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October 29, 1992

VIA FEDERAL EXPRESS

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Document Processing Center (TS-790)
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 the chemicals MB 46030 [CAS number: 120068-37-3; CAS name: 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile], RPA 098900 [CAS number:

; CAS name:
, RPA 200668 [CAS number: ; CAS name:

, RPA 200911 [CAS number: ; CAS name:

, RPA 098602 [chemical name:
, and RPA 99086 [CAS number: ; CAS name:

]. These chemicals have been synthesized for research and development purposes only.

RPAC claims the alpha-numeric designations, the CAS numbers, and the specific chemical identities of all of the substances at issue except MB 46030 to be confidential business information (CBI). The chemical substances may be nonconfidentially identified as a "heterocycles". The title of the enclosed report is "M&B 46030, : Comparative Toxicity Study by Dietary Administration to CD-1 Mice for Six Weeks". The following is a summary of the adverse effects observed in this study.

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This study is being submitted under Section 8(e) because of the clinical signs observed. Groups of 12 male CD-1 mice received M&B 46030 at dietary concentrations of 5 or 150 ppm or at dietary concentrations of 5, 20, or 50 ppm or at dietary concentrations of 20, 50 or 150 ppm for six weeks. A similarly constituted control group received untreated diet.

For M&B 46030, all animals died during the first 5 weeks of treatment at 150 ppm. Treatment-related signs included overactivity and irritability. Necropsy indicated enlarged livers in three of the animals. Microscopic changes in the liver comprised hypertrophy, vesiculation, and fatty vacuolation of hepatocytes. At 5 ppm, no signs of toxicity were noted.

For _____, all animals died during the first four weeks of treatment at 50 ppm. Treatment-related signs of overactivity, irritability, piloerection, and hunched posture were observed at all doses. At 50 ppm, microscopic changes in the liver comprised hypertrophy, vesiculation, coagulative necrosis, apoptosis, and fatty vacuolation of hepatocytes. At 20 and 5 ppm, microscopic changes included cytoplasmic vesiculation and fatty vacuolation of hepatocytes.

For _____, seven animals died at 50 ppm after exhibiting overactivity, irritability, and aggressiveness. Histologically, fatty vacuolation of the liver and apoptosis were seen. The only effect noted at 20 ppm included irritability. No effects were evident at 5 ppm.

For _____, all animals died at 50 ppm during the first five weeks of treatment. Signs of toxicity included overactivity, irritability, aggressiveness, and hunched posture. Microscopic changes included hepatocytic fatty vacuolation and hypertrophy vesiculation and apoptosis. At 20 ppm, six animals died during treatment and signs of hyperactivity and irritability were evident. No effects were noted at 5 ppm.

For _____, all animals died at 150 ppm, and signs noted included overactivity and aggressiveness. Microscopic changes in the liver comprised hypertrophy, vesiculation and fatty vacuolation of hepatocytes and apoptosis. At 50 ppm, one animal died, and microscopic findings in the liver included hypertrophy, cytoplasmic vesiculation, and apoptosis. No treatment-related signs were seen at 20 ppm.

Finally for _____, all animals died at 150 ppm with signs including overactivity and convulsions. Microscopic changes included hepatocytic fatty vacuolation, hypertrophy, cytoplasmic vesiculation, and perivascular coagulative necrosis. At 20 and 50 ppm, two and four animals died, respectively, during the treatment period, but clinical signs were not observed. Microscopic observations were limited to hepatocytic fatty vacuolation.

Six copies of the report and letter are provided. Three copies are stamped "Confidential Business Information" and have all confidential information circled or underlined. The other three copies are stamped "Public Notice Copy" and have all confidential information deleted.

SUPPORT INFORMATION OF CONFIDENTIALITY CLAIMS

1. Claims of confidentiality are being made on behalf of RPAC.
2. RPAC asserts this claim of confidentiality until such time as the chemicals are approved for use in the United States. In the event that these chemicals are never approved, RPAC asserts that the CBI information should be provided permanent protection. The structure and use of

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these chemicals are unique. Disclosure of this information would provide our competitors with information on facets of our business that would be detrimental to our competitive position.

