834	15.5
	15	48	16.3	8.96	<2	34	54	18	13.4	2.3	9.7	0.1	0.1	0.6	0.6	734	14.7
	16	45	15.9	9.14	<2	35	49	17	13.0	1.2	10.8	0.1	0.0	0.4	0.4	901	15.3
	17	47	16.2	9.17	<2	34	51	18	16.4	2.0	12.9	0.2	0.1	0.5	0.6	923	15.9
	18	47	16.4	8.82	<2	35	53	19	12.6	1.7	9.9	0.1	0.1	0.3	0.4	882	19.3
	19	46	15.8	9.51	<2	34	48	17	14.0	1.4	11.8	0.1	0.1	0.3	0.4	807	16.7
	20	47	16.3	9.22	<2	35	51	18	15.5	1.6	12.3	0.1	0.1	0.6	0.8	704	15.4

APPENDIX 7 - continued

Haematology - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	PCV %	Hb g%	RBC mil/ cmm	Reticu-locytes %	MCHC %	MCV cμ	MCH pg	WBC 1000/cmm Total	N	L	E	B	M	LU	Plat-elets 1000 /cmm	PT secs
3M	21	46	15.9	8.44	<2	35	55	19	14.4	2.6	10.6	0.1	0.1	0.5	0.6	887	13.7
	22	46	15.9	8.99	<2	35	51	18	12.1	2.1	9.0	0.1	0.1	0.4	0.5	979	14.1
	23	45	15.7	8.51	<2	35	53	18	15.5	2.4	12.1	0.1	0.1	0.4	0.4	940	14.5
	24	46	16.3	9.00	<2	35	51	18	12.0	1.6	9.6	0.1	0.0	0.4	0.4	931	14.9
	25	46	16.0	9.14	<2	35	50	18	11.5	1.7	9.3	0.1	0.1	0.1	0.2	889	14.7
	26	45	16.1	8.58	<2	36	52	19	12.6	2.1	9.4	0.1	0.0	0.4	0.4	851	13.9
	27	47	16.6	9.23	<2	35	51	18	12.3	0.9	10.6	0.2	0.0	0.2	0.3	905	14.8
	28	46	16.1	8.65	<2	35	53	19	15.6	1.4	13.4	0.1	0.1	0.2	0.4	878	14.8
	29	45	15.9	8.57	<2	35	53	19	11.3	2.2	8.2	0.2	0.0	0.3	0.3	794	15.5
	30	47	17.2	8.92	<2	37	53	19	15.2	1.4	12.8	0.2	0.1	0.2	0.5	1060	15.7
4M	31	43	15.0	8.44	<2	35	51	18	11.8	1.4	9.6	0.1	0.0	0.2	0.3	1057	14.9
	32	46	16.0	9.04	<2	35	51	18	8.6	1.0	7.0	0.1	0.0	0.2	0.3	955	15.2
	33	47	16.5	8.89	<2	35	53	19	11.9	1.9	9.0	0.1	0.0	0.4	0.4	928	14.9
	34	44	15.2	8.48	<2	35	52	18	13.3	1.4	10.7	0.2	0.1	0.4	0.6	897	14.7
	35	46	16.4	9.21	<2	36	50	18	14.9	2.0	11.4	0.1	0.1	0.5	0.8	992	15.4
	36	45	15.3	8.49	<2	34	53	18	10.8	1.5	8.2	0.1	0.0	0.4	0.5	968	15.7
	37	44	15.4	8.64	<2	35	51	18	11.6	1.1	9.7	0.1	0.0	0.3	0.3	1030	15.7
	38	45	16.1	8.58	<2	36	52	19	13.2	1.9	10.3	0.2	0.1	0.3	0.4	957	16.6
	39	46	16.2	8.70	<2	35	53	19	8.6	1.1	7.0	0.1	0.0	0.2	0.2	875	14.2
	40	47	16.5	9.23	<2	35	51	18	14.4	1.2	12.2	0.2	0.1	0.4	0.4	817	14.2

APPENDIX 7 - continued

Haematology - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	PCV %	Hb g%	RBC mil/ cmm	Reticu-locytes %	MCHC %	MCV cμ	MCH pg	WBC 1000/cmm Total	N	L	E	B	M	LU	Plat-elets 1000 /cmm	PT secs
5M	41	43	14.9	8.44	<2	35	51	18	7.7	0.9	6.3	0.1	0.0	0.2	0.2	986	14.5
	42	46	15.4	8.97	<2	33	51	17	11.5	1.5	9.0	0.1	0.0	0.5	0.5	771	13.9
	43	50	16.4	8.92	<2	33	56	18	19.7	2.4	15.3	0.2	0.1	0.6	0.9	933	14.3
	44	44	15.1	8.82	<2	34	50	17	18.7	1.5	15.8	0.2	0.1	0.5	0.6	938	14.5
	45	45	15.4	8.63	<2	34	52	18	13.4	2.4	10.1	0.1	0.0	0.3	0.5	1015	13.9
	46	41	14.0	7.78	<2	34	53	18	16.4	3.0	11.6	0.2	0.1	0.6	0.9	1178	14.7
	47	44	15.3	8.98	<2	35	49	17	10.4	1.1	8.0	0.2	0.0	0.5	0.6	893	15.3
	48	44	14.9	8.55	<2	34	51	17	14.5	1.5	12.3	0.1	0.1	0.2	0.3	916	15.9
	49	46	15.7	9.21	<2	34	50	17	14.5	2.2	10.9	0.2	0.1	0.5	0.6	802	15.4
	50	46	15.7	8.54	<2	34	54	18	13.6	1.9	10.3	0.3	0.1	0.5	0.6	826	14.9

APPENDIX 7 - continued

Haematology - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	PCV %	Hb g%	RBC mil/ cmm	Reticu- locytes %	MCHC %	MCV cμ	MCH pg	WBC 1000/cmm Total	N	L	E	B	M	LU	Plat- elets 1000 /cmm	PT secs
1F	51	44	15.7	8.21	<2	36	54	19	8.8	0.7	7.5	0.1	0.0	0.2	0.3	1009	14.1
	52	46	16.0	8.46	<2	35	54	19	6.7	0.8	5.1	0.1	0.0	0.3	0.4	822	14.4
	53	45	16.4	8.43	<2	36	53	19	8.6	0.7	7.4	0.1	0.0	0.2	0.2	840	CS
	54	44	15.4	8.24	<2	35	53	19	6.8	0.9	5.4	0.1	0.0	0.2	0.2	911	13.7
	55	45	16.0	8.48	<2	36	53	19	10.7	1.2	8.5	0.2	0.0	0.4	0.3	904	14.1
	56	42	15.1	8.10	<2	36	52	19	9.6	1.5	7.5	0.2	0.0	0.2	0.3	865	13.9
	57	45	15.8	8.00	<2	35	56	20	12.3	1.0	10.6	0.1	0.0	0.3	0.3	745	13.8
	58	45	16.3	8.37	<2	36	54	19	6.1	1.1	4.7	0.1	0.0	0.1	0.2	951	14.9
	59	43	15.6	8.22	<2	36	52	19	8.4	0.7	6.7	0.2	0.0	0.3	0.4	1093	14.5
	60	46	16.7	8.58	<2	36	54	19	11.0	1.5	8.7	0.2	0.0	0.4	0.3	993	14.2
2F	61	43	15.3	8.11	<2	36	53	19	8.9	0.8	7.7	0.1	0.0	0.1	0.2	894	14.8
	62	43	15.4	8.29	<2	36	52	19	8.7	1.2	6.8	0.1	0.0	0.3	0.3	1064	13.9
	63	44	15.7	8.09	<2	36	54	19	7.6	0.5	6.7	0.1	0.0	0.1	0.2	775	14.6
	64	44	15.4	8.23	<2	35	53	19	13.9	1.7	11.1	0.2	0.1	0.4	0.4	880	14.5
	65	44	15.6	7.99	<2	35	55	20	12.1	1.6	9.8	0.1	0.0	0.3	0.3	1084	14.2
	66	44	15.5	8.09	<2	35	54	19	11.1	1.6	8.2	0.1	0.0	0.5	0.6	841	14.1
	67	45	16.1	8.28	<2	36	54	19	10.6	1.6	8.4	0.1	0.0	0.4	0.2	860	14.9
	68	44	15.7	8.41	<2	36	52	19	9.1	1.8	6.7	0.1	0.0	0.2	0.2	1023	14.2
	69	44	15.5	8.28	<2	35	53	19	6.3	1.1	4.7	0.1	0.0	0.2	0.2	1079	14.2
	70	44	15.3	8.41	<2	35	52	18	12.2	1.3	10.1	0.1	0.0	0.3	0.4	874	14.4

CS Clotted sample

APPENDIX 7 - continued

Haematology - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------ M&B 46030 ------			
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	PCV %	Hb g%	RBC mil/cmm	Reticulocytes %	MCHC %	MCV cμ	MCH pg	WBC 1000/cmm Total	N	L	E	B	M	LU	Platelets 1000/cmm	PT secs
3F	71	43	15.3	8.30	<2	36	52	18	7.7	1.0	6.1	0.1	0.0	0.2	0.3	901	13.0
	72	44	15.5	8.19	<2	35	54	19	6.5	0.5	5.7	0.1	0.0	0.1	0.2	956	14.4
	73	43	14.9	7.88	<2	35	55	19	6.6	1.8	4.4	0.1	0.0	0.2	0.1	809	13.8
	74	44	15.9	8.16	<2	36	54	19	10.5	0.5	9.4	0.1	0.0	0.2	0.2	1116	14.1
	75	46	16.3	8.52	<2	35	54	19	7.4	0.7	6.3	0.1	0.0	0.1	0.2	897	14.5
	76	42	15.2	7.98	<2	36	53	19	8.2	0.8	6.9	0.1	0.0	0.2	0.2	1003	14.0
	77	44	15.6	8.20	<2	35	54	19	7.0	0.5	6.0	0.1	0.0	0.2	0.2	1024	14.0
	78	42	15.1	7.98	<2	36	53	19	8.2	0.8	6.9	0.1	0.0	0.2	0.2	893	13.8
	79	44	15.6	8.09	<2	35	54	19	10.6	1.3	8.4	0.3	0.0	0.3	0.3	899	13.7
	80	44	15.3	8.12	<2	35	54	19	7.9	0.6	6.8	0.1	0.0	0.2	0.3	830	14.7
4F	81	43	15.4	8.07	<2	36	53	19	6.6	0.5	5.8	0.1	0.0	0.1	0.1	1032	14.1
	82	42	15.0	7.95	<2	36	53	19	5.7	0.5	4.9	0.1	0.0	0.1	0.1	1067	13.9
	83	44	15.8	8.15	<2	36	54	19	7.5	1.4	5.5	0.1	0.0	0.2	0.3	1032	13.4
	84	42	15.1	8.34	<2	36	50	18	8.6	1.3	6.7	0.1	0.0	0.2	0.3	1105	13.3
	85	45	16.1	8.22	<2	36	55	20	6.2	1.4	4.3	0.1	0.0	0.2	0.2	930	13.3
	86	44	15.6	8.57	<2	35	51	18	4.6	0.8	3.5	0.1	0.0	0.1	0.2	875	14.1
	87	43	15.2	8.13	<2	35	53	19	4.4	0.8	3.3	0.1	0.0	0.1	0.1	811	13.4
	88	44	15.6	8.05	<2	35	55	19	6.1	0.6	5.2	0.1	0.0	0.1	0.1	910	15.1
	89	43	14.9	7.82	<2	35	55	19	8.2	0.6	7.0	0.1	0.0	0.2	0.3	1121	13.5
	90	45	15.6	8.46	<2	35	53	18	9.2	1.1	7.5	0.1	0.0	0.2	0.3	1045	12.9

APPENDIX 7 - continued

Haematology - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	PCV %	Hb g%	RBC mil/cmm	Reticulocytes %	MCHC %	MCV cμ	MCH pg	WBC 1000/cmm Total	N	L	E	B	M	LU	Platelets 1000/cmm	PT secs
5F	91	43	15.4	8.22	<2	36	52	19	5.3	0.4	4.5	0.1	0.0	0.2	0.2	1105	13.8
	92	43	15.3	8.03	<2	36	54	19	10.4	0.8	8.8	0.1	0.0	0.3	0.4	947	13.4
	93	41	14.7	7.99	<2	36	51	18	7.0	1.5	5.0	0.1	0.0	0.2	0.2	1150	13.1
	94	42	15.1	8.59	<2	36	49	18	9.5	1.4	6.9	0.2	0.1	0.4	0.4	969	13.7
	95	42	15.2	8.25	<2	36	51	18	10.3	0.7	8.9	0.1	0.0	0.2	0.3	1045	13.4
	96	43	15.5	8.69	<2	36	49	18	9.4	2.0	6.7	0.1	0.0	0.3	0.3	990	13.6
	97	42	14.9	8.30	<2	35	51	18	10.5	2.0	7.7	0.1	0.0	0.3	0.4	1000	13.8
	98	44	15.4	8.78	<2	35	50	18	9.0	0.9	7.4	0.1	0.0	0.3	0.3	1033	13.3
	99	45	15.9	8.55	<2	35	53	19	11.4	1.3	9.5	0.1	0.0	0.2	0.3	1083	13.6
	100	43	15.1	8.05	<2	35	53	19	7.8	0.6	6.3	0.1	0.0	0.4	0.3	956	13.3

APPENDIX 8

Blood chemistry - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	AP iu/l	ALT iu/l	AST iu/l	Urea mg%	Creat-inine mg%	Glu-cose mg%	Total Bili-rubin mg%	Plasma Proteins g% Total	Alb-umin	Globulins α1	α2	β	γ	A/G ratio -:1	Electrolytes mMol/l Na	K	Cl	Ca	P
1M	1	103	23	60	21	0.6	115	0.1	6.9	3.2	1.4	0.4	1.6	0.3	0.8	144	3.5	105	2.6	1.9
	2	97	24	74	27	0.8	114	0.1	7.0	3.1	1.4	0.4	1.7	0.4	0.8	144	3.6	106	2.6	2.0
	3	115	34	78	21	0.8	143	0.1	6.8	3.1	1.2	0.4	1.6	0.5	0.8	142	4.1	105	2.6	2.0
	4	76	67	101	25	0.7	162	0.1	7.3	3.3	1.4	0.4	1.7	0.5	0.8	144	3.4	106	2.6	2.1
	5	73	34	89	31	0.8	158	0.1	6.5	3.0	1.2	0.4	1.6	0.4	0.8	143	4.0	103	2.5	1.9
	6	75	29	56	31	0.7	130	0.1	6.6	3.1	1.2	0.4	1.6	0.3	0.9	145	4.0	105	2.7	2.3
	7	88	30	67	21	0.7	127	0.1	6.4	3.1	1.0	0.3	1.7	0.3	0.9	143	3.7	105	2.6	2.0
	8	58	25	65	26	0.7	116	0.1	6.8	3.4	1.3	0.4	1.5	0.2	1.0	144	3.6	103	2.7	2.2
	9	86	29	62	25	0.8	189	0.1	6.9	2.4	1.6	0.4	1.9	0.5	0.6	145	4.2	103	2.7	2.2
	10	101	44	75	22	0.6	150	0.1	6.3	2.7	1.1	0.4	1.8	0.4	0.7	144	3.5	104	2.5	1.8
2M	11	122	28	68	28	0.8	95	0.1	7.0	3.2	1.1	0.4	1.8	0.5	0.9	143	3.6	105	2.7	2.1
	12	89	32	76	32	0.8	123	0.1	6.8	3.2	1.5	0.4	1.3	0.4	0.9	143	3.7	106	2.6	2.0
	13	122	28	52	28	0.8	137	0.1	6.8	3.5	1.2	0.3	1.6	0.3	1.0	144	3.6	106	2.7	2.2
	14	83	24	51	31	0.7	129	0.1	6.8	3.0	1.2	0.3	2.0	0.2	0.8	144	3.8	105	2.6	2.1
	15	101	41	63	29	0.7	147	0.1	7.1	3.2	1.4	0.4	1.6	0.5	0.8	143	3.8	105	2.7	2.1
	16	73	32	59	31	0.6	120	0.1	6.7	2.9	1.4	0.4	1.5	0.4	0.8	145	3.8	106	2.6	2.1
	17	75	30	71	28	0.6	131	0.1	6.8	3.3	1.2	0.5	1.6	0.3	0.9	145	4.0	108	2.6	2.1
	18	102	33	67	26	0.7	121	0.2	7.3	3.6	1.4	0.5	1.5	0.4	0.9	145	3.6	103	2.6	2.0
	19	107	32	61	31	0.7	150	0.1	7.1	3.3	1.4	0.5	1.6	0.4	0.9	145	3.7	106	2.5	1.9
	20	103	31	60	26	0.7	168	0.1	6.9	3.6	1.2	0.4	1.4	0.3	1.1	145	3.8	102	2.7	2.1

APPENDIX 8 - continued

Blood chemistry - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	AP iu/l	ALT iu/l	AST iu/l	Urea mg%	Creat-inine mg%	Glu-cose mg%	Total Bili-rubin mg%	Plasma Proteins g% Total	Albumin	Globulins α1	α2	β	γ	A/G ratio -:1	Electrolytes mMol/l Na	K	Cl	Ca	P
3M	21	100	32	60	27	0.7	112	0.1	7.4	2.5	1.5	0.5	2.4	0.5	0.5	142	3.7	108	2.5	1.8
	22	60	25	66	26	0.6	120	0.1	7.2	2.6	1.7	0.5	2.0	0.4	0.6	144	4.2	107	2.7	2.3
	23	119	32	60	30	0.7	138	0.1	7.1	2.7	1.5	0.5	1.9	0.5	0.6	144	3.8	108	2.7	2.0
	24	82	31	76	32	0.7	157	0.2	7.1	3.3	1.2	0.5	1.8	0.4	0.9	145	3.8	104	2.6	2.0
	25	115	32	60	29	0.8	122	0.1	6.9	3.3	1.3	0.4	1.5	0.3	0.9	145	3.6	106	2.7	2.2
	26	67	27	66	26	0.6	114	0.1	7.2	3.3	1.5	0.4	1.7	0.4	0.8	145	3.9	103	2.5	2.2
	27	84	32	52	28	0.7	123	0.1	7.0	3.2	1.7	0.4	0.8	0.9	0.8	142	3.7	105	2.5	1.9
	28	80	31	65	37	0.7	130	0.1	6.5	3.0	1.2	0.4	1.5	0.3	0.9	144	3.4	107	2.6	2.0
	29	68	32	63	38	0.7	125	0.1	7.3	3.0	1.5	0.3	2.1	0.4	0.7	146	4.2	105	2.6	2.1
	30	67	27	60	28	0.7	126	0.1	7.5	3.1	1.6	0.4	1.9	0.5	0.7	145	3.3	106	2.6	1.8
4M	31	81	21	63	24	0.7	100	0.1	6.6	3.3	1.3	0.4	1.3	0.2	1.0	144	3.9	103	2.7	2.0
	32	93	22	45	33	0.8	119	0.1	7.1	3.2	1.5	0.4	1.6	0.4	0.8	143	4.0	105	2.6	1.6
	33	90	39	79	36	0.8	143	0.1	6.9	3.1	1.5	0.4	1.5	0.3	0.8	144	3.6	103	2.8	2.2
	34	96	34	56	32	0.8	180	0.1	7.3	3.4	1.7	0.4	1.6	0.3	0.9	145	3.6	106	2.7	2.0
	35	78	25	59	31	0.7	130	0.1	7.3	3.2	1.7	0.4	1.6	0.4	0.8	143	3.6	104	2.8	2.3
	36	97	27	62	32	0.7	126	0.1	6.7	3.2	1.1	0.5	1.5	0.4	0.9	144	3.7	103	2.7	2.0
	37	107	31	62	28	0.7	113	0.1	6.9	3.3	1.4	0.4	1.5	0.3	0.9	145	3.6	104	2.6	2.0
	38	102	29	54	35	0.7	133	0.1	7.4	3.3	1.6	0.4	1.6	0.4	0.8	144	3.6	102	2.7	2.1
	39	90	27	60	29	0.7	147	0.1	7.3	3.0	1.8	0.5	1.7	0.3	0.7	144	3.7	102	2.7	2.1
	40	86	28	74	30	0.7	160	0.1	7.5	3.3	1.5	0.5	1.7	0.4	0.8	143	3.6	102	2.7	2.0

APPENDIX 8 - continued

Blood chemistry - individual values after 12 weeks of treatment

Group :	1	2	3	4	5
Compound :	Control	------ M&B 46030 ------			
Level (ppm) :	0	1	5	30	300