3. The information claimed as confidential has not been previously disclosed to any other governmental agency or to EPA.
4. This information has been disclosed to only a very limited number of investigators outside of RPAC who have performed either toxicity or efficacy testing. These individuals operate under a strict secrecy agreement. Any individuals who may work with these chemicals will have all health/toxicology information disclosed to them as well, but only on the basis of strict secrecy and respect for the CBI nature of the information.
5. Any individual to whom the CBI is revealed are warned of the nature of the information. Further, they are informed of their obligations to maintain secrecy should they terminate their employment with RPAC.
6. None of the information claimed as confidential appears in or is referred to in any advertising or promotional materials for the chemical or the end product containing it, professional or trade publications, or any other media available to the public or to our competitors. Appropriate warnings do appear on safety data sheets, as RPAC considers that individuals who are requested to work with this chemical have every right to know as much about the chemical's toxicity as possible. Further, the information is only considered to be CBI with respect to the general public, insofar as our competitors could use the information in an unfairly competitive nature.
7. No previous confidentiality determinations have been made by EPA, other Federal agencies or courts in connection with this information.
8. RPAC believes that disclosure of this information to the general public would be likely to result in substantial harm to its competitive position. Disclosure of the alpha numeric designations, chemical names and CAS numbers would provide some competitors with information about the specific chemistry of this area of our research and our business. Further, the type of toxicological testing being reported in the TSCA 8(e) notice would provide competitive information about this chemical's status in the research and development process and, therefore, the time remaining until commercialization.
9. Patent have not been issued for the specific chemical structures. However, the generic chemical structures are covered by a patents that are currently pending.
10. These chemicals are not available commercially. They are in the earliest stages of research and development for pesticide use and are unlikely to be developed into a commercial product.
11. We believe that disclosure of the chemical names would allow a competitor to synthesize the chemicals. RPAC has invested a large amount of time and money into research of this particular chemical family, and information on specific chemical structures would harm our competitive position.
12. Disclosure of the chemical structures might reveal information on processes used to synthesize and manufacture these compounds.
13. The available CAS numbers for these chemicals are provided in the first page of this letter. These numbers are claimed as confidential as they provide access to the chemical names.

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14. Currently, these chemicals are not the subject of FIFRA regulation or reporting.

15. RPAC is not claiming "health and safety data" as CBI. Rather, we are claiming the exact chemical names as CBI.

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

Sincerely yours,



Glenn S. Simon, PhD, DABT
Director of Toxicology

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LSR Schedule No : RHA/390/COMP
LSR Report No : 90/RHA390/0898

COMPANY SANITIZED

M&B 46030.

**COMPARATIVE TOXICITY
STUDY BY DIETARY ADMINISTRATION
TO CD-1 MICE FOR SIX WEEKS**

FINAL REPORT

Data requirement

Guideline No. Not applicable

Study Period Completed on

5 February 1991

Study Director

S. Cracknell

**To:
Rhône-Poulenc Agrochimie
14-20 rue Pierre Baizet
B.P. 9163
69263 Lyon Cedex 07
France**

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

**Draft: 11 December 1990
Final: 26 February 1991**

M&B 46030.

COMPARATIVE TOXICITY
STUDY BY DIETARY ADMINISTRATION
TO CD-1 MICE FOR SIX WEEKS

FINAL REPORT

LSR Schedule No : RHA/390/COMP
LSR Report No : 90/RHA390/0898

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,

**COMPARATIVE TOXICITY
STUDY BY DIETARY ADMINISTRATION
TO CD-1 MICE FOR SIX WEEKS**

FINAL REPORT

**LSR Schedule No : RHA/390/COMP
LSR Report No : 90/RHA390/0898**

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 EPA Pesticide Programs Good Laboratory Practice Standards (40 CFR Part 160)
- Current OECD Good Laboratory Practice Principles
- Current UK DH Principles of Good Laboratory Practice
- Current Japanese Good Laboratory Practice Standards on Agricultural Chemicals

The following exception applied:

Owing to its preliminary nature no Quality Assurance procedures were conducted on this particular study. Inspections were however conducted and data and reports reviewed on other studies carried out in the same animal and laboratory areas during the same period as this study.