Group / sex	Animal number	AP iu/l	ALT iu/l	AST iu/l	Urea mg%	Creat-inine mg%	Glu-cose mg%	Total Bili-rubin mg%	Plasma Proteins g% Total	Alb-umin	Globulins α1	α2	β	γ	A/G ratio -:1	Electrolytes mMol/l Na	K	Cl	Ca	P
5M	41	115	30	71	26	0.7	116	0.1	7.0	1.7	1.8	0.7	2.5	0.3	0.3	143	3.6	103	2.7	2.0
	42	78	39	64	27	0.7	130	0.1	7.3	2.9	1.7	0.5	1.9	0.2	0.7	144	4.1	103	2.7	2.1
	43	95	25	59	29	0.8	122	0.1	7.3	3.1	1.6	0.5	1.8	0.4	0.7	143	3.8	104	2.7	2.1
	44	82	36	104	29	0.7	165	0.1	7.4	2.6	1.7	0.5	2.1	0.4	0.6	145	4.1	103	2.6	2.1
	45	136	28	62	35	0.7	151	0.1	7.9	3.1	1.6	0.5	2.3	0.5	0.6	144	3.6	105	2.7	2.0
	46	73	29	69	37	0.8	141	0.1	7.7	3.2	1.5	0.5	2.1	0.4	0.7	143	3.9	105	2.7	2.3
	47	104	31	52	36	0.7	149	0.1	7.5	3.1	1.7	0.5	2.1	0.1	0.7	145	4.0	103	2.8	2.0
	48	138	27	68	30	0.7	140	0.1	7.1	3.0	1.6	0.4	1.8	0.3	0.7	144	4.0	105	2.8	2.0
	49	74	41	66	27	0.7	192	0.1	7.2	2.9	1.6	0.5	1.8	0.4	0.7	145	4.0	105	2.6	1.6
	50	149	35	90	31	0.8	153	0.1	7.7	3.1	1.8	0.6	1.7	0.4	0.7	145	4.6	104	2.7	2.0

APPENDIX 8 - continued

Blood chemistry - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	AP iu/l	ALT iu/l	AST iu/l	Urea mg%	Creat-inine mg%	Glu-cose mg%	Total Bili-rubin mg%	Plasma Proteins g% Total	Albumin	Globulins α1	α2	β	γ	A/G ratio -:1	Electrolytes mMol/l Na	K	Cl	Ca	P
1F	51	42	29	47	45	0.8	109	0.1	6.8	3.3	1.0	0.4	1.7	0.4	1.0	141	3.4	103	2.7	2.4
	52	43	23	65	32	0.7	129	0.1	7.8	4.1	1.2	0.4	1.3	0.9	1.1	141	3.7	106	2.7	2.0
	53	62	25	59	29	0.7	147	0.1	6.7	3.8	1.0	0.3	1.0	0.6	1.3	143	3.1	107	2.6	1.5
	54	26	20	82	33	0.8	144	0.1	7.0	3.8	1.1	0.4	1.3	0.3	1.2	144	3.1	108	2.6	1.7
	55	43	36	106	28	0.7	119	0.1	7.2	3.8	1.0	0.4	1.6	0.5	1.1	143	3.4	105	2.6	2.0
	56	44	32	75	54	0.8	114	0.1	7.4	4.1	0.9	0.4	1.1	0.9	1.2	142	3.4	106	2.7	2.1
	57	45	33	78	35	0.7	113	0.1	6.9	3.2	1.3	0.3	1.4	0.7	0.9	144	3.4	108	2.7	2.1
	58	80	35	77	27	0.7	147	0.1	7.3	3.8	0.9	0.4	1.7	0.5	1.1	144	3.1	106	2.5	1.6
	59	39	37	76	30	0.7	118	0.1	7.5	4.0	1.1	0.4	1.4	0.5	1.1	143	3.6	106	2.7	1.8
	60	62	27	74	28	0.6	108	0.1	7.1	3.7	1.1	0.4	1.4	0.5	1.1	142	3.5	104	2.6	1.8
2F	61	46	26	49	35	0.7	123	0.1	7.9	4.3	1.2	0.4	1.1	0.9	1.2	140	3.7	104	2.6	1.7
	62	39	26	54	38	0.7	129	0.1	7.6	4.2	1.1	0.4	1.4	0.5	1.2	140	3.5	105	2.6	2.1
	63	37	24	41	43	0.7	128	0.1	7.6	3.9	1.3	0.4	1.5	0.5	1.0	140	4.0	104	2.7	2.0
	64	50	46	105	38	0.7	135	0.1	9.0	4.8	1.4	0.5	1.7	0.6	1.1	140	3.1	104	2.8	1.9
	65	74	28	62	35	0.8	145	0.1	7.6	3.9	1.1	0.5	1.6	0.5	1.1	140	3.0	104	2.6	1.8
	66	44	23	49	46	0.8	151	0.1	7.8	4.1	1.0	0.5	1.7	0.6	1.1	142	3.5	105	2.6	2.1
	67	48	27	62	34	0.7	124	0.1	7.5	3.8	1.1	0.4	1.7	0.4	1.0	140	3.3	104	2.7	1.9
	68	37	28	50	44	0.8	131	0.1	7.7	4.0	1.1	0.5	1.5	0.6	1.1	139	3.4	102	2.6	1.8
	69	68	25	50	28	0.8	146	0.1	7.3	3.1	1.0	0.5	2.2	0.5	0.7	140	3.1	104	2.5	1.9
	70	68	31	63	39	0.9	148	0.1	7.6	3.4	1.1	0.4	1.9	0.8	0.8	141	3.3	103	2.6	1.8

APPENDIX 8 - continued

Blood chemistry - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	AP iu/l	ALT iu/l	AST iu/l	Urea mg%	Creat-inine mg%	Glu-cose mg%	Total Bili-rubin mg%	Plasma Proteins g% Total	Albumin	Globulins α1	α2	β	γ	A/G ratio -:1	Electrolytes mMol/l Na	K	Cl	Ca	P
3F	71	52	25	51	38	0.7	126	0.2	9.1	4.6	1.5	0.4	2.0	0.5	1.0	142	3.4	103	2.8	1.8
	72	74	39	61	34	0.7	135	0.1	7.8	4.2	1.1	0.4	1.5	0.5	1.2	141	3.3	106	2.6	1.9
	73	57	25	36	45	1.0	151	0.1	7.2	3.8	1.0	0.4	1.6	0.5	1.1	142	3.1	108	2.4	1.6
	74	54	22	60	35	0.7	143	0.1	7.9	4.2	1.3	0.4	1.5	0.5	1.1	141	3.1	104	2.7	1.9
	75	67	24	57	36	0.8	134	0.1	7.3	3.7	1.1	0.4	1.6	0.4	1.0	141	3.1	105	2.5	1.4
	76	61	27	47	27	0.7	118	0.1	6.9	3.5	1.1	0.4	1.5	0.5	1.0	140	3.5	103	2.6	1.9
	77	78	24	48	28	0.6	154	0.1	7.7	4.2	1.2	0.5	1.3	0.4	1.2	141	3.4	106	2.7	2.2
	78	53	21	52	28	0.8	150	0.1	7.9	4.4	1.2	0.5	1.4	0.5	1.2	141	3.2	105	2.7	1.7
	79	62	32	53	32	0.7	164	0.1	7.6	3.7	1.4	0.5	1.5	0.5	1.0	140	3.5	103	2.6	2.1
	80	71	28	60	30	0.7	129	0.1	6.9	3.5	0.8	0.4	1.7	0.5	1.0	141	3.5	108	2.5	2.0
4F	81	69	27	45	28	0.7	146	0.2	7.6	3.8	1.2	0.4	1.6	0.5	1.0	141	3.3	104	2.5	1.6
	82	26	23	51	33	0.7	127	0.1	7.5	3.4	1.5	0.4	1.7	0.5	0.8	141	3.3	105	2.6	1.7
	83	52	21	37	45	0.8	155	0.1	8.3	4.2	1.5	0.5	1.7	0.5	1.0	142	3.3	102	2.7	1.7
	84	44	24	51	43	0.8	134	0.1	7.7	4.1	1.2	0.4	1.5	0.5	1.1	141	3.5	103	2.6	2.0
	85	45	27	42	30	0.8	162	0.1	8.0	4.1	1.4	0.4	1.6	0.5	1.1	141	3.2	105	2.6	1.7
	86	52	18	33	30	0.7	140	0.1	6.9	3.5	1.0	0.4	1.5	0.4	1.0	140	3.4	104	2.5	1.7
	87	52	21	36	27	0.7	162	0.1	7.5	3.9	1.2	0.5	1.5	0.5	1.1	141	3.2	104	2.5	1.6
	88	77	28	41	40	0.7	170	0.1	8.3	4.3	1.4	0.5	1.6	0.5	1.1	141	3.3	103	2.7	1.8
	89	45	24	30	42	0.8	156	0.1	8.0	3.7	1.4	0.5	1.9	0.5	0.9	143	3.8	106	2.7	2.0
	90	63	27	38	51	0.9	161	0.1	8.5	4.4	0.9	0.5	2.0	0.7	1.1	142	3.1	107	2.7	1.8

APPENDIX 8 - continued

Blood chemistry - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	AP iu/l	ALT iu/l	AST iu/l	Urea mg%	Creat-inine mg%	Glu-cose mg%	Total Bili-rubin mg%	Plasma Proteins g% Total	Albumin	Globulins α1	α2	β	γ	A/G ratio -:1	Electrolytes mMol/l Na	K	Cl	Ca	P
5F	91	49	24	33	39	0.8	135	0.1	7.9	3.7	1.5	0.5	1.8	0.5	0.9	144	3.4	107	2.7	2.0
	92	46	26	68	30	0.7	143	0.1	8.1	3.6	1.4	0.6	1.9	0.6	0.8	142	3.1	102	2.7	1.9
	93	35	26	55	31	0.8	153	0.1	7.6	3.5	1.2	0.6	1.8	0.6	0.8	143	3.3	107	2.6	1.5
	94	60	23	51	24	0.7	141	0.1	8.6	4.0	1.7	0.6	1.9	0.5	0.9	142	3.8	105	2.8	2.1
	95	43	18	40	29	0.7	154	0.1	8.2	3.9	1.5	0.5	1.8	0.5	0.9	142	3.4	105	2.7	1.9
	96	96	32	67	30	0.7	127	0.1	7.9	3.5	1.1	0.6	1.9	0.7	0.8	143	3.2	102	2.7	2.1
	97	47	20	41	30	0.7	158	0.1	7.1	3.2	1.2	0.6	1.7	0.4	0.8	141	3.6	106	2.6	2.0
	98	49	18	42	29	0.8	139	0.1	7.7	3.8	1.2	0.6	1.7	0.4	1.0	142	3.1	105	2.7	2.1
	99	66	22	60	40	0.8	137	0.1	7.5	3.3	1.3	0.6	1.8	0.4	0.8	144	3.0	104	2.6	1.8
	100	36	26	21	34	0.7	153	0.1	8.7	4.3	1.8	0.6	1.6	0.4	1.0	142	3.7	102	2.9	2.0

APPENDIX 9

Urinalysis - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	Appearance	Volume ml	pH	SG	Protein mg%	Total red. subs.	Glu-cose	Ket-ones	Bili-rubin	Urob-ilin-ogen	Nit-rite	Blood	Microscopy E	P	R	C	S	A
1M	1	Clear yellow	3.0	7.1	1074	150	0	0	0	0	0	0	0	1	1	0	3	0	0
	2	Clear yellow	6.0	6.7	1070	150	0	0	0	0	0	0	0	1	1	0	3	2	0
	3	Clear yellow	6.0	6.5	1060	150	0	0	0	0	0	0	0	1	1	0	2	0	0
	4	Clear yellow	4.0	6.5	1060	150	0	0	0	0	0	0	0	2	1	0	2	1	0
	5	Clear yellow	3.0	6.5	1072	150	0	0	0	0	0	0	1	2	1	1	2	0	0
	6	Clear yellow	4.0	6.9	1074	200	0	0	0	0	0	0	0	2	1	0	2	2	0
	7	Clear yellow	3.0	7.1	1072	30	0	0	0	0	0	0	0	1	1	0	2	1	0
	8	Clear yellow	5.0	6.7	1078	150	0	0	0	0	0	0	0	1	1	0	3	0	0
	9	Clear yellow	4.0	6.5	1070	30	0	0	0	0	0	0	0	1	1	0	2	1	0
	10	Clear yellow	4.0	6.6	1070	40	0	0	0	0	0	0	0	1	1	0	2	0	0
2M	11	Clear yellow	3.0	6.6	1070	100	0	0	0	0	0	0	0	1	1	0	2	1	0
	12	Clear yellow	3.5	6.7	1078	150	0	0	0	0	0	0	0	1	1	0	1	2	0
	13	Clear yellow	4.0	6.5	1080	70	0	0	0	0	0	0	0	1	1	0	2	2	0
	14	Cloudy yellow	6.0	6.5	1076	90	0	0	0	0	0	0	0	1	1	0	3	3	0
	15	Clear yellow	5.5	6.6	1070	100	0	0	0	0	0	0	0	1	1	0	2	3	0
	16	Clear yellow	3.0	6.6	1068	80	0	0	0	0	0	0	0	1	0	0	2	1	0
	17	Clear yellow	4.0	6.7	1076	90	0	0	0	0	0	0	0	1	1	0	2	1	0
	18	Clear yellow	6.0	6.7	1070	90	0	0	0	0	0	0	0	1	1	0	3	1	0
	19	Clear yellow	5.0	6.7	1060	90	0	0	0	0	0	0	0	1	0	0	2	0	0
	20	Clear yellow	3.0	6.8	1060	80	0	0	0	0	0	0	0	2	1	0	3	0	0

APPENDIX 9 - continued

Urinalysis - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	Appearance	Volume ml	pH	SG	Protein mg%	Total red. subs.	Glu-cose	Ket-ones	Bili-rubin	Urob-ilin-ogen	Nit-rite	Blood	Microscopy E	P	R	C	S	A
3M	21	Pale yellow	6.5	7.3	1049	50	0	0	0	0	0	1	0	1	1	0	3	1	0
	22	Clear yellow	3.0	6.5	1076	40	0	0	0	0	0	0	0	1	1	0	1	1	0
	23	Pale yellow	7.0	7.1	1049	20	0	0	0	0	0	0	0	1	1	0	3	2	0
	24	Clear yellow	6.0	6.6	1060	50	0	0	0	0	0	0	0	1	1	0	2	3	0
	25	Clear yellow	3.0	6.6	1068	40	0	0	0	0	0	0	0	1	1	0	1	1	0
	26	Clear yellow	3.0	6.4	1070	40	0	0	0	0	0	0	0	1	1	0	1	1	0
	27	Clear yellow	3.0	6.6	1068	80	0	0	0	0	0	0	0	1	1	0	2	2	0
	28	Clear yellow	3.5	6.6	1066	10	0	0	0	0	0	0	0	1	1	0	2	0	0
	29	Pale yellow	6.0	6.6	1060	100	0	0	0	0	0	0	0	2	1	0	3	1	0
	30	Clear yellow	4.0	6.8	1052	30	0	0	0	0	0	0	0	1	1	0	2	2	0
4M	31	Clear yellow	4.0	6.5	1072	60	0	0	0	0	0	0	0	1	1	0	2	1	0
	32	Clear yellow	4.0	6.6	1070	50	0	0	0	0	0	0	0	1	1	0	2	1	0
	33	Clear yellow	4.0	6.5	1070	50	0	0	0	0	0	0	0	1	1	0	1	1	0
	34	Clear yellow	5.0	6.5	1068	100	0	0	0	0	0	0	0	1	1	0	2	3	0
	35	Pale yellow	7.0	7.3	1050	30	0	0	0	0	0	0	0	1	1	0	3	3	0
	36	Pale yellow	8.0	7.1	1052	30	0	0	0	0	0	0	0	1	1	0	3	1	0
	37	Clear yellow	3.0	6.6	1058	60	0	0	0	0	0	0	0	1	1	0	2	1	0
	38	Clear yellow	4.0	6.5	1066	60	0	0	0	0	0	0	0	1	1	0	2	1	0
	39	Clear yellow	4.5	6.5	1064	30	0	0	0	0	0	0	0	1	1	0	2	0	0
	40	Clear yellow	3.0	6.5	1070	80	0	0	0	0	0	0	0	2	1	0	3	2	0

APPENDIX 9 - continued

Urinalysis - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	Appearance	Volume ml	pH	SG	Protein mg%	Total red. subs.	Glu-cose	Ket-ones	Bili-rubin	Urob-ilin-ogen	Nit-rite	Blood	Microscopy E	P	R	C	S	A
5M	41	Clear yellow	5.0	6.8	1064	20	0	0	0	0	0	0	0	1	1	0	3	2	0
	42	Clear yellow	4.0	6.7	1070	30	0	0	0	0	0	0	0	1	1	0	2	3	0
	43	Clear yellow	3.0	6.4	1078	40	0	0	0	0	0	0	0	1	1	0	2	1	0
	44	Clear yellow	3.5	6.2	1074	90	0	0	0	0	0	0	0	2	1	0	2	1	0
	45	Clear yellow	6.0	6.4	1068	100	0	0	0	0	0	0	0	1	1	0	2	1	0
	46	Clear yellow	5.0	6.6	1062	150	0	0	0	0	0	0	0	1	1	0	3	0	0
	47	Clear yellow	5.5	6.7	1062	90	0	0	0	0	0	0	0	1	1	0	2	3	0
	48	Cloudy yellow	6.0	7.1	1054	90	0	0	0	0	0	1	0	1	1	0	2	2	0
	49	Clear yellow	4.0	6.7	1068	90	0	0	0	0	0	0	0	2	1	0	3	1	0
	50	Clear yellow	3.5	6.7	1074	90	0	0	0	0	0	0	0	1	1	0	1	1	0

APPENDIX 9 - continued

Urinalysis - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	Appearance	Volume ml	pH	SG	Protein mg%	Total red. subs.	Glu-cose	Ket-ones	Bili-rubin	Urob-ilin-ogen	Nit-rite	Blood	Microscopy E	P	R	C	S	A
1F	51	Cloudy yellow	11.0	8.6	1038	20	0	0	0	0	0	0	0	0	0	0	1	0	0
	52	Pale yellow	9.5	7.8	1032	10	0	0	0	0	0	0	0	1	1	0	1	0	0
	53	Clear yellow	5.5	8.4	1050	20	0	0	0	0	0	0	0	1	1	0	2	0	0
	54	Clear yellow	5.0	6.5	1052	10	0	0	0	0	0	0	0	1	0	0	0	0	0
	55	Clear yellow	4.5	6.4	1058	10	0	0	0	0	0	0	0	1	1	0	1	0	0
	56	Clear yellow	8.5	6.7	1050	10	0	0	0	0	0	0	0	1	1	0	2	0	0
	57	Clear yellow	6.0	6.5	1044	10	0	0	0	0	0	0	0	2	1	0	2	0	0
	58	Clear yellow	4.5	6.2	1054	10	0	0	0	0	0	1	0	1	1	0	1	0	0
	59	Clear yellow	7.5	6.7	1040	10	0	0	0	0	0	1	0	1	1	0	1	0	0
	60	Clear yellow	5.0	6.8	1044	10	0	0	0	0	0	0	0	1	0	0	1	0	0
2F	61	Clear yellow	5.5	6.6	1050	10	0	0	0	0	0	1	0	1	1	0	1	0	0
	62	Clear yellow	3.0	6.2	1074	10	0	0	0	0	0	0	0	1	1	0	1	0	0
	63	Cloudy yellow	4.5	8.1	1054	20	0	0	0	0	0	0	0	1	0	0	2	0	0
	64	Clear yellow	7.0	6.7	1048	20	0	0	0	0	0	0	0	1	1	0	1	0	0
	65	Clear yellow	2.0	6.2	1072	10	0	0	0	0	0	0	0	1	0	0	1	0	0
	66	Pale yellow	7.5	7.4	1049	40	0	0	0	0	0	1	0	1	1	0	2	0	0
	67	Clear yellow	5.0	6.7	1049	10	0	0	0	0	0	0	0	1	1	0	2	0	0
	68	Clear yellow	3.0	6.2	1064	10	0	0	0	0	0	0	0	1	1	0	2	0	0
	69	Clear yellow	6.5	6.4	1050	10	0	0	0	0	0	0	0	1	3	0	1	0	0
	70	Clear yellow	5.5	6.5	1050	10	0	0	0	0	0	0	0	1	2	0	2	0	0