It is not considered that this exception from GLP influenced the validity of the data or report.

The Study Director fulfilled the responsibilities required by these regulations.

S. Cracknell, H.TEC.
(Study Director)

..... *S. Cracknell*

Date: *25 February 1991*

.....

Date:

(For Submitter)

.....

Date:

(For Sponsor)

0009

M&B 46030,

COMPARATIVE TOXICITY
STUDY BY DIETARY ADMINISTRATION
TO CD-1 MICE FOR SIX WEEKS

FINAL REPORT

LSR Schedule No : RHA/390/COMP
LSR Report No : 90/RHA390/0898

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,

COMPARATIVE TOXICITY
STUDY BY DIETARY ADMINISTRATION
TO CD-1 MICE FOR SIX WEEKS

FINAL REPORT

LSR Schedule No : RH/390/COMP
LSR Report No : 90/RHA390/0896

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, Special Projects)

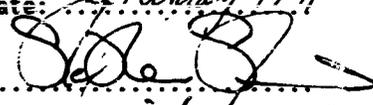

Date: 22 February 1991

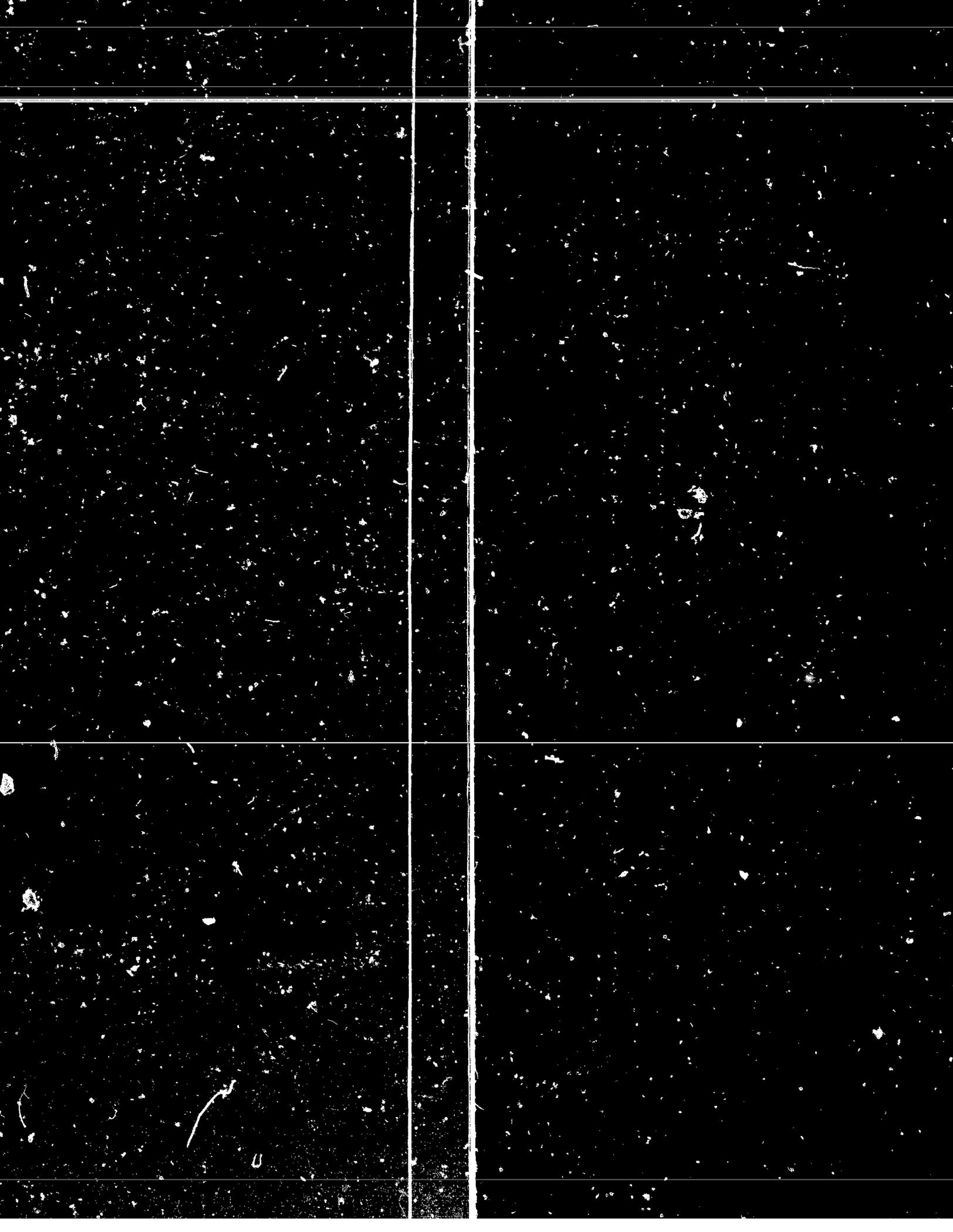
We, the undersigned, were responsible for the conduct of the work and reporting of the results in the listed sections; we concur with the views expressed in the Discussion.

J.P. Ellis.
(Staff Toxicologist)
Sections 5.1 to 5.7


Date: 22 February 1991

S. Sparrow, Ph.D., B.Vet.Med., M.R.C.V.S.
(Head, Department of Pathology)
Sections 5.8 and 5.9


Date: 25 February 1991



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1. SUMMARY

1.1 Groups of 12 male CF 1 mice received M&B 46030 at dietary concentrations of 5, 20, 50 or 150 ppm or at dietary concentrations of 5, 20 or 50 ppm, or at dietary concentrations of 20, 50 or 150 ppm for six weeks. A similarly constituted control group received untreated diet.

1.2 M&B 46030150 ppm

All animals died during the first five weeks of treatment. Treatment-related signs comprised overactivity and irritability from Week 1.

Food consumption was low during the first week of treatment and high during weeks 4 and 5. Bodyweight loss was recorded during the first two weeks of treatment; thereafter animals gained weight at a reduced rate prior to death. The efficiency of food utilisation was inferior to that of the controls.

Necropsy indicated enlarged livers in three animals.

Microscopic changes in the liver comprised hypertrophy/vesiculation and fatty vacuolation of hepatocytes.

5 ppm

There were no signs of reaction to treatment.

Food consumption was unaffected by treatment.

Overall bodyweight gain and the efficiency of food utilisation were slightly inferior to those of the untreated controls.

There were no microscopic changes in the liver which were attributed to treatment.

1.3

50 ppm

All animals died during the first four weeks of treatment.

Signs of reactions to treatment comprised overactivity, irritability and hunched posture from the first week of treatment.

Food consumption was unaffected by treatment.

Markedly low bodyweight gains were observed in comparison with untreated controls and the efficiency of food utilisation was inferior to that of the untreated animals.

Necropsy included enlarged liver in four decedents; liver weight was high for all animals.

Microscopic changes comprised hepatocytic fatty vacuolation, hepatocytic hypertrophy/vesiculation, coagulative necrosis and apoptosis.

20 ppm

Two animals died during the treatment period; other signs of reaction to treatment in this group included convulsions, reduced respiratory rate, hypoactivity, hunched posture, piloerection, dark eyes, irritability and hyperactivity.

Food consumption was unaffected by treatment.

Overall bodyweight gains and the efficiency of food utilisation were inferior to those of the controls.

Necropsy revealed an enlarged liver in one decedent animal; liver weight was also higher than normal for both of the decedents.

Necropsy observations for survivors were unremarkable; however, liver weights for all animals were higher than those recorded for the controls.

Microscopic changes included cytoplasmic vesiculation and fatty vacuolation of hepatocytes.

5 ppm

One animal was killed during Week 2 of the treatment period; signs evident for this animal comprised underactivity, piloerection, increased respiratory rate, shallow respiratory movements, hunched posture and dark eyes.

There were no signs of reaction to treatment among animals killed after 6 weeks of treatment.

Overall food consumption was unaffected by treatment.

Bodyweight gains were unaffected by treatment.