APPENDIX 9 - continued

Urinalysis - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	Appearance	Volume ml	pH	SG	Protein mg%	Total red. subs.	Glu-cose	Ket-ones	Bili-rubin	Urob-ilin-ogen	Nit-rite	Blood	Microscopy E	P	R	C	S	A
3F	71	Pale yellow	7.5	6.4	1040	100	0	0	0	0	0	1	0	1	1	0	1	0	0
	72	Pale yellow	6.0	6.6	1032	10	0	0	0	0	0	1	0	1	1	0	1	0	0
	73	Pale yellow	6.0	8.7	1039	30	0	0	0	0	0	0	0	2	1	0	3	0	0
	74	Pale yellow	8.5	8.8	1038	20	0	0	0	0	0	0	0	1	1	0	3	0	0
	75	Pale yellow	8.5	6.9	1031	10	0	0	0	0	0	1	0	1	1	0	3	0	0
	76	Clear yellow	6.0	6.6	1040	10	0	0	0	0	0	0	0	1	1	0	3	0	0
	77	Pale yellow	8.0	6.8	1040	10	0	0	0	0	0	0	0	1	1	0	3	0	0
	78	Clear yellow	3.0	6.4	1058	30	0	0	0	0	0	0	0	1	1	0	2	0	0
	79	Clear yellow	6.0	6.5	1048	100	0	0	0	0	0	0	0	2	1	0	3	0	0
	80	Clear yellow	5.0	6.6	1047	10	0	0	0	0	0	0	0	1	1	0	3	0	0
4F	81	Clear yellow	5.5	6.7	1048	10	0	0	0	0	0	0	0	2	0	0	2	0	0
	82	Clear yellow	5.0	6.7	1048	10	0	0	0	0	0	0	0	1	1	0	2	0	0
	83	Pale yellow	7.0	8.5	1040	100	0	0	0	0	0	1	0	1	1	0	2	0	0
	84	Clear yellow	5.0	6.5	1060	10	0	0	0	0	0	0	0	1	0	0	1	0	0
	85	Clear yellow	5.5	6.5	1052	30	0	0	0	0	0	0	0	1	0	0	2	0	0
	86	Clear yellow	2.5	6.3	1072	10	0	0	0	0	0	0	0	2	0	0	1	0	0
	87	Clear yellow	2.5	6.1	1078	10	0	0	0	0	0	0	0	1	1	0	1	0	0
	88	Clear yellow	5.0	6.6	1054	20	0	0	0	0	0	0	0	1	1	0	3	0	0
	89	Pale yellow	6.0	6.5	1044	10	0	0	0	0	0	0	0	1	0	0	2	0	0
	90	Pale yellow	8.0	7.3	1040	10	0	0	0	0	0	1	0	1	1	0	3	0	0

APPENDIX 9 - continued

Urinalysis - individual values after 12 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Control	------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Group / sex	Animal number	Appearance	Volume ml	pH	SG	Protein mg%	Total red. subs.	Glu-cose	Ket-ones	Bili-rubin	Urob-ilin-ogen	Nit-rite	Blood	Microscopy E	P	R	C	S	A
5F	91	Clear yellow	7.0	6.4	1044	10	0	0	0	0	0	0	0	0	0	0	1	0	0
	92	Clear yellow	6.0	6.5	1050	10	0	0	0	0	0	0	0	1	1	0	1	0	0
	93	Clear yellow	7.0	8.4	1040	30	0	0	0	0	0	0	0	1	1	0	3	0	0
	94	Clear yellow	5.5	7.1	1040	10	0	0	0	0	0	0	0	1	0	0	3	0	0
	95	Clear yellow	6.0	6.3	1050	10	0	0	0	0	0	0	0	2	1	0	2	0	0
	96	Clear yellow	6.5	6.7	1044	10	0	0	0	0	0	0	0	1	1	0	2	0	0
	97	Clear yellow	6.0	6.4	1044	10	0	0	0	0	0	0	0	2	1	0	1	0	0
	98	Clear yellow	4.5	6.2	1050	10	0	0	0	0	0	0	0	1	0	0	0	0	0
	99	Clear yellow	5.0	6.2	1050	10	0	0	0	0	0	0	0	1	1	0	1	0	0
	100	Clear yellow	6.0	6.5	1050	10	0	0	0	0	0	0	0	1	0	0	2	0	0

APPENDIX 10A

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
1M	1	495.7	2.20	0.009	0.023	0.021	1.45	1.85	1.87	20.4	2.35
	2	553.8	2.14	0.006	0.030	0.024	1.57	2.00	1.97	20.7	1.93
	3	561.2	2.14	0.013	0.035	0.034	1.53	1.95	2.04	22.3	2.21
	4	573.2	2.11	0.012	0.028	0.028	1.41	1.97	2.04	22.2	1.87
	5	560.1	1.73	0.008	0.022	0.021	1.45	1.62	1.70	18.8	1.71
	6	522.3	2.14	0.009	0.024	0.025	1.91	2.04	2.08	18.6	1.89
	7	509.3	2.24	0.011	0.020	0.019	1.62	1.98	1.98	15.9	2.02
	8	575.9	2.25	0.007	0.024	0.033	1.73	2.15	2.05	20.5	1.83
	9	539.4	2.07	0.011	0.032	0.028	1.74	1.91	1.99	16.4	2.43
	10	513.9	2.18	0.011	0.018	0.018	1.64	1.94	1.99	15.6	1.93

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	PROSTATE	LT SUBMAND	RT SUBMAND	SPLEEN	LT TESTIS	RT TESTIS	THYMUS	LT THYROID	RT THYROID
1M	1	495.7	0.704	0.304	0.334	0.639	1.81	1.82	0.646	0.011	0.013
	2	553.8	0.679	0.282	0.284	0.658	1.73	1.76	0.515	0.008	0.012
	3	561.2	0.855	0.357	0.338	0.832	1.77	1.74	0.604	0.013	0.017
	4	573.2	0.595	0.311	0.308	0.859	1.94	2.03	0.371	0.012	0.017
	5	560.1	0.609	0.248	0.271	0.819	1.42	1.41	0.510	0.009	0.009
	6	522.3	0.772	0.325	0.343	0.911	1.95	1.88	0.529	0.014	0.016
	7	509.3	0.750	0.283	0.279	0.662	1.67	1.67	0.343	0.011	0.013
	8	575.9	0.837	0.405	0.390	0.803	1.88	1.85	0.629	0.008	0.013
	9	539.4	0.510	0.353	0.352	0.795	1.77	1.83	0.425	0.011	0.013
	10	513.9	0.542	0.295	0.303	0.884	1.68	1.74	0.471	0.009	0.009

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
2M	11	525.3	2.07	0.012	0.021	0.024	1.41	1.80	1.88	19.8	1.81
	12	562.4	2.26	0.006	0.026	0.029	1.72	1.82	2.01	19.8	2.13
	13	497.5	2.20	0.012	0.023	0.026	1.54	1.88	1.78	16.8	2.07
	14	574.0	2.12	0.011	0.028	0.026	1.66	2.14	2.28	21.0	1.84
	15	623.1	2.19	0.007	0.029	0.028	1.88	2.16	2.22	21.8	2.62
	16	553.9	2.22	0.011	0.028	0.025	1.58	2.29	2.26	23.9	1.72
	17	538.9	2.29	0.012	0.024	0.022	1.63	1.95	2.02	20.9	1.98
	18	575.9	2.37	0.013	0.030	0.028	1.83	2.06	2.14	22.1	2.18
	19	549.6	2.05	0.009	0.024	0.023	1.45	1.69	1.87	20.1	1.77
	20	638.1	2.19	0.015	0.032	0.032	1.93	1.96	1.97	24.0	2.27

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	PROSTATE	LT SUBMAND	RT SUBMAND	SPLEEN	LT TESTIS	RT TESTIS	THYMUS	LT THYROID	RT THYROID
2M	11	525.3	0.779	0.323	0.326	0.746	1.69	1.71	0.399	0.010	0.010
	12	562.4	0.688	0.336	0.340	0.979	1.80	1.86	0.439	0.010	0.008
	13	497.5	0.539	0.252	0.283	0.729	1.79	1.76	0.486	0.007	0.006
	14	574.0	0.616	0.287	0.282	0.736	1.62	1.67	0.670	0.013	0.008
	15	623.1	0.754	0.417	0.404	1.055	2.07	2.01	0.545	0.015	0.014
	16	553.9	0.872	0.318	0.303	0.677	1.77	1.72	0.451	0.014	0.015
	17	538.9	0.676	0.311	0.319	0.853	1.62	1.70	0.396	0.017	0.019
	18	575.9	0.711	0.366	0.351	0.902	1.83	1.93	0.470	0.007	0.013
	19	549.6	0.553	0.284	0.283	0.817	1.60	1.55	0.576	0.011	0.016
	20	638.1	0.718	0.352	0.404	1.058	1.94	1.97	0.692	MISSING	0.021

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-91
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
3M	21	549.5	2.16	0.011	0.023	0.024	1.61	2.09	2.05	23.3	1.99
	22	493.0	2.09	0.007	0.020	0.017	1.61	2.09	2.14	18.6	2.03
	23	536.1	2.15	0.012	0.026	0.022	1.58	2.07	2.09	18.7	1.98
	24	588.4	2.42	0.018	0.036	0.033	1.94	2.37	2.37	22.5	2.76
	25	500.0	2.05	0.008	0.024	0.016	1.50	1.74	1.81	18.4	1.75
	26	587.7	2.20	0.010	0.026	0.022	1.63	2.20	2.36	21.9	2.03
	27	578.6	2.27	0.006	0.022	0.025	1.66	1.95	1.99	18.9	2.21
	28	571.0	2.34	0.009	0.031	0.035	1.68	1.90	2.14	18.1	2.09
	29	543.3	2.05	0.007	0.026	0.028	1.50	1.86	1.94	18.9	1.78
	30	455.5	2.13	0.009	0.034	0.035	1.48	1.88	1.88	15.2	1.87

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	PROSTATE	LT SUBMAND	RT SUBMAND	SPLEEN	LT TESTIS	RT TESTIS	THYMUS	LT THYROID	RT THYROID
3M	21	549.5	0.556	0.328	0.338	0.986	1.80	1.80	0.458	0.019	0.016
	22	493.0	0.632	0.318	0.321	0.683	1.60	1.67	0.392	0.008	0.012
	23	536.1	0.676	0.336	0.326	1.039	1.79	1.83	0.480	0.012	0.011
	24	588.4	0.636	0.394	0.402	0.835	1.92	1.92	0.462	0.016	0.014
	25	500.0	0.565	0.364	0.390	0.872	1.85	1.77	0.438	0.010	0.013
	26	587.7	1.254	0.384	0.456	0.838	1.87	1.82	0.454	0.018	0.022
	27	578.6	0.567	0.263	0.246	0.796	1.99	1.95	0.555	0.010	0.011
	28	571.0	0.593	0.283	0.300	0.980	1.96	1.98	0.542	0.013	0.009
	29	543.3	0.825	0.296	0.299	0.699	1.77	1.90	0.456	0.007	0.009
	30	455.5	0.444	0.269	0.288	0.802	1.82	1.81	0.523	0.012	0.010

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030	------	
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
4M	31	603.4	2.17	0.013	0.024	0.025	1.68	1.88	2.01	23.1	2.02
	32	502.0	2.27	0.007	0.035	0.020	1.58	1.84	2.15	19.4	1.81
	33	534.4	2.06	0.011	0.030	0.030	1.68	1.99	1.99	25.2	1.89
	34	578.7	2.14	0.011	0.020	0.021	1.72	1.98	2.18	24.5	2.19
	35	515.4	2.17	UNSUITABLE	0.029	0.030	1.54	1.89	1.94	23.3	1.71
	36	545.2	2.14	0.006	0.024	0.026	1.54	1.94	2.01	24.2	1.89
	37	498.7	2.24	0.015	0.024	0.022	1.70	1.62	1.70	17.9	2.20
	38	561.4	2.16	0.008	0.030	0.027	1.51	1.92	1.97	18.6	2.27
	39	549.3	2.07	0.013	0.034	0.033	1.55	2.00	2.13	20.2	2.21
	40	579.0	2.08	0.013	0.022	0.018	1.74	1.87	2.05	21.2	2.27

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	.....	M&B 46030		.....
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	PROSTATE	LT SUBMAND	RT SUBMAND	SPLEEN	LT TESTIS	RT TESTIS	THYMUS	LT THYROID	RT THYROID
4M	31	603.4	0.518	0.333	0.341	0.910	2.18	2.13	0.719	0.011	0.014
	32	502.0	0.936	0.267	0.237	0.603	1.82	1.78	0.448	0.011	0.016
	33	534.4	0.603	0.345	0.363	0.726	1.65	1.68	0.426	0.015	0.016
	34	578.7	0.698	0.341	0.352	0.890	2.04	1.96	0.491	0.010	0.013
	35	515.4	0.718	0.374	0.373	0.932	1.62	1.68	0.527	0.014	0.016
	36	545.2	0.524	0.320	0.307	0.904	1.70	1.70	0.578	0.017	0.021
	37	498.7	0.622	0.396	0.453	0.716	2.02	2.03	0.605	0.007	0.009
	38	561.4	0.868	0.329	0.313	0.825	1.88	1.85	0.584	0.017	0.015
	39	549.3	0.521	0.357	0.382	0.935	1.74	1.78	0.543	0.018	0.020
	40	579.0	0.570	0.310	0.342	1.056	1.74	1.80	0.694	0.021	0.017

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
5M	41	510.6	2.16	0.011	0.028	0.026	1.68	1.99	1.99	24.7	2.17
	42	567.2	1.99	0.009	0.026	0.023	1.63	2.00	2.12	29.9	1.85
	43	587.1	2.25	0.012	0.031	0.028	1.80	2.06	2.27	26.4	2.06
	44	488.2	2.19	0.009	0.029	0.016	1.52	1.80	1.92	24.4	1.77
	45	557.4	1.99	0.010	0.030	0.029	1.85	2.15	2.31	27.2	2.29
	46	591.7	2.15	0.011	0.034	0.025	1.57	2.08	2.12	34.1	2.09
	47	514.0	2.14	0.007	0.031	0.028	1.35	1.92	1.91	25.1	2.05
	48	500.9	2.20	0.008	0.033	0.031	1.41	2.01	2.09	27.0	1.76
	49	473.4	2.12	0.010	0.033	0.031	1.36	1.61	1.71	23.5	1.80
	50	600.1	2.31	0.012	0.032	0.018	1.58	2.15	2.18	29.9	2.00

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	.....	M&B 46030		.....
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	PROSTATE	LT SUBMAND	RT SUBMAND	SPLEEN	LT TESTIS	RT TESTIS	THYMUS	LT THYROID	RT THYROID
5M	41	510.6	0.707	0.310	0.343	0.875	1.94	2.00	0.476	0.020	0.019
	42	567.2	0.520	0.276	0.265	0.823	1.41	1.45	0.453	0.020	0.019
	43	587.1	1.184	0.342	0.314	0.996	2.02	1.96	0.737	0.027	0.029
	44	488.2	0.483	0.322	0.291	1.125	1.97	1.91	0.397	0.019	0.026
	45	557.4	0.571	0.284	0.319	0.945	1.92	1.86	0.589	0.026	0.023
	46	591.7	0.539	0.339	0.340	0.997	1.66	1.72	0.694	0.022	0.020
	47	514.0	0.703	0.322	0.335	0.705	1.72	1.67	0.359	0.023	0.028
	48	500.9	0.592	0.305	0.311	0.770	1.75	1.79	0.517	0.019	0.029
	49	473.4	0.410	0.337	0.314	0.697	1.82	1.84	0.531	0.031	0.039
	50	600.1	0.571	0.287	0.287	0.783	1.93	2.01	0.532	0.025	0.019

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
1F	51	363.1	2.22	0.009	0.032	0.039	1.03	1.49	1.42	13.4	1.47
	52	293.1	2.02	0.011	0.037	0.026	1.09	1.12	1.14	10.9	1.43
	53	280.0	2.00	0.013	0.029	0.031	1.05	1.14	1.22	9.6	1.61
	54	334.3	1.92	0.015	0.050	0.044	1.31	1.28	1.30	13.1	1.79
	55	298.5	1.96	0.012	0.029	0.032	1.07	0.96	1.05	9.6	1.33
	56	298.2	2.19	0.014	0.028	0.030	1.09	1.22	1.19	10.2	1.60
	57	292.8	2.05	0.015	0.037	0.034	1.06	1.19	1.24	9.7	1.50
	58	308.5	2.13	0.007	0.034	0.031	1.01	1.20	1.19	10.5	2.34
	59	310.1	2.14	0.019	0.035	0.033	1.25	1.33	1.40	11.3	1.73
	60	270.7	2.06	0.009	0.029	0.025	0.96	1.06	1.18	9.3	1.38

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	LT OVARY	RT OVARY	LT SUBMAND	RT SUBMAND	SPLEEN	THYMUS	UTERUS+CER	LT THYROID	RT THYROID
1F	51	363.1	0.051	0.065	0.255	0.270	0.656	0.499	0.42	0.008	0.011
	52	293.1	0.050	0.057	0.238	0.249	0.488	0.418	0.44	0.009	0.008
	53	280.0	0.050	0.046	0.239	0.226	0.501	0.382	0.52	0.007	0.007
	54	334.3	0.046	0.055	0.185	0.163	0.640	0.348	0.54	0.008	0.017
	55	298.5	0.035	0.051	0.192	0.217	0.500	0.465	1.17	0.010	0.016
	56	298.2	0.033	0.043	0.215	0.221	0.614	0.367	1.13	0.008	0.007
	57	292.8	0.054	0.044	0.221	0.210	0.678	0.341	0.95	0.010	0.010
	58	308.5	0.041	0.036	0.183	0.175	0.507	0.382	0.77	0.010	0.009
	59	310.1	0.088	0.068	0.203	0.204	0.793	0.401	0.72	0.008	0.008
	60	270.7	0.046	0.032	0.205	0.202	0.568	0.286	0.46	0.008	0.006

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-91
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
2F	61	311.1	1.99	0.012	0.029	0.026	0.90	1.17	1.19	11.4	1.59
	62	298.8	1.88	0.012	0.029	0.029	0.92	1.15	1.19	10.0	1.53
	63	332.0	2.01	0.012	0.042	0.040	1.07	1.17	1.24	12.4	1.52
	64	326.5	2.09	0.012	0.039	0.036	1.25	1.23	1.23	12.0	1.45
	65	334.3	1.98	0.007	0.039	0.037	1.14	1.17	1.28	11.1	1.60
	66	372.5	1.96	0.013	0.035	0.033	1.24	1.44	1.35	12.9	1.68
	67	290.8	2.16	0.011	0.036	0.036	0.98	1.17	1.20	11.4	1.48
	68	280.7	1.89	0.011	0.031	0.029	0.99	1.07	1.06	9.2	1.82
	69	342.9	2.13	0.009	0.026	0.026	0.94	1.21	1.22	11.9	1.40
	70	356.2	2.04	0.013	0.027	0.026	1.29	1.05	1.13	10.7	1.64

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	LT OVARY	RT OVARY	LT SUBMAND	RT SUBMAND	SPLEEN	THYMUS	UTERUS+CER	LT THYROID	RT THYROID
2F	61	311.1	0.044	0.040	0.201	0.210	0.461	0.245	0.90	0.012	0.011
	62	298.8	0.033	0.036	0.168	0.149	0.416	0.367	0.81	0.009	0.011
	63	332.0	0.045	0.052	0.185	0.223	0.509	0.422	0.51	0.010	0.008
	64	326.5	0.040	0.044	0.178	0.193	0.583	0.399	0.83	0.011	0.011
	65	334.3	0.057	0.076	0.200	0.189	0.514	0.351	0.44	0.009	0.013
	66	372.5	0.048	0.045	0.227	0.225	0.643	0.319	0.40	0.010	0.009
	67	290.8	0.039	0.053	0.159	0.185	0.513	0.360	0.55	0.007	0.009
	68	280.7	0.035	0.037	0.165	0.166	0.442	0.333	0.88	0.010	0.008
	69	342.9	0.034	0.043	0.233	0.181	0.649	0.347	0.36	0.008	0.008
	70	356.2	0.037	0.063	0.198	0.209	0.606	0.595	0.87	0.009	0.008

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030		------
Level (ppm) :	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
3F	71	333.6	2.16	0.018	0.029	0.036	1.11	1.28	1.34	12.7	1.65
	72	315.7	2.06	0.016	0.034	0.036	1.08	1.21	1.29	11.1	2.07
	73	301.0	1.99	0.012	0.031	0.035	1.22	1.23	1.21	11.9	2.09
	74	327.5	2.01	0.014	0.044	0.046	1.05	1.25	1.26	11.6	1.57
	75	274.8	2.07	0.014	0.037	0.037	0.96	1.05	1.16	11.6	1.52
	76	334.2	2.01	0.017	0.042	0.040	1.04	1.20	1.28	12.6	1.56
	77	358.4	2.16	0.015	0.039	0.036	1.12	1.44	1.52	15.2	1.37
	78	328.9	1.93	0.014	0.027	0.030	1.05	1.30	1.40	13.3	1.51
	79	433.0	2.12	0.011	0.043	0.044	1.34	1.49	1.51	16.4	1.87
	80	298.5	1.92	0.018	0.033	0.039	1.07	1.19	1.26	11.1	1.40