Necropsy findings for both the decedent and the survivors were unremarkable; however, liver weight for the decedent was higher than expected.

Microscopic changes in the liver comprised hepatocytic hypertrophy and cytoplasmic vesiculation.

1.4

50 ppm

Seven animals died.

Treatment-related signs comprised overactivity, irritability and aggressiveness from Week 2 of treatment.

Food consumption was unaffected by treatment.

Slightly overall low bodyweight gains and inferior food conversion ratios were observed when compared with controls.

There were no necropsy findings which were attributable to treatment. Bodyweight-relative liver weights for both the premature decedents and animals which were killed after six weeks of treatment were higher than those for the controls.

Microscopic change was confined to premature decedents and in the liver comprised fatty vacuolation of hepatocytes and apoptosis.

20 ppm

There were no deaths. Signs of reaction to treatment, irritability from Week 4.

Food consumption was unaffected by treatment.

Slightly low bodyweight gains and inferior food utilisation efficiency were evident for these animals.

Necropsy findings and the weights of liver, kidneys and brain were unremarkable for all animals.

There were no microscopic changes in the liver which were attributed to treatment.

5 ppm

There were no treatment-related changes at this dietary concentration.

1.5

50 ppm

All animals died during the first five weeks of treatment.

Signs evident before death comprised overactivity, irritability, aggressiveness and hunched posture from Week 1.

Markedly low bodyweight gains and inferior efficiency of food utilisation were evident when compared with the controls.

Food consumption was unaffected by treatment.

Necropsy indicated an enlarged liver in one animal; however, liver weights were considered unaffected by treatment.

Microscopic changes in the liver comprised hepatocytic fatty vacuolation, hepatocytic hypertrophy vesiculation and apoptosis.

20 ppm

Six animals died during the treatment period. Other treatment-related signs comprised hyperactivity and irritability.

Slightly low bodyweight gains and marginally inferior efficiency of food utilisation were seen when compared to the controls.

Food consumption was unaffected by treatment.

There were no treatment-related macroscopic pathology findings or organ weights effects.

Microscopic change in the liver considered attributable to treatment was limited to apoptosis which was seen for one premature decedent.

5 ppm

There were no treatment-related changes at this dietary concentration.

1.6

150 ppm

All animals died during the first five weeks of treatment. Treatment-related signs comprised overactivity and aggressiveness from Week 1.

Bodyweight gain and the efficiency of food utilisation were inferior to those of the untreated controls during the first three weeks of treatment.

Necropsy indicated an enlarged liver in one decedent animal; liver weight was high for all animals.

Microscopic changes in the liver comprised hepatocytic fatty vacuolation, hepatocytic hypertrophy/cytoplasmic vesiculation and apoptosis.

50 ppm

One animal died during the treatment period.

Bodyweight gain, food consumption and food utilisation efficiency were unaffected by treatment.

Necropsy observations for both the decedent and for the survivors were unremarkable.

Examination of organ weights revealed a higher than expected liver weight for the decedent; the liver weights recorded for animals which were killed after six weeks of treatment were unaffected in this respect.

Microscopic changes in the liver comprised hepatocytic hypertrophy/cytoplasmic vesiculation and apoptosis.

20 ppm

There were no changes related to treatment at this dietary concentration.

1.7

150 ppm

All of the animals receiving 150 ppm died or were killed for humane reasons during the first eight days of treatment.

Signs evident before death comprised overactivity and convulsions.

Necropsy indicated enlarged livers in seven decedent animals; liver weights were markedly high for all animals.

Microscopic changes in the liver comprised hepatocytic fatty vacuolation, hepatocytic hypertrophy/cytoplasmic vesiculation, and perivascular coagulative necrosis.

50 ppm

Four animals died during the treatment period.

Food consumption was lower than for the controls during the first three weeks of treatment, overall food consumption was unaffected by treatment.

Markedly low bodyweight gains and inferior efficiency of food utilisation were evident when compared with the controls.

Necropsy indicated enlarged livers in two decedent animals. Enlarged and pale livers were found in four animals at the terminal sacrifice. Liver weights were high for both decedents and the survivors.

Microscopic change in the liver, which was attributed to treatment, was limited to hepatocytic fatty vacuolation.