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	LT OVARY	RT OVARY	LT SUBMAND	RT SUBMAND	SPLEEN	THYMUS	UTERUS+CER	LT THYROID	RT THYROID
3F	71	333.6	0.036	0.035	0.188	0.182	0.517	0.496	0.62	0.012	0.010
	72	315.7	0.045	0.044	0.184	0.188	0.457	0.355	0.50	0.013	0.010
	73	301.0	0.035	0.037	0.167	0.189	0.578	0.452	0.49	0.009	0.009
	74	327.5	0.056	0.059	0.167	0.184	0.648	0.398	0.48	0.013	0.014
	75	274.8	0.075	0.073	0.220	0.192	0.597	0.492	0.56	0.010	0.008
	76	334.2	0.042	0.048	0.213	0.225	0.591	0.490	0.42	0.009	0.013
	77	358.4	0.057	0.066	0.215	0.205	0.530	0.612	0.43	0.007	0.009
	78	328.9	0.053	0.048	0.166	0.216	0.635	0.353	0.65	0.011	0.010
	79	433.0	0.055	0.061	0.220	0.231	0.552	0.536	0.42	0.011	0.011
	80	298.5	0.058	0.060	0.219	0.203	0.511	0.307	0.86	0.007	0.010

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-91
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
4F	81	327.2	2.21	0.016	0.052	0.048	1.15	1.25	1.38	14.3	1.83
	82	308.6	2.14	0.014	0.034	0.034	1.29	1.29	1.37	13.1	1.79
	83	327.2	2.01	0.010	0.031	0.033	1.16	1.27	1.27	13.2	1.56
	84	294.5	1.91	0.012	0.031	0.030	1.12	1.15	1.11	12.9	2.12
	85	385.3	2.17	0.012	0.051	0.048	1.35	1.45	1.45	15.4	1.93
	86	343.6	2.14	0.011	0.035	0.039	1.16	1.38	1.46	13.1	1.47
	87	312.7	2.03	0.012	0.035	0.033	1.10	1.08	1.19	11.9	1.42
	88	327.0	2.16	0.012	0.033	0.033	1.21	1.31	1.41	13.8	1.45
	89	289.3	1.97	0.010	0.031	0.026	1.07	1.13	1.16	13.2	1.69
	90	342.1	2.05	0.014	0.036	0.040	1.20	1.15	1.22	13.4	1.52

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	.....	M&B 46030		.....
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	LT OVARY	RT OVARY	LT SUBMAND	RT SUBMAND	SPLEEN	THYMUS	UTERUS+CER	LT THYROID	RT THYROID
4F	81	327.2	0.063	0.042	0.239	0.255	0.593	0.293	0.80	0.010	0.010
	82	308.6	0.042	0.043	0.202	0.197	0.512	0.291	0.51	0.014	0.017
	83	327.2	0.040	0.056	0.193	0.183	0.594	0.365	0.40	0.013	0.013
	84	294.5	0.025	0.042	0.225	0.216	0.413	0.294	0.99	0.007	0.009
	85	385.3	0.060	0.050	0.212	0.225	0.795	0.452	0.54	0.012	0.015
	86	343.6	0.072	0.063	0.222	0.249	0.610	0.534	0.54	0.013	0.014
	87	312.7	0.047	0.054	0.170	0.196	0.506	0.358	0.50	0.007	0.011
	88	327.0	0.036	0.055	0.251	0.257	0.538	0.387	0.46	0.012	0.012
	89	289.3	0.051	0.065	0.145	0.146	0.566	0.426	0.43	0.009	0.012
	90	342.1	0.044	0.048	0.225	0.217	0.537	0.408	0.77	0.010	0.012

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
5F	91	280.6	2.21	0.012	0.029	0.027	0.94	1.06	1.11	15.1	1.50
	92	289.4	1.92	0.010	0.047	0.045	1.07	1.25	1.34	16.9	1.32
	93	271.3	2.01	0.008	0.042	0.039	1.05	1.16	1.22	15.9	1.15
	94	296.8	2.06	0.012	0.038	0.032	1.11	1.11	1.23	15.0	1.42
	95	327.5	2.05	0.009	0.037	0.035	1.07	1.22	1.27	17.3	1.62
	96	299.0	2.08	0.010	0.037	0.033	0.96	1.12	1.12	16.1	1.70
	97	282.9	1.90	0.006	0.031	0.032	0.93	1.03	1.00	14.5	1.30
	98	304.5	2.11	0.014	0.041	0.034	1.00	1.16	1.29	15.9	1.42
	99	317.5	2.24	0.011	0.056	0.052	1.11	1.15	1.16	18.8	1.40
	100	310.0	2.11	0.015	0.028	0.040	1.18	1.23	1.26	20.7	1.44

APPENDIX 10A - continued.

Absolute organ weights - individual values (g) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	LT OVARY	RT OVARY	LT SUBMAND	RT SUBMAND	SPLEEN	THYMUS	UTERUS+CER	LT THYROID	RT THYROID
5F	91	280.6	0.042	0.031	0.193	0.210	0.479	0.329	0.54	0.017	0.016
	92	289.4	0.053	0.047	0.185	0.203	0.592	0.277	0.57	0.014	0.022
	93	271.3	0.043	0.051	0.170	0.174	0.458	0.314	0.38	0.011	0.016
	94	296.8	0.031	0.038	0.191	0.157	0.590	0.318	0.61	0.022	0.022
	95	327.5	0.031	0.045	0.202	0.206	0.494	0.426	0.47	0.017	0.024
	96	299.0	0.035	0.041	0.167	0.171	0.510	0.420	0.71	0.011	0.014
	97	282.9	0.041	0.056	0.176	0.162	0.430	0.515	0.36	0.012	0.012
	98	304.5	0.047	0.046	0.181	0.170	0.526	0.360	0.58	0.013	0.018
	99	317.5	0.081	0.077	0.175	0.167	0.699	0.385	0.62	0.010	0.012
	100	310.0	0.049	0.062	0.203	0.184	0.604	0.296	0.52	0.017	0.019

APPENDIX 10B

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	·····	M&B 46030		·····
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
1M	1	495.7	0.443	0.0018	0.0046	0.0042	0.293	0.374	0.377	4.12	0.474
	2	553.8	0.386	0.0011	0.0054	0.0043	0.283	0.362	0.356	3.74	0.348
	3	561.2	0.382	0.0023	0.0062	0.0061	0.272	0.347	0.364	3.98	0.394
	4	573.2	0.368	0.0021	0.0049	0.0049	0.246	0.343	0.356	3.87	0.326
	5	560.1	0.309	0.0014	0.0039	0.0037	0.259	0.290	0.304	3.35	0.306
	6	522.3	0.411	0.0017	0.0046	0.0048	0.365	0.390	0.398	3.55	0.362
	7	509.3	0.439	0.0022	0.0039	0.0037	0.319	0.388	0.389	3.13	0.396
	8	575.9	0.390	0.0012	0.0042	0.0057	0.300	0.373	0.356	3.56	0.318
	9	539.4	0.384	0.0020	0.0059	0.0052	0.323	0.355	0.369	3.04	0.451
	10	513.9	0.424	0.0021	0.0035	0.0035	0.320	0.378	0.387	3.04	0.376

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	PROSTATE	LT SUBMAND	RT SUBMAND	SPLEEN	LT TESTIS	RT TESTIS	THYMUS	LT THYROID	RT THYROID
1M	1	495.7	0.1420	0.0613	0.0674	0.1289	0.365	0.368	0.1303	0.0022	0.0026
	2	553.8	0.1226	0.0509	0.0513	0.1188	0.313	0.318	0.0930	0.0014	0.0022
	3	561.2	0.1524	0.0636	0.0602	0.1483	0.315	0.311	0.1076	0.0023	0.0030
	4	573.2	0.1038	0.0543	0.0537	0.1499	0.339	0.355	0.0647	0.0021	0.0030
	5	560.1	0.1087	0.0443	0.0484	0.1462	0.253	0.252	0.0911	0.0016	0.0016
	6	522.3	0.1478	0.0622	0.0657	0.1744	0.374	0.361	0.1013	0.0027	0.0031
	7	509.3	0.1473	0.0556	0.0548	0.1300	0.329	0.328	0.0673	0.0022	0.0026
	8	575.9	0.1453	0.0703	0.0677	0.1394	0.326	0.320	0.1092	0.0014	0.0023
	9	539.4	0.0945	0.0654	0.0653	0.1474	0.329	0.340	0.0788	0.0020	0.0024
	10	513.9	0.1055	0.0574	0.0590	0.1720	0.327	0.339	0.0917	0.0018	0.0018

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
2M	11	525.3	0.395	0.0023	0.0040	0.0046	0.269	0.343	0.357	3.76	0.345
	12	562.4	0.401	0.0011	0.0046	0.0052	0.305	0.324	0.357	3.51	0.379
	13	497.5	0.442	0.0024	0.0046	0.0052	0.310	0.378	0.358	3.37	0.416
	14	574.0	0.370	0.0019	0.0049	0.0045	0.290	0.373	0.397	3.66	0.320
	15	623.1	0.351	0.0011	0.0047	0.0045	0.301	0.346	0.356	3.50	0.420
	16	553.9	0.401	0.0020	0.0051	0.0045	0.285	0.413	0.407	4.32	0.310
	17	538.9	0.424	0.0022	0.0045	0.0041	0.302	0.362	0.376	3.87	0.367
	18	575.9	0.411	0.0023	0.0052	0.0049	0.317	0.358	0.371	3.83	0.378
	19	549.6	0.374	0.0016	0.0044	0.0042	0.264	0.308	0.340	3.66	0.323
	20	638.1	0.343	0.0024	0.0050	0.0050	0.302	0.307	0.309	3.76	0.356

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	PROSTATE	LT SUBMAND	RT SUBMAND	SPLEEN	LT TESTIS	RT TESTIS	THYMUS	LT THYROID	RT THYROID
2M	11	525.3	0.1483	0.0615	0.0621	0.1420	0.322	0.325	0.0760	0.0019	0.0019
	12	562.4	0.1223	0.0597	0.0605	0.1741	0.321	0.331	0.0781	0.0018	0.0014
	13	497.5	0.1083	0.0507	0.0569	0.1465	0.360	0.353	0.0977	0.0014	0.0012
	14	574.0	0.1073	0.0500	0.0491	0.1282	0.283	0.291	0.1167	0.0023	0.0014
	15	623.1	0.1210	0.0669	0.0648	0.1693	0.333	0.322	0.0875	0.0024	0.0022
	16	553.9	0.1574	0.0574	0.0547	0.1222	0.319	0.310	0.0814	0.0025	0.0027
	17	538.9	0.1254	0.0577	0.0592	0.1583	0.301	0.316	0.0735	0.0032	0.0035
	18	575.9	0.1235	0.0636	0.0609	0.1566	0.317	0.335	0.0816	0.0012	0.0023
	19	549.6	0.1006	0.0517	0.0515	0.1487	0.290	0.281	0.1048	0.0020	0.0029
	20	638.1	0.1125	0.0552	0.0633	0.1658	0.304	0.308	0.1084	MISSING	0.0033

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
3M	21	549.5	0.394	0.0020	0.0042	0.0044	0.293	0.381	0.374	4.24	0.361
	22	493.0	0.424	0.0014	0.0041	0.0034	0.327	0.424	0.434	3.76	0.413
	23	536.1	0.401	0.0022	0.0048	0.0041	0.295	0.386	0.390	3.48	0.369
	24	588.4	0.411	0.0031	0.0061	0.0056	0.329	0.403	0.403	3.82	0.469
	25	500.0	0.410	0.0016	0.0048	0.0032	0.301	0.349	0.362	3.68	0.349
	26	587.7	0.375	0.0017	0.0044	0.0037	0.277	0.374	0.401	3.72	0.345
	27	578.6	0.392	0.0010	0.0038	0.0043	0.288	0.338	0.344	3.26	0.381
	28	571.0	0.409	0.0016	0.0054	0.0061	0.294	0.333	0.375	3.16	0.367
	29	543.3	0.377	0.0013	0.0048	0.0052	0.276	0.343	0.357	3.47	0.327
	30	455.5	0.467	0.0020	0.0075	0.0077	0.326	0.413	0.412	3.33	0.410

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	PROSTATE	LT SUBMAND	RT SUBMAND	SPLEEN	LT TESTIS	RT TESTIS	THYMUS	LT THYROID	RT THYROID
3M	21	549.5	0.1012	0.0597	0.0615	0.1794	0.327	0.327	0.0833	0.0035	0.0029
	22	493.0	0.1282	0.0645	0.0651	0.1385	0.325	0.338	0.0795	0.0016	0.0024
	23	536.1	0.1261	0.0627	0.0608	0.1938	0.335	0.341	0.0895	0.0022	0.0021
	24	588.4	0.1081	0.0670	0.0683	0.1419	0.326	0.327	0.0785	0.0027	0.0024
	25	500.0	0.1130	0.0728	0.0780	0.1744	0.370	0.354	0.0876	0.0020	0.0026
	26	587.7	0.2134	0.0653	0.0776	0.1426	0.318	0.309	0.0773	0.0031	0.0037
	27	578.6	0.0980	0.0455	0.0425	0.1376	0.344	0.338	0.0959	0.0017	0.0019
	28	571.0	0.1039	0.0496	0.0525	0.1716	0.344	0.347	0.0949	0.0023	0.0016
	29	543.3	0.1518	0.0545	0.0550	0.1287	0.326	0.350	0.0839	0.0013	0.0017
	30	455.5	0.0975	0.0591	0.0632	0.1761	0.399	0.398	0.1148	0.0026	0.0022

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&8	46030	------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
4M	31	603.4	0.360	0.0022	0.0040	0.0041	0.278	0.311	0.332	3.83	0.335
	32	502.0	0.453	0.0014	0.0070	0.0040	0.314	0.366	0.428	3.87	0.360
	33	534.4	0.386	0.0021	0.0056	0.0056	0.315	0.372	0.373	4.72	0.354
	34	578.7	0.371	0.0019	0.0035	0.0036	0.297	0.342	0.376	4.23	0.379
	35	515.4	0.421	UNSUITABLE	0.0056	0.0058	0.299	0.366	0.376	4.52	0.331
	36	545.2	0.392	0.0011	0.0044	0.0048	0.283	0.357	0.369	4.44	0.346
	37	498.7	0.450	0.0030	0.0048	0.0044	0.341	0.325	0.341	3.59	0.440
	38	561.4	0.385	0.0014	0.0053	0.0048	0.269	0.341	0.351	3.32	0.405
	39	549.3	0.377	0.0024	0.0062	0.0060	0.282	0.364	0.387	3.68	0.403
	40	579.0	0.359	0.0022	0.0038	0.0031	0.301	0.322	0.355	3.66	0.392

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	PROSTATE	LT SUBMAND	RT SUBMAND	SPLEEN	LT TESTIS	RT TESTIS	THYMUS	LT THYROID	RT THYROID
4M	31	603.4	0.0858	0.0552	0.0565	0.1508	0.361	0.352	0.1192	0.0018	0.0023
	32	502.0	0.1865	0.0532	0.0472	0.1201	0.363	0.355	0.0892	0.0022	0.0032
	33	534.4	0.1128	0.0646	0.0679	0.1359	0.309	0.315	0.0797	0.0028	0.0030
	34	578.7	0.1206	0.0589	0.0608	0.1538	0.353	0.340	0.0848	0.0017	0.0022
	35	515.4	0.1393	0.0726	0.0724	0.1808	0.314	0.326	0.1023	0.0027	0.0031
	36	545.2	0.0961	0.0587	0.0563	0.1658	0.312	0.313	0.1060	0.0031	0.0039
	37	498.7	0.1247	0.0794	0.0908	0.1436	0.406	0.406	0.1213	0.0014	0.0018
	38	561.4	0.1546	0.0586	0.0558	0.1470	0.335	0.330	0.1040	0.0030	0.0027
	39	549.3	0.0948	0.0650	0.0695	0.1702	0.317	0.323	0.0989	0.0033	0.0036
	40	579.0	0.0984	0.0535	0.0591	0.1824	0.300	0.312	0.1199	0.0036	0.0029

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
5M	41	510.6	0.424	0.0022	0.0055	0.0051	0.328	0.389	0.390	4.84	0.425
	42	567.2	0.350	0.0016	0.0046	0.0041	0.288	0.353	0.374	5.27	0.326
	43	587.1	0.383	0.0020	0.0053	0.0048	0.307	0.351	0.386	4.50	0.351
	44	488.2	0.448	0.0018	0.0059	0.0033	0.312	0.368	0.393	5.00	0.362
	45	557.4	0.356	0.0018	0.0054	0.0052	0.332	0.385	0.414	4.88	0.411
	46	591.7	0.364	0.0019	0.0057	0.0042	0.265	0.351	0.358	5.77	0.354
	47	514.0	0.415	0.0014	0.0060	0.0054	0.263	0.373	0.372	4.87	0.400
	48	500.9	0.439	0.0016	0.0066	0.0062	0.282	0.400	0.417	5.39	0.350
	49	473.4	0.448	0.0021	0.0070	0.0065	0.287	0.340	0.362	4.96	0.380
	50	600.1	0.385	0.0020	0.0053	0.0030	0.263	0.358	0.363	4.98	0.333

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030	------	
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	PROSTATE	LT SUBMAND	RT SUBMAND	SPLEEN	LT TESTIS	RT TESTIS	THYMUS	LT THYROID	RT THYROID
5M	41	510.6	0.1385	0.0607	0.0672	0.1714	0.380	0.391	0.0932	0.0039	0.0037
	42	567.2	0.0917	0.0487	0.0467	0.1451	0.248	0.256	0.0799	0.0035	0.0033
	43	587.1	0.2017	0.0583	0.0535	0.1696	0.343	0.335	0.1255	0.0046	0.0049
	44	488.2	0.0989	0.0660	0.0596	0.2304	0.404	0.391	0.0813	0.0039	0.0053
	45	557.4	0.1024	0.0510	0.0572	0.1695	0.345	0.334	0.1057	0.0047	0.0041
	46	591.7	0.0911	0.0573	0.0575	0.1685	0.280	0.291	0.1173	0.0037	0.0034
	47	514.0	0.1368	0.0626	0.0652	0.1372	0.334	0.326	0.0698	0.0045	0.0054
	48	500.9	0.1182	0.0609	0.0621	0.1537	0.349	0.357	0.1032	0.0038	0.0058
	49	473.4	0.0866	0.0712	0.0663	0.1472	0.384	0.389	0.1122	0.0065	0.0082
	50	600.1	0.0952	0.0478	0.0478	0.1305	0.322	0.334	0.0887	0.0042	0.0032

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030		------
Level (ppm) :	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
1F	51	363.1	0.612	0.0025	0.0088	0.0107	0.284	0.410	0.392	3.70	0.405
	52	293.1	0.689	0.0038	0.0126	0.0089	0.371	0.383	0.388	3.72	0.489
	53	280.0	0.714	0.0046	0.0104	0.0111	0.376	0.406	0.434	3.43	0.574
	54	334.3	0.573	0.0045	0.0150	0.0132	0.393	0.384	0.388	3.92	0.536
	55	298.5	0.658	0.0040	0.0097	0.0107	0.357	0.322	0.353	3.21	0.446
	56	298.2	0.735	0.0047	0.0094	0.0101	0.366	0.408	0.398	3.43	0.536
	57	292.8	0.702	0.0051	0.0126	0.0116	0.361	0.406	0.425	3.30	0.512
	58	308.5	0.689	0.0023	0.0110	0.0100	0.327	0.390	0.387	3.41	0.758
	59	310.1	0.691	0.0061	0.0113	0.0106	0.403	0.427	0.451	3.65	0.559
	60	270.7	0.760	0.0033	0.0107	0.0092	0.355	0.391	0.437	3.43	0.511

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	LT OVARY	RT OVARY	LT SUBMAND	RT SUBMAND	SPLEEN	THYMUS	UTERUS+CER	LT THYROID	RT THYROID
1F	51	363.1	0.0140	0.0179	0.0702	0.0744	0.1807	0.1374	0.115	0.0022	0.0030
	52	293.1	0.0171	0.0194	0.0812	0.0850	0.1665	0.1426	0.152	0.0031	0.0027
	53	280.0	0.0179	0.0164	0.0854	0.0807	0.1789	0.1364	0.188	0.0025	0.0025
	54	334.3	0.0138	0.0165	0.0553	0.0488	0.1914	0.1041	0.162	0.0024	0.0051
	55	298.5	0.0117	0.0171	0.0643	0.0727	0.1675	0.1558	0.393	0.0034	0.0054
	56	298.2	0.0111	0.0144	0.0721	0.0741	0.2059	0.1231	0.379	0.0027	0.0023
	57	292.8	0.0184	0.0150	0.0755	0.0717	0.2316	0.1165	0.324	0.0034	0.0034
	58	308.5	0.0133	0.0117	0.0593	0.0567	0.1643	0.1238	0.249	0.0032	0.0029
	59	310.1	0.0284	0.0219	0.0655	0.0658	0.2557	0.1293	0.232	0.0026	0.0026
	60	270.7	0.0170	0.0118	0.0757	0.0746	0.2098	0.1057	0.169	0.0030	0.0022

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
2F	61	311.1	0.639	0.0039	0.0093	0.0084	0.289	0.378	0.383	3.66	0.510
	62	298.8	0.628	0.0040	0.0097	0.0097	0.307	0.384	0.397	3.34	0.513
	63	332.0	0.607	0.0036	0.0127	0.0120	0.323	0.352	0.374	3.75	0.458
	64	326.5	0.639	0.0037	0.0119	0.0110	0.383	0.377	0.377	3.68	0.445
	65	334.3	0.593	0.0021	0.0117	0.0111	0.341	0.351	0.383	3.31	0.479
	66	372.5	0.525	0.0035	0.0094	0.0089	0.334	0.386	0.363	3.45	0.452
	67	290.8	0.743	0.0038	0.0124	0.0124	0.336	0.403	0.413	3.91	0.510
	68	280.7	0.674	0.0039	0.0110	0.0103	0.353	0.380	0.377	3.27	0.647
	69	342.9	0.621	0.0026	0.0076	0.0076	0.274	0.353	0.357	3.47	0.410
	70	356.2	0.572	0.0036	0.0076	0.0073	0.361	0.295	0.316	3.00	0.461

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	LT OVARY	RT OVARY	LT SUBMAND	RT SUBMAND	SPLEEN	THYMUS	UTERUS+CER	LT THYROID	RT THYROID
2F	61	311.1	0.0141	0.0129	0.0646	0.0675	0.1482	0.0788	0.290	0.0039	0.0035
	62	298.8	0.0110	0.0120	0.0562	0.0499	0.1392	0.1228	0.271	0.0030	0.0037
	63	332.0	0.0136	0.0157	0.0557	0.0672	0.1533	0.1271	0.154	0.0030	0.0024
	64	326.5	0.0123	0.0135	0.0545	0.0591	0.1786	0.1222	0.254	0.0034	0.0034
	65	334.3	0.0171	0.0227	0.0598	0.0565	0.1538	0.1050	0.131	0.0027	0.0039
	66	372.5	0.0129	0.0121	0.0609	0.0604	0.1726	0.0856	0.107	0.0027	0.0024
	67	290.8	0.0134	0.0182	0.0547	0.0636	0.1764	0.1238	0.190	0.0024	0.0031
	68	280.7	0.0125	0.0132	0.0588	0.0591	0.1575	0.1186	0.312	0.0036	0.0029
	69	342.9	0.0099	0.0125	0.0679	0.0528	0.1893	0.1012	0.104	0.0023	0.0023
	70	356.2	0.0104	0.0177	0.0556	0.0587	0.1701	0.1670	0.243	0.0025	0.0022

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
3F	71	333.6	0.646	0.0054	0.0087	0.0108	0.332	0.383	0.401	3.80	0.495
	72	315.7	0.653	0.0051	0.0108	0.0114	0.342	0.382	0.408	3.53	0.656
	73	301.0	0.661	0.0040	0.0103	0.0116	0.407	0.409	0.401	3.94	0.695
	74	327.5	0.615	0.0043	0.0134	0.0140	0.322	0.381	0.383	3.55	0.480
	75	274.8	0.755	0.0051	0.0135	0.0135	0.350	0.384	0.421	4.21	0.552
	76	334.2	0.601	0.0051	0.0126	0.0120	0.312	0.359	0.383	3.76	0.466
	77	358.4	0.604	0.0042	0.0109	0.0100	0.311	0.402	0.423	4.24	0.383
	78	328.9	0.586	0.0043	0.0082	0.0091	0.318	0.396	0.427	4.05	0.459
	79	433.0	0.491	0.0025	0.0099	0.0102	0.309	0.345	0.348	3.79	0.432
	80	298.5	0.645	0.0060	0.0111	0.0131	0.358	0.399	0.423	3.72	0.469

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	LT OVARY	RT OVARY	LT SUBMAND	RT SUBMAND	SPLEEN	THYMUS	UTERUS+CER	LT THYROID	RT THYROID
3F	71	333.6	0.0108	0.0105	0.0564	0.0546	0.1550	0.1487	0.184	0.0036	0.0030
	72	315.7	0.0143	0.0139	0.0583	0.0596	0.1448	0.1124	0.159	0.0041	0.0032
	73	301.0	0.0116	0.0123	0.0555	0.0628	0.1920	0.1502	0.162	0.0030	0.0030
	74	327.5	0.0171	0.0180	0.0510	0.0562	0.1979	0.1215	0.146	0.0040	0.0043
	75	274.8	0.0273	0.0266	0.0801	0.0699	0.2172	0.1790	0.205	0.0036	0.0029
	76	334.2	0.0126	0.0144	0.0637	0.0673	0.1768	0.1466	0.125	0.0027	0.0039
	77	358.4	0.0159	0.0184	0.0600	0.0572	0.1479	0.1708	0.119	0.0020	0.0025
	78	328.9	0.0161	0.0146	0.0505	0.0657	0.1931	0.1073	0.197	0.0033	0.0030
	79	433.0	0.0127	0.0141	0.0508	0.0533	0.1275	0.1238	0.097	0.0025	0.0025
	80	298.5	0.0194	0.0201	0.0734	0.0680	0.1712	0.1028	0.288	0.0023	0.0034

APPENDIX 10B · continued.

Organ weights relative to bodyweight · individual values (%) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
4F	81	327.2	0.675	0.0049	0.0159	0.0147	0.352	0.383	0.421	4.36	0.558
	82	308.6	0.694	0.0045	0.0110	0.0110	0.418	0.419	0.443	4.26	0.579
	83	327.2	0.613	0.0031	0.0095	0.0101	0.353	0.387	0.389	4.03	0.477
	84	294.5	0.649	0.0041	0.0105	0.0102	0.381	0.389	0.378	4.37	0.719
	85	385.3	0.563	0.0031	0.0132	0.0125	0.349	0.375	0.376	4.00	0.502
	86	343.6	0.623	0.0032	0.0102	0.0114	0.339	0.400	0.425	3.81	0.429
	87	312.7	0.649	0.0038	0.0112	0.0106	0.353	0.344	0.381	3.79	0.454
	88	327.0	0.661	0.0037	0.0101	0.0101	0.369	0.401	0.433	4.23	0.443
	89	289.3	0.681	0.0035	0.0107	0.0090	0.371	0.389	0.401	4.55	0.585
	90	342.1	0.599	0.0041	0.0105	0.0117	0.352	0.337	0.355	3.91	0.443

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

GROUP	ANIMAL	TERMINAL BODY WT (g)	LT OVARY	RT OVARY	LT SUBMAND	RT SUBMAND	SPLEEN	THYMUS	UTERUS+CER	LT THYROID	RT THYROID
4F	81	327.2	0.0193	0.0128	0.0730	0.0779	0.1812	0.0895	0.245	0.0031	0.0031
	82	308.6	0.0136	0.0139	0.0655	0.0638	0.1659	0.0943	0.167	0.0045	0.0055
	83	327.2	0.0122	0.0171	0.0590	0.0559	0.1815	0.1116	0.122	0.0040	0.0040
	84	294.5	0.0085	0.0143	0.0764	0.0733	0.1402	0.0998	0.336	0.0024	0.0031
	85	385.3	0.0156	0.0130	0.0550	0.0584	0.2063	0.1173	0.141	0.0031	0.0039
	86	343.6	0.0210	0.0183	0.0646	0.0725	0.1775	0.1554	0.158	0.0038	0.0041
	87	312.7	0.0150	0.0173	0.0544	0.0627	0.1618	0.1145	0.159	0.0022	0.0035
	88	327.0	0.0110	0.0168	0.0768	0.0786	0.1645	0.1183	0.142	0.0037	0.0037
	89	289.3	0.0176	0.0225	0.0501	0.0505	0.1956	0.1473	0.149	0.0031	0.0041
	90	342.1	0.0129	0.0140	0.0658	0.0634	0.1570	0.1193	0.225	0.0029	0.0035

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	PITUITARY	LT ADRENAL	RT ADRENAL	HEART	LT KIDNEY	RT KIDNEY	LIVER	LUNGS
5f	91	280.6	0.788	0.0043	0.0103	0.0096	0.334	0.377	0.397	5.39	0.533
	92	289.4	0.664	0.0035	0.0162	0.0155	0.368	0.432	0.463	5.84	0.457
	93	271.3	0.742	0.0029	0.0155	0.0144	0.387	0.429	0.451	5.87	0.425
	94	296.8	0.694	0.0040	0.0128	0.0108	0.373	0.374	0.416	5.04	0.480
	95	327.5	0.626	0.0027	0.0113	0.0107	0.328	0.372	0.387	5.27	0.494
	96	299.0	0.696	0.0033	0.0124	0.0110	0.320	0.375	0.375	5.37	0.569
	97	282.9	0.673	0.0021	0.0110	0.0113	0.330	0.363	0.354	5.12	0.460
	98	304.5	0.693	0.0046	0.0135	0.0112	0.329	0.382	0.425	5.21	0.466
	99	317.5	0.707	0.0035	0.0176	0.0164	0.348	0.361	0.365	5.92	0.441
	100	310.0	0.680	0.0048	0.0090	0.0129	0.380	0.397	0.408	6.68	0.466

APPENDIX 10B - continued.

Organ weights relative to bodyweight - individual values (%) for animals killed after 13 weeks of the treatment period.

Printed: 21-MAR-9
Page: 2

Schedule number: RHA 298

Group	1	2	3	4	5
Compound	Control	-------	M&B 46030		------
Level (ppm)	0	1	5	30	300

GROUP	ANIMAL	TERMINAL BODY WT (g)	LT OVARY	RT OVARY	LT SUBMAND	RT SUBMAND	SPLEEN	THYMUS	UTERUS+CER	LT THYROID	RT THYROID
5F	91	280.6	0.0150	0.0110	0.0688	0.0748	0.1707	0.1172	0.191	0.0061	0.0057
	92	289.4	0.0183	0.0162	0.0639	0.0701	0.2046	0.0957	0.198	0.0048	0.0076
	93	271.3	0.0158	0.0188	0.0627	0.0641	0.1688	0.1157	0.140	0.0041	0.0059
	94	296.8	0.0104	0.0128	0.0644	0.0529	0.1988	0.1071	0.205	0.0074	0.0074
	95	327.5	0.0095	0.0137	0.0617	0.0629	0.1508	0.1301	0.144	0.0052	0.0073
	96	299.0	0.0117	0.0137	0.0559	0.0572	0.1706	0.1405	0.236	0.0037	0.0047
	97	282.9	0.0145	0.0198	0.0622	0.0573	0.1520	0.1820	0.129	0.0042	0.0042
	98	304.5	0.0154	0.0151	0.0594	0.0558	0.1727	0.1182	0.190	0.0043	0.0059
	99	317.5	0.0255	0.0243	0.0551	0.0526	0.2202	0.1213	0.194	0.0031	0.0038
	100	310.0	0.0158	0.0200	0.0655	0.0594	0.1948	0.0955	0.169	0.0055	0.0061

APPENDIX 11

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Printed: 21-MAR-9
Page: 1

Schedule number: RHA 298

ANIMAL NUMBER: 0001 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 495.7 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LEFT PARATHYROID : >TISSUE MISSING
	LEFT THYROID : -LYMPHOCYTIC INFILTRATION,-MINIMAL

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 · continued.

Macropathology and histopathology · individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	·····	M&B 46030	·····	
Level (ppm)	:	0	1	5	30	300

Printed: 21·MAR·9
Page: 2

Schedule number: RHA 298

ANIMAL NUMBER: 0002 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 553.8 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
L N MANDIBULAR : ·APPEAR LARGE; <7X4X2MM. ·DARK	L N MANDIBULAR : ·PARAFOLLICULAR HYPERPLASIA,·MINIMAL LIVER X 2 : ·CONGESTION,·MINIMAL LUNGS X 2 : ·INTERSTITIAL PNEUMONITIS,·MODERATE

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	.....	M&B 46030	.....	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0003 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 561.2 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
L N MANDIBULAR : -DARK	L N MANDIBULAR : -HAEMORRHAGE,-MINIMAL LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT LIVER X 2 : -CONGESTION,-SLIGHT RIGHT PARATHYROID : >TISSUE MISSING

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0004 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 573.2 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	L N MESENTERIC : -FOLLICULAR HYPERPLASIA,-SLIGHT PROSTATE : -CHRONIC INFLAMMATION,-MODERATE

SKIN, OTHER :
-NON-SPECIFIC STAINING; BROWN STAINING ON DORSAL CERVICAL REGION.

APPENDIX 11 · continued.

Macropathology and histopathology · individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	·····	M&B 46030	·····	
Level (ppm) :	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0005 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 560.1 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

EYE RT :
·ABNORMAL SHAPE; APPEARS LARGE.
·DARK

HISTOPATHOLOGY

EYE RT :
·DISRUPTION/FIBROSIS,·PRESENT

LIVER OIL RED O :
·CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,·SLIGHT

LIVER X 2 :
·CONGESTION,·SLIGHT

RIGHT PARATHYROID :
>TISSUE MISSING

LEFT THYROID :
·HYPERTROPHY OF FOLLICULAR EPITHELIUM,·SLIGHT
·FOLLICULAR CELL HYPERPLASIA,·MINIMAL

RIGHT THYROID :
·HYPERTROPHY OF FOLLICULAR EPITHELIUM,·MINIMAL

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0006 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 522.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

SKIN, OTHER :
-NON-SPECIFIC STAINING; DARK RED STAINING ON LEFT PINNA.

HISTOPATHOLOGY

RIGHT KIDNEY :
-DILATED CORTICAL TUBULES,-MINIMAL, FOCAL

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT

LEFT THYROID :
-HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

RIGHT THYROID :
-HYPERTROPHY OF FOLLICULAR EPITHELIUM,-MINIMAL

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Printed: 21-MAR-9
Page: 7

Schedule number: RHA 298

ANIMAL NUMBER: 0007 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 509.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER X 2 : -ARTERITIS,-MINIMAL LEFT PARATHYROID : >TISSUE MISSING RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT -FOLLICULAR CELL HYPERPLASIA,-SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0008 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 575.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER X 2 : -CONGESTION,-SLIGHT

SKIN, OTHER :
-HAIRLOSS MODERATE; ON HEAD.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 9

Schedule number: RHA 298

ANIMAL NUMBER: 0009 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 539.4 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

HISTOPATHOLOGY

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT

LIVER X 2 :
-FOCI OF LEUCOCYTES WITHIN SINUSOIDS,-MINIMAL
-ARTERITIS,-SLIGHT

LEFT PARATHYROID :
>TISSUE MISSING

RIGHT PARATHYROID :
>TISSUE MISSING

SKIN, OTHER :
-FACIAL STAINING; SLIGHT BROWN STAINING ON HEAD.
-NON-SPECIFIC STAINING; BROWN STAINING ON DORSAL CERVICAL REGION.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 10

Schedule number: RHA 298

ANIMAL NUMBER: 0010 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 513.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	PROSTATE : -CHRONIC INFLAMMATION,-MODERATE

SKIN, OTHER :
-HAIRLOSS MODERATE; ON HEAD.
-NON-SPECIFIC STAINING; BROWN STAINING ON CERVICAL REGION.
-ENCRUSTATION(S); OCCASIONAL PUNCTATE, DARK AREAS, ADJACENT TO RIGHT EYE.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0011 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 525.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
	LIVER X 2 : -CONGESTION,-SLIGHT
	LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-MARKED

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0012 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 562.4 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER X 2 : -CONGESTION,-SLIGHT
	LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-MODERATE
SKIN, OTHER : -HAIRLOSS MODERATE; ON HEAD.	
STOMACH X 2 : -THICKENED WALL; GLANDULAR MUCOSA.	STOMACH X 2 : >NO SIGNIFICANT LESION

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Printed: 21-MAR-9
Page: 13

Schedule number: RHA 298

ANIMAL NUMBER: 0013 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 497.5 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O :
	-PANACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 14

Schedule number: RHA 298

ANIMAL NUMBER: 0014 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 574.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
	LEFT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0015 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 623.1 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LUNGS X 2 : -FOCAL ALVEOLAR WALL EPITHELIALISATION,-MINIMAL RIGHT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0016 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 553.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
L N MANDIBULAR : -DARK	L N MANDIBULAR : -FOLLICULAR HYPERPLASIA,-MINIMAL LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-MINIMAL RIGHT PARATHYROID : >TISSUE MISSING

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0017 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 538.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	RIGHT PARATHYROID : >TISSUE MISSING RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-MINIMAL

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0018 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 575.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

HISTOPATHOLOGY

SKIN, OTHER :
-HAIRLOSS MODERATE; ON FORELIMBS AND RIGHT HINDLIMB.

*** ANIMAL HAS NO MICROSCOPIC FINDINGS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0019 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 549.6 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -PANACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0020 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 638.1 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

HISTOPATHOLOGY

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE

LEFT PARATHYROID :
>TISSUE MISSING

RIGHT PARATHYROID :
>TISSUE MISSING

LEFT THYROID :
>TISSUE MISSING

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0021 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 549.5 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
	LIVER X 2 : -CONGESTION,-SLIGHT

SKIN, OTHER :
-HAIRLOSS MODERATE; ON FORELIMBS.
-FACIAL STAINING; BROWN STAINING ON HEAD.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-M
Page: 22

Schedule number: RHA

ANIMAL NUMBER: 0022 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 493.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER X 2 : -ARTERITIS,-MINIMAL RIGHT PARATHYROID : >TISSUE MISSING

THYMUS :
-AREA(S) OF CHANGE; -OCCASIONAL PUNCTATE, DARK FOCI.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 2

ANIMAL NUMBER: 0023 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 536.1 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

*** ANIMAL HAS NO MICROSCOPIC FINDINGS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 2

ANIMAL NUMBER: 0024 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 588.4 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER X 2 : -CONGESTION, SLIGHT -ARTERITIS, SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 2

ANIMAL NUMBER: 0025 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 500.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-SLIGHT LEFT PARATHYROID : >TISSUE MISSING

SKIN, OTHER :
-NON-SPECIFIC STAINING; BROWN STAINING ON DORSAL CERVICAL REGION.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	.....	M&B 46030	.....	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA

ANIMAL NUMBER: 0026 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 587.7 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT LIVER X 2 : -CONGESTION,-SLIGHT -ARTERITIS,-MINIMAL LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-MODERATE RIGHT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 2

ANIMAL NUMBER: 0027 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 578.6 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT RIGHT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0028 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 571.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	RIGHT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0029 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 543.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
L N MANDIBULAR : -DARK	L N MANDIBULAR : -FOLLICULAR HYPERPLASIA,-MINIMAL LEFT PARATHYROID : >TISSUE MISSING RIGHT PARATHYROID : >TISSUE MISSING

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0030 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 455.5 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LEFT PARATHYROID :
	>TISSUE MISSING

SKIN, OTHER :
-HAIRLOSS MODERATE; ON HEAD.
-TRAUMA; SCAR TISSUE ON LEFT LOWER LIP.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0031 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 603.4 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-MINIMAL

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0032 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 502.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
RIGHT KIDNEY : -CYSTIC; MULTIPLE PALE CYSTS, <4MM DIA., ON CAUDAL REGION.	RIGHT KIDNEY : -PAPILLARY CYST(S),-SLIGHT, MULTI-FOCAL -CORTICAL CYST(S),-MODERATE, MULTI-FOCAL -MEDULLARY CYST(S),-MODERATE LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-----	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0033 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 534.4 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : ·PANACINAR HEPATOCYTIC FATTY VACUOLATION,·SLIGHT RIGHT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0034 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 578.7 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

RIGHT KIDNEY :
-HYDRONEPHROSIS; MODERATE.

HISTOPATHOLOGY

RIGHT KIDNEY :
-HYDRONEPHROSIS, SLIGHT

RIGHT PARATHYROID :
>TISSUE MISSING

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0035 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 515.4 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
L N MANDIBULAR : -DARK	L N MANDIBULAR : >NO SIGNIFICANT LESION
	LIVER X 2 : -CONGESTION,-MINIMAL -FOCI OF LEUCOCYTES WITHIN SINUSOIDS,-MINIMAL
	LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-SLIGHT
	RIGHT PARATHYROID : >TISSUE MISSING
PITUITARY : -MASS(ES); SOFT, PUNCTATE, PALE MASS, IN ANTERIOR REGION.	PITUITARY : >NO SIGNIFICANT LESION
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT
	RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	.....	M&B 46030	.....	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0036 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 545.2 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
	LIVER X 2 : -CONGESTION,-MINIMAL
TAIL : -AREA(S) OF CHANGE; TIP DARK.	
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-MINIMAL
	RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-MINIMAL

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0037 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 498.7 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
	RIGHT PARATHYROID : >TISSUE MISSING

SKIN, OTHER :
-HAIRLOSS MODERATE; ON RIGHT FORELIMB.

TAIL :
-AREA(S) OF CHANGE; TIP DARK.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0038 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 561.4 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT
	RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Printed: 21-MAR-9
Page: 39

Schedule number: RHA 298

ANIMAL NUMBER: 0039 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 549.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION, MODERATE
TAIL : -AREA(S) OF CHANGE; TIP DARK. -ENCRUSTATION(S); OCCASIONAL FIRM, PUNCTATE, DARK AREAS, ON TIP.	
	RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM, MINIMAL

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0040 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 579.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
	LIVER X 2 : -CONGESTION,-MINIMAL
TAIL : -AREA(S) OF CHANGE; TIP DARK.	
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT -FOLLICULAR CELL HYPERPLASIA,-MINIMAL

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0041 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 510.6 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

HISTOPATHOLOGY

LIVER OIL RED O :
-PANACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT

LIVER X 2 :
-CONGESTION,-SLIGHT

LUNGS X 2 :
-INTERSTITIAL PNEUMONITIS,-SLIGHT

SKIN, OTHER :
-HAIRLOSS MODERATE; ON FORELIMBS.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0042 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 567.2 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	HEART, VENTRICLE : -CHRONIC MYOCARDITIS,-MINIMAL
	LIVER OIL RED O : -PANACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
	LIVER X 2 : -PANACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT -CONGESTION,-MINIMAL
	LEFT PARATHYROID : >TISSUE MISSING
	RIGHT PARATHYROID : >TISSUE MISSING
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0043 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 587.1 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
L N MANDIBULAR : -APPEAR LARGE; <10X5X4MM.	L N MANDIBULAR : >NO SIGNIFICANT LESION
	LIVER OIL RED O : -PANACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE
SKIN, OTHER : -HAIRLOSS MODERATE; ON HEAD.	
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT -FOLLICULAR CELL HYPERPLASIA,-SLIGHT

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0044 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 488.2 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY

L N MANDIBULAR :
-DARK

SKIN, OTHER :
-FACIAL STAINING; BROWN STAINING AROUND LEFT EYE AND ON NARES.

HISTOPATHOLOGY

L N MANDIBULAR :
-PARAFOLLICULAR HYPERPLASIA,-SLIGHT

LIVER OIL RED O :
-PANACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT

LIVER X 2 :
-CONGESTION,-MINIMAL

LUNGS X 2 :
-INTERSTITIAL PNEUMONITIS,-SLIGHT

RECTUM :
-LYMPHOID HYPERPLASIA,-SLIGHT

STOMACH X 2 :
-GLANDULAR REGION: CHRONIC INFLAMMATION,-MINIMAL

LEFT THYROID :
-HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

RIGHT THYROID :
-HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

APPENDIX 11 · continued.

Macropathology and histopathology · individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	·····	M&B 46030	·····	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0045 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 19-FEB-90 STUDY DAY OF DEATH: 92 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 557.4 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

SKIN, OTHER :
·FACIAL STAINING; BROWN STAINING ON NARES.

HISTOPATHOLOGY

L N MANDIBULAR :
-HAEMORRHAGE,·SLIGHT
-PARAFOLLICULAR HYPERPLASIA,·SLIGHT

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,·SLIGHT

LIVER X 2 :
-FOCI OF LEUCOCYTES WITHIN SINUSOIDS,·SLIGHT
-ARTERITIS,·MINIMAL

RIGHT PARATHYROID :
>TISSUE MISSING

RECTUM :
-LYMPHOID HYPERPLASIA,·SLIGHT

LEFT THYROID :
-HYPERTROPHY OF FOLLICULAR EPITHELIUM,·SLIGHT
-FOLLICULAR CELL HYPERPLASIA,·SLIGHT

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0046 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 591.7 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY

HISTOPATHOLOGY

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE

LIVER X 2 :
-CONGESTION,-SLIGHT

PANCREAS :
-ACINAR ATROPHY WITH CHRONIC INFLAMMATION,-SLIGHT

LEFT THYROID :
-HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT
-FOLLICULAR CELL HYPERPLASIA,-SLIGHT

RIGHT THYROID :
-HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT
-FOLLICULAR CELL HYPERPLASIA,-SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 47

Schedule number: RHA 298

ANIMAL NUMBER: 0047 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 514.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT -FOLLICULAR CELL HYPERPLASIA,-MODERATE RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT -FOLLICULAR CELL HYPERPLASIA,-MODERATE

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 48

Schedule number: RHA 298

ANIMAL NUMBER: 0048 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 500.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -PANACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE
	LEFT PARATHYROID : >TISSUE MISSING
SKIN, OTHER : -FACIAL STAINING; BROWN STAINING ON HEAD EXTENDING BETWEEN PINNAE.	
	RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT -FOLLICULAR CELL HYPERPLASIA,-SLIGHT

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0049 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 473.4 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY

EYE RT :
- ABNORMAL SHAPE; APPEARS LARGE, 9X9X8MM.
- OPAQUE
- EXOPHTHALMIC

RIGHT HARDERIAN GLAND :
- EXCESS FLUID; ORBIT CONTAINS CLOTTED BLOOD.

HISTOPATHOLOGY

EYE RT :
- DISRUPTION/FIBROSIS, PRESENT

RIGHT HARDERIAN GLAND :
> TISSUE MISSING

LEFT KIDNEY :
- MEDULLARY CYST(S), SLIGHT

LIVER OIL RED O :
- PANACINAR HEPATOCYTIC FATTY VACUOLATION, MARKED

LIVER X 2 :
- PANACINAR HEPATOCYTIC FATTY VACUOLATION, SLIGHT
- CONGESTION, SLIGHT

LEFT PARATHYROID :
> TISSUE MISSING

RIGHT PARATHYROID :
> TISSUE MISSING

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0050 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 600.1 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

HISTOPATHOLOGY

LIVER OIL RED O :
-PANACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT

LIVER X 2 :
-CONGESTION,-SLIGHT
-FOCI OF LEUCOCYTES WITHIN SINUSOIDS,-MINIMAL

LEFT PARATHYROID :
>TISSUE MISSING

LEFT THYROID :
-HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT
-FOLLICULAR CELL HYPERPLASIA,-SLIGHT

RIGHT THYROID :
-HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT
-FOLLICULAR CELL HYPERPLASIA,-SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0051 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 363.1 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

HISTOPATHOLOGY

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE

UTERINE CERVIX :
>TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0052 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 293.1 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MARKED UTERINE CERVIX : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030		------
Level (ppm) :	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0053 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 280.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

HISTOPATHOLOGY

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION, MARKED

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 54

Schedule number: RHA 298

ANIMAL NUMBER: 0054 SEX: FEMALE DOSE GROUP: 1 . SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 334.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	AORTA : >TISSUE MISSING
	RIGHT KIDNEY : -CORTICAL MINERALISATION,-MINIMAL
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE
	LEFT OPTIC NERVE : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0055 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 298.5 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	BRAIN X 3 : -MICROCAVITATION OF WHITE MATTER,-SLIGHT
	LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-SLIGHT
	LEFT PARATHYROID : >TISSUE MISSING
UTERUS : -FLUID DISTENSION; 4MM DIA.	UTERUS : -POLYLUMINAL DILATATION,-SLIGHT

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0056 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 298.2 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-SLIGHT
	RIGHT PARATHYROID : >TISSUE MISSING
UTERUS : -FLUID DISTENSION; <5MM DIA.	UTERUS : >NO SIGNIFICANT LESION

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0057 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 292.8 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-MINIMAL
	RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-MINIMAL
UTERUS : -FLUID DISTENSION; <5MM DIA.	UTERUS : >NO SIGNIFICANT LESION

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0058 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 308.5 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

HISTOPATHOLOGY

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT

LIVER X 2 :
-CONGESTION,-MINIMAL

LEFT PARATHYROID :
>TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		------
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0059 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 310.1 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

*** ANIMAL HAS NO MICROSCOPIC FINDINGS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0060 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 270.7 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	CAECUM : -LYMPHOID HYPERPLASIA,-SLIGHT
JEJUNUM : -ABNORMAL CONTENTS; CONTAINS YELLOW, VISCOUS FLUID.	JEJUNUM : >NO SIGNIFICANT LESION
L N POPLITEAL : -DARK	L N POPLITEAL : >NO SIGNIFICANT LESION
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
	LIVER X 2 : -CONGESTION,-MINIMAL
TAIL : -TRAUMA; TIP ABSENT.	

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0061 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 311.1 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	RIGHT PARATHYROID : >TISSUE MISSING
SKIN, OTHER : -HAIRLOSS MODERATE; ADJACENT TO PINNAE. -FACIAL STAINING; BROWN STAINING ON HEAD. -NON-SPECIFIC STAINING; BROWN STAINING ON DORSAL CERVICAL REGION.	
UTERUS : -FLUID DISTENSION; <4MM DIA.	UTERUS : -POLYLUMINAL DILATATION,-MINIMAL

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0062 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 298.8 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

HISTOPATHOLOGY

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE

LEFT PARATHYROID :
>TISSUE MISSING

RIGHT PARATHYROID :
>TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	.....	M&B 46030	.....	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0063 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 332.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LEFT KIDNEY : -CORTICAL MINERALISATION,-MINIMAL
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0064 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 326.5 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LEFT KIDNEY : -CORTICAL MINERALISATION,-MINIMAL RIGHT KIDNEY : -CORTICAL MINERALISATION,-MINIMAL LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-SLIGHT LEFT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0065 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 334.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

HISTOPATHOLOGY

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MARKED

RIGHT PARATHYROID :
>TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology : individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0066 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 372.5 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

HISTOPATHOLOGY

RIGHT KIDNEY :
-CORTICAL MINERALISATION,-MINIMAL

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT

RIGHT PARATHYROID :
>TISSUE MISSING

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0067 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 290.8 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MARKED
	LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-MARKED
	RIGHT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	.....	M&B 46030	.....	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0068 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 280.7 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE LEFT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Schedule number: RHA 298

Group	:	1	2	3	4	5
Compound	:	Control -	-------	M&B 46030	------
Level (ppm)	:	0	1	5	30	300

ANIMAL NUMBER: 0069 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 342.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
L N MANDIBULAR : -DARK	L N MANDIBULAR : -FOLLICULAR HYPERPLASIA, -SLIGHT
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION, -SLIGHT

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0070 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 356.2 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

HISTOPATHOLOGY

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MARKED

LUNGS X 2 :
-INTERSTITIAL PNEUMONITIS,-MINIMAL

RIGHT PARATHYROID :
>TISSUE MISSING

SKIN, OTHER :
-HAIRLOSS MODERATE; ON FORELIMBS.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0071 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 333.6 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LEFT KIDNEY : -CORTICAL MINERALISATION,-MINIMAL LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT LEFT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0072 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 315.7 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-MINIMAL RIGHT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Printed: 21-MAR-9
Page: 73

Schedule number: RHA 298

ANIMAL NUMBER: 0073 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 301.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LEFT KIDNEY : -CORTICAL MINERALISATION,-MINIMAL RIGHT KIDNEY : -CORTICO-MEDULLARY MINERALISATION,-SLIGHT LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT LUNGS X 2 : -FOCAL ALVEOLAR WALL EPITHELIALISATION,-SLIGHT LEFT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0074 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 - STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 327.5 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY

FOOT/FEET :
-ABNORMAL SHAPE; THIRD DIGIT OF RIGHT FOREFOOT MISSHAPEN.

HISTOPATHOLOGY

FOOT/FEET :
>NO SIGNIFICANT LESION

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE

LIVER X 2 :
-CONGESTION,-SLIGHT

RIGHT PARATHYROID :
>TISSUE MISSING

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0075 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 274.8 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION, SLIGHT
	LEFT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0076 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 334.2 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

SKIN, OTHER :
-NON-SPECIFIC STAINING; BROWN STAINING ON DORSAL CERVICAL REGION.

HISTOPATHOLOGY

*** ANIMAL HAS NO MICROSCOPIC FINDINGS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0077 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 358.4 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-SLIGHT LEFT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	: 1	2	3	4	5
Compound	: Control	-------	M&B 46030		------
Level (ppm)	: 0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0078 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 328.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER X 2 : -FOCI OF LEUCOCYTES WITHIN SINUSOIDS,-MINIMAL LEFT PARATHYROID : >TISSUE MISSING RIGHT PARATHYROID : >TISSUE MISSING LEFT THYROID : -FOLLICULAR CELL HYPERPLASIA,-MINIMAL RIGHT THYROID : -FOLLICULAR CELL HYPERPLASIA,-MINIMAL

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	--------	M&B 46030	-------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0079 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 433.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
JEJUNUM : -ABNORMAL CONTENTS; CONTAINS PALE, AERATED FLUID. -DISTENDED; <5MM DIA.	
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
	RIGHT PARATHYROID : >TISSUE MISSING

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0080 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 298.5 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
SKIN, OTHER : -NON-SPECIFIC STAINING; BROWN STAINING ON DORSAL CERVICAL REGION.	
UTERUS : -FLUID DISTENSION; <5MM DIA.	UTERUS : -POLYLUMINAL DILATATION,-SLIGHT

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0081 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 327.2 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT

SKIN, OTHER :
-FACIAL STAINING; DARK BROWN STAINING ON HEAD.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0082 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 308.6 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE
	RIGHT PARATHYROID : >TISSUE MISSING

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0083 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 327.2 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION, MODERATE

SKIN, OTHER :
-FACIAL STAINING; BROWN STAINING ON HEAD.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group :	1	2	3	4	5
Compound :	Control	-------	M&B 46030	------	
Level (ppm) :	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0084 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 294.5 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
LUNGS X 2 : -DARK	LUNGS X 2 : >NO SIGNIFICANT LESION
SKIN, OTHER : -FACIAL STAINING; BROWN STAINING ON HEAD.	

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0085 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 385.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT LEFT PARATHYROID : >TISSUE MISSING

SKIN, OTHER :
-FACIAL STAINING; BROWN STAINING ON HEAD.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0086 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 343.6 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE
	LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0087 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 312.7 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE
	LEFT PARATHYROID : >TISSUE MISSING
	RIGHT PARATHYROID : >TISSUE MISSING
THYMUS : -AREA(S) OF CHANGE; OCCASIONAL PUNCTATE, DARK FOCI.	
	LEFT THYROID : -FOLLICULAR CELL HYPERPLASIA,-MINIMAL
	RIGHT THYROID : -FOLLICULAR CELL HYPERPLASIA,-MINIMAL

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-----	:
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0088 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 327.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

HISTOPATHOLOGY

LEFT KIDNEY :
-PAPILLARY CYST(S),-SLIGHT, FOCAL

LIVER OIL RED O :
-CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT

LUNGS X 2 :
-INTERSTITIAL PNEUMONITIS,-SLIGHT

RIGHT PARATHYROID :
>TISSUE MISSING

SKIN, OTHER :
-HAIRLOSS MODERATE; ON LEFT FORELIMB.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0089 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 289.3 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
LUNGS X 2 : -DARK	LUNGS X 2 : -INTERSTITIAL PNEUMONITIS,-SLIGHT

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0090 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 342.1 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE

THYMUS :
-AREA(S) OF CHANGE; OCCASIONAL PUNCTATE, DARK FOCI.

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0091 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 280.6 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	BRAIN X 3 : -MICROCAVITATION OF WHITE MATTER,-SLIGHT
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE
	LIVER X 2 : -CONGESTION,-SLIGHT
TAIL : -ENCRUSTATION(S); MULTIPLE POORLY DEFINED, PALE AND DARK AREAS, ON POSTERIOR REGION.	
	RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-MINIMAL

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0092 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 289.4 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY

ADRENAL CTX LT :
- APPEARS LARGE
- AREA(S) OF CHANGE; OCCASIONAL POORLY DEFINED, PALE AREAS.

ADRENAL CTX RT :
- APPEARS LARGE
- AREA(S) OF CHANGE; OCCASIONAL POORLY DEFINED, PALE AREAS.

TAIL :
- AREA(S) OF CHANGE; TIP DARK.
- ENCRUSTATION(S); OCCASIONAL PUNCTATE, DARK AREAS.

HISTOPATHOLOGY

ADRENAL CTX LT :
- >NO SIGNIFICANT LESION

ADRENAL CTX RT :
- >NO SIGNIFICANT LESION

BRAIN X 3 :
- MICROCAVITATION OF WHITE MATTER, SLIGHT

LIVER OIL RED O :
- CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION, MODERATE

LIVER X 2 :
- CONGESTION, SLIGHT

LEFT PARATHYROID :
- >TISSUE MISSING

RIGHT PARATHYROID :
- >TISSUE MISSING

LEFT THYROID :
- HYPERTROPHY OF FOLLICULAR EPITHELIUM, MINIMAL

RIGHT THYROID :
- HYPERTROPHY OF FOLLICULAR EPITHELIUM, MINIMAL

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0093 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 271.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	BRAIN X 3 : -MICROCAVITATION OF WHITE MATTER,-SLIGHT
EYE RT : -DARK -OPAQUE	EYE RT : -DISRUPTION/FIBROSIS,-PRESENT
L N MANDIBULAR : -DARK	L N MANDIBULAR : >NO SIGNIFICANT LESION
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE
	LIVER X 2 : -CONGESTION,-SLIGHT
	LEFT PARATHYROID : >TISSUE MISSING
SKIN, OTHER : -HAIRLOSS MODERATE; AROUND RIGHT EYE AND ON FORELIMBS.	
TAIL : -ENCRUSTATION(S); OCCASIONAL DARK AREAS, <2X1MM, ON TIP.	
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT
	RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0094 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 296.8 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION, MARKED
	LIVER X 2 : -PANACINAR HEPATOCYTIC FATTY VACUOLATION, SLIGHT
TAIL : -AREA(S) OF CHANGE; TIP DARK. -ENCRUSTATION(S); DARK AREA, 2X2MM, ON TIP.	
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM, SLIGHT -FOLLICULAR CELL HYPERPLASIA, MINIMAL
	RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM, SLIGHT -FOLLICULAR CELL HYPERPLASIA, MINIMAL

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0095 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 20-FEB-90 STUDY DAY OF DEATH: 93 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 327.5 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE
	LIVER X 2 : -CONGESTION,-SLIGHT
TAIL : -AREA(S) OF CHANGE; TIP DARK. -ENCRUSTATION(S); OCCASIONAL PALE AREAS, <3X2MM.	
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-MODERATE
	RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29E

ANIMAL NUMBER: 0096 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 299.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	--------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 298

ANIMAL NUMBER: 0097 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 282.9 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
	L N MANDIBULAR : >TISSUE MISSING
	LIVER OIL RED O : -CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION,-SLIGHT
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT
	RIGHT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0098 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 304.5 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY

HISTOPATHOLOGY

LIVER OIL RED O :
-PANACINAR HEPATOCYTIC FATTY VACUOLATION,-MODERATE

LIVER X 2 :
-PANACINAR HEPATOCYTIC FATTY VACUOLATION,-MINIMAL
-CONGESTION,-SLIGHT

LEFT THYROID :
-HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

RIGHT THYROID :
-HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	------	
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0099 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 317.5 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

HISTOPATHOLOGY

LIVER OIL RED O :
- CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION, - SLIGHT

LEFT THYROID :
- HYPERTROPHY OF FOLLICULAR EPITHELIUM, - SLIGHT
- FOLLICULAR CELL HYPERPLASIA, - MINIMAL

RIGHT THYROID :
- HYPERTROPHY OF FOLLICULAR EPITHELIUM, - SLIGHT
- FOLLICULAR CELL HYPERPLASIA, - MINIMAL

APPENDIX 11 - continued.

Macropathology and histopathology - individual findings for animals killed after 13 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	------- M&B 46030 ------			
Level (ppm)	:	0	1	5	30	300

Schedule number: RHA 29

ANIMAL NUMBER: 0100 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 22-FEB-90 STUDY DAY OF DEATH: 95 STUDY WEEK OF DEATH: 14 TERMINAL BODY WEIGHT: 310.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
	RIGHT PARATHYROID : >TISSUE MISSING
	LEFT THYROID : -HYPERTROPHY OF FOLLICULAR EPITHELIUM,-SLIGHT

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

LIFE SCIENCE RESEARCH

RECEIVED
31 JUL 1989

LSR Schedule No : RHA/298/46030
LSR Enquiry No : 3179H
Protocol Issue No : 1
No. of pages : 21

M&B 46030 : TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR 13 WEEKS

Protocol prepared for

Rhône-Poulenc Agrochimie

by

Life Science Research Limited
Eye, Suffolk, IP23 7PX
England

2 May 1989

LSR Schedule No : RHA/298/46030
LSR Enquiry No : 3179H
Protocol Issue No : 1

PROTOCOL DEVELOPMENT : Cumulative history

Issue No.	Date sent to Sponsor	Actions and responses
1	9/5/89	

MANAGEMENT OF STUDY

Project Co-ordinator : W. Davies, B.Sc., M.Sc., Ph.D.

Study Director : P. Holmes, B.Sc., C.Biol., M.I.Biol.

Sponsor : Rhône-Poulenc Agrochimie
14-20 rue Pierre Baizet
B.P. 9163
69263 Lyon Cedex 09
France

Monitor : Mr B. Ingham

Executive monitor : Dr C. Silice

Project licence : 70/00710. Repeat dose toxicology and oncology (procedure ref. No. 6)

Project licensee : S.J. Amyes, Ph.D.

APPROVED PROTOCOL

LSR Schedule No : RHA/298/46030
LSR Enquiry No : 3179H
Protocol Issue No : 1

PROTOCOL APPROVAL

For LIFE SCIENCE RESEARCH LIMITED

Issued by : _____ Date : 8 May 1989

Released by : _____ Date : 8 May 1989

For RHONE-POULENC AGROCHIMIE

(Please read Sections A and B, and complete the appropriate section. Please note that the study cannot begin unless Life Science Research Limited is in receipt of a protocol signed in Section A)

A. STUDY TO BE CONDUCTED USING THIS PROTOCOL

This document is the working protocol for the study and will be reproduced in the final report. Any modifications that are required have been made on the document, and have been initialled and dated. These, and any changes made subsequent to the date of my signature below, will be documented in formal amendments.

Approved by : _____ Date : 27/07/89
(for RHONE-POULENC AGROCHIMIE)

Please note

To comply with Good Laboratory Practice, and to allow the study to be conducted correctly and in a timely manner, it is VERY IMPORTANT that:

i) All changes to the protocol are clearly identifiable, intelligible and legible. The original content should not be obscured.

ii) The protocol is returned to Life Science Research Limited as soon as possible, and certainly before the proposed start date for the study.

STUDY DIRECTOR

The Sponsor has approved the initiation of the study according to the procedures described in this document. I have read and agreed the contents of this document and authorise its distribution.

Study Director : _____ Date : 31 July 1989
(for LIFE SCIENCE RESEARCH LIMITED)

B. STUDY NOT TO BE STARTED. MODIFICATIONS REQUIRED

This protocol requires revision and may not be used to initiate the study. A further issue of the protocol must be prepared and signed on behalf of the Sponsor before the study may start.

Reviewed by : _____ Date : _____
(for RHONE-POULENC AGROCHIMIE)

APPROVED PROTOCOL

M&B 46030 : TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR 13 WEEKS

1. Introduction

1.1 Objective

The toxic effects of M&B 46030 will be assessed in a 13 week feeding study in rats. The study will be performed in compliance with Good Laboratory Practice Standards which are acceptable to the U.K., European, Japanese and U.S.A. regulatory authorities.

The study has been designed to meet the MAFF (January 1985) and EPA/FIFRA (November 1984) guidelines for Japan and the U.S.A. respectively and the requirements for Europe (including the U.K.).

1.2 Choice of animal model

The rat has been chosen because of its acceptance as a predictor of toxic change in man and the requirement for a rodent species by regulatory agencies. The CD strain has been chosen because of the historical control data available in this laboratory.

1.3 Choice of route of administration and dosages

Oral administration has been selected to accord with the major potential route of exposure in manufacture and use; for convenience the test substance will be administered by admixture with the diet. Dietary concentrations will be selected by the Sponsor.

1.4 Safety precautions

The precautions necessary when handling either the test substance or prepared formulations of the test substance will be based on information supplied by the Sponsor. The minimum safety precautions necessary are detailed under the LSR hazard class 3 (to be up-dated, if required, in an amendment to the protocol).

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1.5 Location of study : Life Science Research Limited
Eye
Suffolk IP23 7PX
England

Tel: (0379) 644122
Telex: 975 389 LIFSCI G
Fax: (037971) 427

2. Scheduled time plan (to be up-dated as required in an amendment to the protocol)

Sample of M&B 46030 to arrive	:	
Test diet assays to be completed	:	
Animals to arrive	:	
Treatment to commence	:	
Terminal sacrifice to commence	:	
Histopathology to be completed	:	(estimated)
Draft report to be issued	:	(estimated)

3. Animal management

3.1 Animals

Rats of the CD strain (ordered at 21 to 28 days of age, 60 to 80 g bodyweight) will be obtained from Charles River (UK) Limited, Margate, Kent, England.

If the animals are considered unsuitable for any reason, all animals will be replaced (no extra cost to Sponsor).

3.2 Pre-commencement animal replacement

Ten spare animals will be ordered to replace any individuals rejected during the acclimatisation period using the following criteria:

i) signs of ill-health

ii) abnormalities indicated in the pre-treatment investigations described below (Section 5)

iii) on completion of i) and ii), extremes of the bodyweight range

If the number of animals required for i) and ii) exceeds that supplied as spares the Sponsor will be advised and all animals will be replaced as indicated in Section 3.1.

3.3 Identification

After random allocation to groups (Section 3.9) each rat will be assigned a number and identified uniquely within the study by a tail tattoo. Tattoos will be checked at regular intervals and repeated if necessary.

3.4 Acclimatisation

The rats will be allowed to acclimatise to the husbandry conditions described below for not more than fourteen days before commencement of treatment; their health status will be assessed from daily observations.

3.5 Environmental control

Rats will be housed inside a barriered rodent facility.

Each animal room is kept at positive pressure with respect to the outside by its own supply of filtered fresh air which is passed to atmosphere and not re-circulated. Target values within the study room are 21°C for temperature, 55% for relative humidity and at least 15 air changes per hour. Lighting is controlled to provide a 12-hour light : 12-hour dark cycle.

The facility is designed and operated to minimise the entry of external biological and chemical agents and to minimise the transference of such agents between rooms. Before and after each study the room is cleaned and disinfected with a bactericide.

Access is limited to authorised personnel who are required to wash and change into clean protective clothing. Where practicable, materials and equipment enter the facility through an autoclave or a chamber in which their external surfaces are treated with a bactericide.

Alarms are activated if the ventilation system fails, or the temperature limits are exceeded. Periodic checks are made on the number of air changes in the study room. Temperature and humidity are monitored daily. These data will be retained in the archives.

A stand-by electricity supply is automatically brought into operation should the public supply fail.

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3.6 Animal accommodation

The rats will be housed five of one sex per cage, unless this number is reduced by mortality or isolation (Section 5.2). The cages used will be Type RC1 (North Kent Plastics Limited, Dartford, Kent, England), which are made of a high density polypropylene body measuring 56 x 38 x 18 cm with a stainless steel mesh lid and floor. The cages will be suspended above absorbent crêpe paper. The latter will be changed three times a week; cages, cage-trays, food hoppers and water bottles will be changed at appropriate intervals.

3.7 Diet and water supply

A commercially-available powdered rodent diet, Laboratory Animal Diet No. 2 (Labsure, Manea, Cambridgeshire, England), will be available *ad libitum*, except when urine is being collected and overnight before routine blood sampling. This is an expanded diet which is subsequently ground by the manufacturer. It contains no added antibiotic or other chemotherapeutic or prophylactic agent. Weighed amounts of diet will be provided at intervals during each week to each cage.

At the end of each treatment week the weight of uneaten food will be recorded and the food discarded.

Water will be available *ad libitum* via polyethylene bottles with sipper tubes, except when urine is being collected.

3.8 Analysis of diet and water

Each batch of diet is routinely analysed by the supplier for various nutritional components and chemical and microbiological contaminants. At approximately six-month intervals the potential contaminants investigated by the supplier will also be analysed by a laboratory independent of the supplier.

Water will be taken from the public supply (East Anglian Water Company) which meets the European Economic Community and the World Health Organisation International Standards. At approximately six-month intervals water is routinely analysed, by a laboratory independent of the supplier, for selected chlorinated and organophosphorus pesticides, polychlorinated biphenyls, and lead and cadmium contaminants; it will also be examined for coliform bacteria.

Results of all analyses will be retained in the archives.

No other specific contaminants, likely to be present in the diet or water, are known that may interfere with or prejudice the outcome of the study. Any such contaminants notified by the Sponsor before or during the study will be documented in an amendment to the protocol and analysed, if requested by the Sponsor.

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3.9 Allocation to treatment groups

On arrival animals will be assigned to cages using a set of computer-generated random numbers, resulting in a random allocation of animals to treatment groups. All animals will be weighed during the acclimatisation period; animals at the extremes of the weight distribution will be discarded and replaced with surplus animals selected from the same batch.

As far as is practicable the cage distribution will be designed to minimise the effect of any spatially variable component of the environment. The distribution will be documented in the final report.

4. Treatment

4.1 Identity of treatment groups (to be selected from 90 rats ordered)

Group	Treatment	Dietary concentration (ppm)	Cage numbers Male	Cage numbers Female	Animal numbers Male	Animal numbers Female
1	Control	0	1-2	9-10	1-10	41-50
2	M&B 46030	Low	3-4	11-12	11-20	51-60
3	M&B 46030	Intermediate	5-6	13-14	21-30	61-70
4	M&B 46030	High	7-8	15-16	31-40	71-80

Cage labels, identifying the occupants by experiment, animal number, sex and treatment group will be colour-coded; white labels will denote animals not assigned to study groups.

All remaining spare animals will be removed from the study room on the first day of treatment.

4.2 Test substance

Before use the identity, strength, purity and composition, or other characteristics which appropriately define the batch from which the test substance for this study is to be drawn, will be determined by the Sponsor. Stability of the test substance and methods of synthesis, fabrication or derivation will be documented by the Sponsor.

The test substance will be stored at ambient temperature or in a cool store (not exceeding 15°C) and protected from light.

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In order to demonstrate the integrity of the test substance under the conditions in which it is to be stored at these laboratories, a single 10 g sample will be returned to the Sponsor every six months for reanalysis throughout, and on completion of, the programme of work using this test substance. Results of these analyses will be communicated to LSR for inclusion in the relevant final report.

Before any consignment of the test substance is used in the programme of work at these laboratories, the Pharmacy Department of LSR will ensure that a 10 g representative sample has been taken. This sample will be placed in a well-closed glass container, stored under the conditions specified for the bulk supply of the test substance and retained in the archives.

Similar procedures will be adopted for any additional consignments of the test substance used during the course of the programme.

4.3 Formulation

The M&B 46030 will be incorporated into the ground diet to provide the required dietary concentrations by initial preparation of a premix, followed by dilution with further quantities of the diet and mixing in an electrically grounded (earthed) mixer. Assuming no stability problem (see section 4.4) batches of each test diet will be prepared each week and issued in sealed polyethylene bags. The unused residue at the end of each week will be discarded.

On those occasions when test diet samples are to be taken for quality control purposes (see Section 4.4), 100 g aliquots of each test diet will be sealed in aluminium foil laminate sachets and stored in a refrigerator (approximately 4°C) pending possible future analytical requirements or until the approved final report has been issued. The samples will then be either sent to the Sponsor or destroyed, as directed by the Sponsor.

On all other occasions, 100 g aliquots of each test diet will be sealed in aluminium foil laminate sachets and stored at ambient temperature. In the event of an unexpected reaction by the animals, the aliquots from the diets fed during the period in which the reaction occurred will be analysed. The unused aliquots will be discarded after three months.

4.4 Quality control of dosage form

On each day that quantities of test substance are to be weighed out for test diet preparation, the stock container of test substance will be weighed before the first and after the last removal of part of its contents. The reduction in the weight of the stock container will be documented as a check that the required amount of the test substance has been used.

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Before commencement of treatment the suitability of the proposed mixing procedure will be determined by a trial preparation. The details of the mixing procedure will be documented for inclusion in the final report. Diet samples will be assayed by the Department of Biomedical and Environmental Chemistry at Life Science Research as detailed below:

Samples prepared for the highest and lowest dietary concentration groups in this study, taken from six positions in the mixer, will be assayed for homogeneity. This procedure will be repeated before instituting any change in the mixing process during the study.

Stability will be determined for the highest and lowest dietary concentration groups from the trial preparation, unless dietary concentrations anticipated in this study are within the range analysed for stability in any other studies at these laboratories. Representative samples for stability testing will be obtained by pooling the unused portions of the homogeneity samples for each group. Assays will be performed after one and two weeks storage at ambient temperature. The mean of the results for the six homogeneity samples will be taken as the initial assay for the stability test.

Spot checks will be performed by LSR to determine the achieved concentration of diet prepared for each group for the first and last week of treatment, based on a method to be supplied by the Sponsor.

4.5 Administration

The test substance will be administered continuously via the diet. The dietary concentration will be maintained at a constant for each group throughout the treatment period.

Animals will not have access to mixed diet beyond the end of its shelf-life as determined by the stability test. Control rats will receive untreated diet at the same frequency, and from the same batch, as treated animals.

4.6 Scheduled duration of treatment

Treatment will be continuous for a minimum period of 13 weeks. The treatment period may be extended for a maximum of one week in order to complete the observations specified in Section 5 below.

The treatment period may be extended, with the Sponsor's consent, to incorporate any additional observations considered necessary; this will be documented in an amendment to the protocol. Throughout any additional period, including the necropsy period, treatment will continue for all surviving animals. The serial observations will be recorded at the appropriate intervals described below (Section 5).

Data pertaining to any additional complete weeks before commencement of the necropsies will be included in the final report.

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5. Serial observations

Examinations scheduled before termination of treatment will be undertaken during the last scheduled week of treatment. The precise times of all examinations will be included in the final report.

5.1 Signs

Rats and their cage-trays will be inspected at least twice daily for evidence of reaction to treatment or ill-health. Any deviations from normal will be recorded at the time in respect of nature and severity, date and time of onset, duration and progress of the observed condition, as appropriate. The observations are designed to identify abnormalities in, at least, the following:

Skin and fur
Eyes and mucous membranes
Respiratory system
Circulatory system
Autonomic and central nervous system
Somatomotor activity
Behaviour pattern

In addition to handling during the dosing procedure, the animals will be palpated once each week. The outcome of this examination will be documented for each animal.

During the acclimatisation period, observations of the animals and their cage-trays will be recorded at least once per day.

5.2 Mortality

Debilitated animals will be observed carefully and may be isolated to prevent cannibalism. Animals judged to be *in extremis* will be killed. Where possible blood samples will be taken *ante mortem* and analysed for the parameters specified in the relevant sections below.

Rats found dead outside the normal work-day will be preserved in a refrigerator (approximately 4°C) provided for this purpose. A necropsy will be performed as soon as possible the following day.

A complete necropsy will be performed in all cases as described in Section 6 below.

5.3 Food consumption

The weight of food supplied to each cage, that remaining and an estimate of the amount spilled will be recorded for each week throughout the treatment period. From these records the mean weekly consumption per rat will be calculated for each cage.

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5.4 Water consumption

Water consumption measurements may be instituted, and documented in an amendment to the protocol, if any observations suggest a treatment-related effect on body fluids balance.

5.5 Bodyweight

Each animal will be weighed on the day that treatment commences, at weekly intervals throughout the treatment period and before necropsy.

More frequent weighings may be instituted for animals displaying ill-health, so that the progress of the observed condition can be monitored. These data will be retained in the archives.

5.6 Food conversion ratio

The group mean food conversion ratios of each sex, expressed as the weight of food consumed per unit gain in bodyweight, will be calculated for each week of treatment.

5.7 Achieved dosage

The group mean achieved dosage for each sex, expressed as mg/kg/day, will be calculated for the same intervals as bodyweights. This will be calculated from the appropriate dietary test substance concentration, food consumption and bodyweight data.

5.8 Neurological examination

Before termination of treatment a full neurological examination will be performed on all surviving animals from Groups 1 and 4.

Reflexes tested and observations performed include, but will not necessarily be restricted to, the following:

Cranial nerve reflexes

- Pupillary light and consensual light
- Palpebral - blink
- Startle
- General examination of the head to assess other cranial nerves

Segmental reflexes

- Flexor (withdrawal)

Postural reactions

- Placing reactions - visual and tactile
- Righting reactions
- Grasping

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General observations

Behavioural changes, e.g. aggression, sedation
Abnormalities of gait and stance
Presence of tremor or other dyskinesias

Other examinations may be performed, as indicated by the signs observed, and documented in an amendment to the protocol.

If treatment-related changes are suspected the examination will be extended to all rats and documented in an amendment to the protocol.

5.9 Ophthalmoscopy

Before commencement of treatment both eyes of all rats will be examined by means of an indirect ophthalmoscope, after the instillation of 0.5% tropicamide. The structures examined include, but will not necessarily be restricted to, the following:

Palpebrae and adjacent structures
Conjuctiva
Cornea and sclera
Anterior chamber and iris
Lens and vitreous
Ocular fundus

Rejected animals will be replaced with rats, with no adverse ocular abnormality, selected from the spare animals ordered for the study.

Before termination of treatment all surviving rats from Groups 1 and 4 will be similarly examined.

If treatment-related changes are suspected the examination will be extended to all rats and documented in an amendment to the protocol.

5.10 Haematology, peripheral blood

Before termination of treatment (before dosing) blood samples will be obtained from all surviving animals.

Blood samples will be withdrawn from the retro-orbital sinus of the rats, held under ether anaesthesia after overnight starvation, using EDTA as anticoagulant. All samples will be examined for the following characteristics:

Packed cell volume
Haemoglobin concentration
Erythrocyte count
Reticulocyte count

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Total leucocyte count
Differential leucocyte count - Neutrophils
Lymphocytes
Eosinophils
Basophils
Monocytes
Normoblasts, or other abnormalities of the blood film
Platelet count
Mean cell haemoglobin
Mean cell volume
Mean cell haemoglobin concentration

Additional blood samples will be taken into citrate anticoagulant and examined in respect of:

Prothrombin time

5.11 Blood chemistry

At the same time as for peripheral haematology further blood samples will be taken, after overnight starvation, using lithium heparin as anticoagulant. After separation the plasma will be examined in respect of:

Alkaline phosphatase
Alanine amino-transferase
Aspartate amino-transferase
Urea
Creatinine
Glucose
Bilirubin (total)
Total protein
Protein electrophoretogram - Albumin
Alpha-one globulin
Alpha-two globulin
Beta globulin
Gamma globulin
Albumin/globulin ratio
Sodium
Potassium
Chloride
Calcium
Phosphorus

5.12 Urinalysis

Before termination of treatment overnight urine samples will be collected from all surviving animals.

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Each rat will be placed in an individual metabolism cage for urine collection under conditions of food and water deprivation. The individual samples will be examined in respect of:

Appearance
Volume
pH
Specific gravity
Protein
Total reducing substances
Glucose
Ketone
Bilirubin
Urobilin
Nitrite
Blood pigments

The deposit, obtained from centrifugation, will be examined microscopically for:

Epithelial cells
Polymorphonuclear leucocytes
Erythrocytes
Crystals
Spermatozoa and precursors
Other abnormal components

Clinical pathology examinations (Sections 5.10 to 5.12) can be extended to include other parameters and the frequency of sampling may be changed, if required by the Sponsor.

5.13 Proof of absorption (Optional)

~~Blood, urine or tissue samples or any combination of these will be obtained as required by the Sponsor and analysed for the test substance or its metabolites, as appropriate, based on a method to be specified by the Sponsor.~~

6. Terminal observations

6.1 Euthanasia

Animals sacrificed during the study and those surviving until the end of the scheduled treatment period will be killed by carbon dioxide inhalation.

The sequence in which the animals are killed after completion of treatment will be selected to allow satisfactory inter-group comparison.

6.2 Macroscopic pathology

All animals killed and any found dead will be subjected to a detailed necropsy.

The necropsy procedure will include a review of the history of each animal and a detailed examination of the external features and orifices, the neck and associated tissues and the cranial, thoracic, abdominal and pelvic cavities and their viscera. The requisite organs will be weighed and external and cut surfaces of the organs and tissues will be examined as appropriate. Abnormalities and interactions will be noted and the required tissue samples preserved in fixative (see below).

Before disposal of the carcase the retained tissues will be checked against the protocol and a senior prosector will review the necropsy report.

Representative photographs will be taken of any significant findings, if considered appropriate.

6.3 Organ weights

The organs will be dissected free of adjacent fat and other contiguous tissue and the weights recorded as specified in the Pathology Procedures Table. The ratio of organ weight to bodyweight (recorded immediately before necropsy) will be calculated for each rat surviving until the end of the scheduled treatment period.

6.4 Tissues preserved in fixative

Samples of the tissues specified in the Pathology Procedures Table will be preserved in buffered 4% formaldehyde saline, except eyes, optic nerves and Harderian glands which will be placed in Davidson's fluid. Bone marrow smears, taken from all animals killed, will be air-dried and fixed in methanol.

In those cases where a lesion is not clearly delineated, contiguous tissue will be fixed with the grossly affected region and sectioned as appropriate.

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LSR Schedule No : RHA/298/46030
LSR Enquiry No : 3179H
Protocol Issue No : 1

PATHOLOGY PROCEDURES

TISSUE	WEIGH	FIX	LIGHT MICROSCOPY
Abnormalities	if poss	*	1
Adrenals	L+R	L+R	L+R
Aorta (thoracic)		*	1
Brain	*	*	3
Caecum		*	1
Colon		*	1
Duodenum		*	1
Epididymides		L+R	L+R
Eyes and optic nerves		L+R	L
Femoral bone and articular surface		*	1
Harderian glands		L+R	ø
Heart	*	*	2
Ileum		*	1
Jejunum		*	1
Kidneys	L+R	L+R	L+R
Liver	*	*	2
Lungs (with mainstem bronchi)	*	*	2
Lymph nodes (mandibular)		*	1
(mesenteric)		*	1
Mammary glands (caudal)		*	1
(cranial)		*	ø
Marrow smear		*	ø
Oesophagus		*	1
Ovaries	L+R	L+R	L+R
Pancreas		*	1
Pituitary	*	*	1
Prostate	*	*	1
Rectum		*	1
Salivary glands (submandibular)	L+R	L+R	L
Sciatic nerves		L+R	L
Seminal vesicles		*	1
Skeletal muscle (thigh)		*	1
Skin		*	1
Spinal cord		*	3
Spleen	*	*	1
Sternum with marrow		*	1
Stomach (keratinised)		*	1
(glandular)		*	1
Testes	L+R	L+R	L+R
Thymus	*	*	1
Thyroid (with parathyroids)§	L+R	L+R	L+R
Tongue		*	ø
Trachea		*	1
Urinary bladder		*	1
Uterus with cervix	*	*	1
Vagina		*	1

ø Examined if effects suspected during the study
§ Weighed after fixation
* Organs to be weighed and/or tissue samples to be fixed
Each number denotes the number of tissue samples or regions examined

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6.5 Histology

The number of tissue samples or regions detailed in the Pathology Procedures Table will be taken from all specified animals and processed as follows:

Bone marrow smears will be stained using a May-Grünwald-Giemsa procedure. The remaining tissues will be dehydrated, embedded in paraffin wax, sectioned at approximately five micron thickness and stained with haematoxylin and eosin.

Tissue from auricular and ventricular regions of the heart, thyroid and parathyroids and cervix and body of the uterus will be prepared. Sections from two lobes of each of the liver and lungs will be similarly processed. The brain will be sectioned to include the cerebellum, cerebral cortex and medulla. The spinal cord will be prepared in transverse section at the cervical, thoracic and lumbar levels.

6.6 Microscopy

Microscopic examination will be performed on the tissue sections, specified in the Pathology Procedures Table, as follows:

i) From all rats of Groups 1 and 4 sacrificed on completion of the scheduled treatment period.

+ thyroid CS 27/04

ii) The kidneys, liver and lungs from all rats of Groups 2 and 3 sacrificed on completion of the scheduled treatment period.

iii) From all rats killed or dying during the study.

iv) From all rats of Groups 2 and 3 sacrificed on completion of the scheduled treatment period in respect of tissues considered to exhibit a reaction to treatment at the high dosage. These will be documented in an amendment to the protocol.

v) All abnormalities (the quoted price allows for examination of one additional tissue section per animal in (i) above).

Any tissue considered to display an effect may be examined further, at the discretion of the pathologist, using processing procedures and stains which may aid the examination as appropriate. Details of these procedures will be recorded for inclusion in the final report.

6.7 Photomicrography (Optional)

CS 27/04

~~Representative photographs will be taken of any treatment-related lesions and documented in an amendment to the protocol.~~

~~Other photomicrographs may be taken as required by the Sponsor.~~

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6.8 Electron microscopy (Optional)

Samples of tissues specified by the Sponsor will be taken from three male and three female animals in Groups 1 and 4 immediately after their sacrifice on completion of the scheduled treatment period. These samples will be fixed in glutaraldehyde, post-fixed in osmium tetroxide and embedded in Araldite. Ultra-thin sections will be prepared and examined by electron microscopy.

Specified tissues may be retained either in fixative for some months or permanently as Araldite blocks pending the outcome of light microscopy.

Alternatively, tissues showing an abnormality detected by light microscopy may be examined using formalin fixed tissue.

7. Data treatment

7.1 Statistical analysis

Standard deviations will be calculated as considered appropriate.

For continuous variables the significance of the differences between group means will usually be assessed by Student's t-test using a pooled error variance, except organ weights which will usually be assessed by Dunnett's test. A suitable transformation may be applied, if the raw data do not justify the use of normal methods; alternatively a distribution-free test (e.g. Rank Sum) may be used. Possible extensions of these procedures can include the identification and rejection of outliers, analysis of covariance, trend tests and repeated-measures analysis of variance. Attribute data will be analysed by the Fisher exact probability test.

Details of all tests used and the data to which they apply will be included in the final report.

7.2 Reporting

Brief summaries will be submitted to the monitor at monthly intervals. Any unexpected findings during the course of the study will be reported immediately.

The final report will include the information and data as required by current internationally recognised regulations.

An advance photocopy (draft) of the final report will be sent to the Sponsor and the Life Science Research Quality Assurance Unit. With the exception of the dated signature of all scientists and other professional staff, the draft will contain all the information and data to be included in the final report. Comments made by the Sponsor and the Q.A. Unit may be incorporated into the draft, after which it will be issued as the final report.

APPROVED PROTOCOL

Four copies of the final report, one unbound and printed single sided, will be issued to the Sponsor.

Any additions or corrections to a final report will be in the form of an amendment by the Study Director. The amendment, clearly identifying that part of the final report that has been added to or corrected and the reasons for the addition or correction, will be signed and dated by the person responsible.

7.3 Archives

The following data and specimens will be retained during the study and subsequently for at least five years. After this period the Sponsor will be contacted for approval before disposal of any data or specimens; no data or specimens will be destroyed without the consent of the Sponsor. Data and specimens will be retained in the archives for a further specified period at the Sponsor's request.

Protocol, Amendments to Protocol and Study Notes

Animal arrival
Tattoo records
Allocation to cages and dosage group
Battery plan

Diet receipt information
Analytical details of - diet : certificates from supplier and in-house work sheets and reports
water : in-house work sheets and reports

Information on the test substance - from Sponsor (e.g. identity, strength, quality, purity and stability)
Record of sample receipt
Formulation requests
Formulation details - weighing out of the test substance
Stored samples of the test substance
Formulation Quality Control records
Formulation stability, homogeneity and achieved concentration assay requests, work sheets and reports

Environmental details of animal rooms : temperature
relative humidity
air-changes
Outside temperature and humidity

Pre-treatment animal observations
Daily animal observation records, including any incidents that may have affected the quality or integrity of the study
Food consumption records
Water consumption records (if performed)
Bodyweight records

Dosing records

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Neurological examination request, work sheets and reports
Ophthalmoscopy requests, work sheets and reports
Haematology requests, work sheets, slides, print outs and reports
Bone marrow requests, work sheets, slides and reports (if examined)
Blood chemistry requests, work sheets, traces, print outs, gel strips and reports
Urinalysis requests, work sheets, print outs and reports
Proof of absorption requests, work sheets, traces and reports (if examined)

Necropsy requests and reports, including organ weights
Histology requests, records of tissues receipt and blocking in histology department
Pathology assessment and final macroscopic and microscopic reports
Tissues, blocks and slides

Quality assurance records and reports, including master schedule
Records of training and experience of all relevant personnel
Records of maintenance and calibration of equipment

Photographic films (if any)
Computer prints and permanent storage discs, including data edits
Correspondence

Reports - typescript and manuscript of draft and final versions

7.4 Quality assurance

This study will be subjected to the following quality assurance procedures:

The protocol will be inspected

Specific procedures and data from this study will be inspected. Other relevant procedures and data will also be inspected periodically.

The final report will be reviewed to assure that it accurately describes the methods and Standard Operating Procedures and that the results accurately reflect the raw data

Reports on these activities will be made to the Study Director and to management.

All raw data pertaining to the study will be available for inspection by any person nominated by the Sponsor.

APPROVED PROTOCOL

RECEIVED
06 NOV 1989

LSR Schedule No : RHA/298/46030
LSR Enquiry No : 3179I
Protocol Amendment No : 1
No. of pages : 6

M&B 46030 : TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR 13 WEEKS

Study Director : P. Holmes, B.Sc., C.Biol., M.I.Biol.

The signature of the Study Director authorises the implementation of this amendment to protocol from the effective date shown on page 2. Any changes to the study design after the date of this authorising signature will be documented in a further formal amendment.

FIRST AMENDMENT APPROVAL

For LIFE SCIENCE RESEARCH LIMITED

Issued by : ..... (Study Director) Date: 17 October 1989

Released by: ..... Date: 17 October 1989

For RHÔNE-POULENC AGROCHIMIE

Approved by: ..... Date: 31/10/89

LSR Schedule No : RHA/298/46030
Protocol Amendment No : 1

M&B 46030 : TOXICITY STUDY BY

DIETARY ADMINISTRATION TO CD RATS FOR 13 WEEKS

Reasons for amendments

: Section 2 : Inclusion of time plan.

: Section 3.1 : Change of animal supplier at request of Sponsor.

: Section 3.2 : Amendment of number of spare animals following change in study design.

: Section 3.4 : Clarification of duration of acclimatisation .

: Section 4.1 : Inclusion of additional treatment group and dietary concentration details.

: Section 4.2 : Amendment of sample size of test substance to be taken.

: Section 4.4 : Clarification of requirements for homogeneity and stability assessments.

: Sections 5.8 and 5.9 : Amendment of reference to Group number following change in study design.

: Section 5.10 : Correction of typographical error.

: Section 5.13 : Deletion of option for proof of absorption investigations.

: Section 6.6 : Extension of histopathology examination to include thyroids and parathyroids of all animals.

: Sections 6.7 and 6.8 : Formalisation of deletion of optional investigations.

Effective date : 11 October 1989.

Amendments

2. Scheduled time plan

To read:

Sample of M&B 46030 to arrive	:	w/b 16 October 1989
Test diet assays to be completed	:	w/b 27 October 1989
Animals to arrive	:	8 November 1989
Treatment to commence	:	w/b 15 November 1989
Terminal sacrifice to commence	:	w/b 14 February 1990
Histopathology to be completed	:	w/b 7 May 1990 (estimated)
Draft report to be issued	:	July 1990 (estimated)

3.1 Animals

First paragraph to read:

Rats of the CD strain (ordered at 21 to 28 days of age, 60 to 80 g bodyweight) will be obtained from Charles River (France), St Aubin-les-Elbeuf, France.

3.2 Pre-commencement animal replacement

First paragraph to read:

Ten spare animals will be ordered to replace any individuals rejected during the acclimatisation period using to following criteria:

Remainder of section unchanged.

3.4 Acclimatisation

To read:

The rats will be allowed to acclimatise to the husbandry conditions described below for at least seven days and not more than fourteen days before commencement of treatment; their health status will be assessed from daily observation.

4.1 Identity of treatment groups (to be selected from 110 rats ordered)

To read:

Group	Treatment	Dietary concentration (ppm)	Cage numbers Male	Cage numbers Female	Animal numbers Male	Animal numbers Female
1	Control	0	1-2	11-12	1-10	51-60
2	M&B 46030	1	3-4	13-14	11-20	61-70
3	M&B 46030	5	5-6	15-16	21-30	71-80
4	M&B 46030	30	7-8	17-18	31-40	81-90
5	M&B 46030	300	9-10	19-20	41-50	91-100

Cage labels, identifying the occupants by experiment, animal number, sex and treatment group, will be colour-coded; white labels will denote animals not assigned to study groups.

4.2 Test substance

Second and third paragraph to read:

In order to demonstrate the integrity of the test substance under the conditions in which it is to be stored at these laboratories, a single 2 g sample will be returned to the Sponsor every six months for reanalysis throughout, and on completion of, the programme of work using this test substance. Results of these analyses will be communicated to LSR for inclusion in the relevant final report.

Before any consignment of the test substance is used in the programme of work at these laboratories, the Pharmacy Department of LSR will ensure that a 2 g representative sample had been taken. This sample will be placed in a well-closed glass container, stored under the conditions specified for the bulk supply of the test substance and retained in the archives.

4.4 Quality control of dosage form

To read:

On each day that quantities of test substance are to be weighed out for test diet preparation, the stock container of test substance will be weighed before the first and after the last removal of part of its contents. The reduction in the weight of the stock container will be documented as a check that the required amount of the test substance has been used.

Before commencement of treatment, an initial trial preparation was performed to determine the suitability of the proposed mixing procedure for a range of levels anticipated to cover the range of concentrations to be employed in this study. Homogeneity was assessed for the highest dietary concentration.

Following the decision by the Sponsor on the treatment levels to be employed and the increase in number of treatment groups, a further trial preparation will be performed. Details of the mixing procedure will be documented for inclusion in the final report. Diet samples will be assayed by the Department of Biomedical and Environmental Chemistry at Life Science Research as detailed below:

Samples prepared for the highest and lowest dietary concentration groups in this study, taken from six positions in the mixer, will be assayed for homogeneity. This procedure will be repeated before instituting any change in the mixing process during the study.

Stability will be determined for the highest and lowest dietary concentration groups from the trial preparation. Representative samples for stability testing will be obtained by pooling the unused portions of the homogeneity samples for each group. Assays will be performed after one and two weeks storage at ambient temperature. The mean of the results for the six homogeneity samples will be taken as the initial assay for the stability test.

Spot checks will be performed by LSR to determine the achieved concentration of diet prepared for each group for the first and last week of treatment, based on a method to be supplied by the Sponsor.

5.8 Neurological examination

First sentence to read:

Before termination of treatment, a full neurological examination will be performed on all surviving animals from Groups 1 and 5.

Remainder of section unchanged.

5.9 Ophthalmoscopy

Third paragraph to read:

Before termination of treatment all surviving rats from Groups 1 and 5 will be similarly examined.

Remainder of section unchanged.

5.10 Haematology, peripheral blood

First paragraph to read:

Before termination of treatment, blood samples will be obtained from all surviving animals.

5.13 - Reference to proof of absorption to be deleted.

6.6 Microscopy

To read:

Microscopic examination will be performed on the tissue sections, specified in the Pathology Procedures Table, as follows:

i) From all rats of Groups 1 and 5 sacrificed on completion of the scheduled treatment period.

ii) From all rats killed or dying during the study.

iii) The thyroids and parathyroids from all rats of Groups 2, 3 and 4 sacrificed on completion of the scheduled treatment period.

iv) From all rats of Groups 2, 3 and 4 sacrificed on completion of the scheduled treatment period in respect of tissues considered to exhibit a reaction to treatment at the high dosage. These will be documented in an amendment to the protocol.

v) All abnormalities (the quoted price allows for examination of one additional tissue section per animal in (i) above).

Any tissue considered to display an effect may be examined further, at the discretion of the pathologist, using processing procedures and stains which may aid the examination as appropriate. Details of these procedures will be recorded for inclusion in the final report.

6.7 & 6.8 - Reference to photomicrography and electron microscopy to be deleted.

RECEIVED
17 NOV 1989

LSR Schedule No : RHA/298/46030
LSR Enquiry No : 3179H
Protocol Amendment No : 2
No. of pages : 2

M&B 46030 : TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR 13 WEEKS

Study Director : P. Holmes, B.Sc., C.Biol., M.I.Biol.

The signature of the Study Director authorises the implementation of this amendment to protocol from the effective date shown on page 2. Any changes to the study design after the date of this authorising signature will be documented in a further formal amendment.

SECOND AMENDMENT APPROVAL

For LIFE SCIENCE RESEARCH LIMITED

Issued by : ..... Date: 30 October 1989
(Study Director)

Released by: ..... Date: 30 October 1989

For RHÔNE-POULENC AGROCHIMIE

Approved by: ..... Date: 13/11/89

LSR Schedule No : RHA/298/46030
Protocol Amendment No : 2

M&B 46030 : TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR 13 WEEKS

Reason for amendment : Clarification of histopathological examination requirements.

Effective date : 24 October 1989

Amendment

Section 6.6 Microscopy

Subsection (iii) to read -

The thyroids, parathyroids, kidneys, liver and lungs from all rats of Groups 2, 3 and 4 sacrificed on completion of the scheduled treatment period.

LIFE SCIENCE RESEARCH

RECEIVED
10 JUL 1990

LSR Schedule No : RHA/298/46030
LSR Enquiry No : 3179H
Protocol Amendment No : 3
No. of pages : 2

M&B 46030: TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR 13 WEEKS

Study Director : P. Holmes, B.Sc., C.Biol., M.I.Biol.

The signature of the Study Director authorises the implementation of this amendment to protocol from the effective date shown on page 2. Any changes to the study design after the date of this authorising signature will be documented in a further formal amendment.

THIRD AMENDMENT APPROVAL

For LIFE SCIENCE RESEARCH LIMITED

Issued by : ..... Date: 11 June 1990
(Study Director)

Released by: ..... Date: 11 June 1990

For RHÔNE-POULENC AGROCHIMIE

Approved by: ..... Date: 21.07.1.90.

LSR Schedule No : RHA/298/46030
Protocol Amendment No : 3

M&B 46030: TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR 13 WEEKS

Reason for amendment : Entension of histopathological examination of liver after consultation with the Sponsor.

Effective date : 7 June 1990

Amendments

2. Scheduled time plan

To read:

Sample of M&B 46030 to arrive	:	w/b 16 October 1989
Test diet assays to be completed	:	w/b 27 October 1989
Animals to arrive	:	8 November 1989
Treatment to commence	:	w/b 15 November 1989
Terminal sacrifice to commence	:	w/b 14 February 1990
Histopathology to be completed	:	w/b 25 June 1990 (estimated)
Draft report to be issued	:	July 1990 (estimated)

6.5 Histology

Additional paragraph to read:

Additional sections of the liver from all animals of all groups will be prepared and stained with Oil-Red-O.

6.6 Microscopy

Final paragraph to read:

In addition, microscopic examination will be performed on the Oil-Red-O stained sections of liver from all animals of all groups.

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 1192 - 12646 SEQ. A

TYPE: INT SUPP FLWP

SUBMITTER NAME: Rhone - Poulenc Inc.

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL. ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
0650 REFER TO CHEMICAL SCREENING
0670 CAP NOTICE

VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/USERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 10/27/92 OTS DATE: 11/02/92 CSRAD DATE: 09/01/95

CHEMICAL NAME:
1H-pyrazole-3-carbonitrile, 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-

CASR
120068-37-3 → m+B 46030

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN	USE:	PRODUCTION:
	YES	YES (DROP/REFER)	RAT	LOW	R&D pesticide	import
CAS SR	NO	NO (CONTINUE)		MED		
	UNKNOWN	REFER		HIGH		

COMMENTS 8EHQ - 0191-11623, 11993, 12323, 12843, 12853, 13153, 25403
Rats recieved test material (pyrazole - carbonitrile derivative) at dietary levels of 0, 1, 5, 30 and 300 ppm for 13 weeks. Liver and thyroid were target organs. Microscopic changes in liver consisted of panacinar hepatocytic fatty vacuolation at 300 ppm; higher incidences of hypertrophy of follicular epithelium were noted in males at 30 and 300 ppm and in females at 300 ppm. The NOAEL was 1 ppm.

Triage of 8(e) Submissions

Date sent to triage: MAY [illegible]

NON-CAP (CAP)

Submission number: 12646A

TSCA Inventory: Y N (D)

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

(STOX) CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

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entire document: (0) 1 2 **pages** 1,2 **pages** 1,2, DABS

Notes: 2-sided

Contractor reviewer : PDR **Date:** 4/26/95