20 ppm

Two animals died during the treatment period.

Low food consumption and bodyweight gains were seen in these animals and the efficiency of food utilisation was inferior to that achieved by the controls.

Necropsy indicated enlarged livers in six animals that survived the treatment period.

Liver weights were higher than normal for the decedents and values recorded for animals killed after six weeks of treatment were slightly higher than those recorded for the untreated controls.

Microscopic change in the liver attributed to treatment was limited to hepatocytic fatty vacuolation.

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1.8 It was concluded that the relative toxicities of each of the test substances were:

M&B 46030 was considered to have comparable toxicity to

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2. INTRODUCTION

The purpose of this study was to aid the assessment of the toxic effects of in comparison with those seen with M&B 46030.

The mouse was chosen because of its known response to M&B 46030, its use as a predictor of toxic and neoplastic change in man and the requirement by regulatory agencies for a rodent species. The CD-1 strain was used because of the availability of background data relating to this strain. The dietary route was selected to accord with the potential major route of exposure in man. The dietary concentrations of 5 and 150 ppm for M&B 46030, 5, 20 and 50 ppm for 20, 50 and 150 ppm for and the duration of six weeks of treatment, were selected by the Sponsor.

Treatment commenced on 17 May 1990 and necropsies were completed on 5 July 1990.

3. TEST SUBSTANCE AND DOSAGE FORM

Samples of 12.5 g of (fawn coloured crystals with a stated purity of 99.7%), a fine white powder of Batch No. 1GB 629B with a stated purity of 99.6%), (a fine white powder of Batch No. MAB 424A with a stated purity of 98.7%), and (a fine white powder with a stated purity of 99.1%) were received from the Sponsor on 26 April 1990 in amber glass jars. A 12 g sample of (a pale yellow powder of Batch No. LAM 394 with a stated purity of 96%) was received on 1 May 1990. The reference material, M&B 46030 (a fine off-white powder of Batch PGS 963 with a stated purity of 95.4%) was received from the Sponsor on 16 October 1989.

The identity, strength, purity, composition, methods of synthesis, fabrication or derivation of the test material are documented by the Sponsor. Before treatment commenced, an aliquot of each test substance was taken and is stored in the archives under the conditions specified for the bulk.

In order to demonstrate the integrity of the test and control substances under the conditions in which they were stored at these laboratories, a sample of each was returned to the Sponsor for reanalysis on completion of the programme of work using these substances. The results of these analyses were not available at the time of preparation of this report.

The test materials were prepared for administration as described in Section 4.2; no allowance was made for purity.

The suitability of the diet preparation was assessed by a trial preparation before treatment commenced. Diet samples prepared using methods and concentrations intended for the highest and lowest treatment groups for the positive control and each test substance are retained deep frozen (approximately -20°C) against possible future requirements for homogeneity and stability assays. Data pertaining to the stability and homogeneity of the control and each test substance at the dietary concentrations used in this study are the responsibility of the Sponsor. In addition, samples of each test and control diet prepared for administration in Weeks 1 and 6 were retained deep frozen (approximately -20°C) against possible future requirements for achieved concentration assays.

4. METHODS4.1 Design conditions4.1.1 Animals

Two hundred and thirty six male CD-1 mice were obtained from Charles River U.K. Limited, Margate, Kent, England. The animals were three to four weeks of age on arrival and had bodyweights within the range 13 to 21 g.

4.1.2 Identification

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

4.1.3 Acclimatisation

The mice were allowed to acclimatise to the management conditions described below for 8 days before commencement of treatment, during which their health status was assessed by daily observations.

4.1.4 Environmental control

The animals were housed in one room with no other study, inside a barriered limited-access rodent facility. Personnel entering were required to shower and change into protective clothing. A gown, plastic overshoes and mask were put on before entering the room and gloves were worn when handling animals.

Before delivery of the animals the rooms were 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 re-circulated. Ventilation equipment was designed to provide approximately 15 air changes per hour and a 12-hour light : 12-hour dark cycle operated. Target values for temperature and humidity were 21°C (18-25°C) and 55% RH (40-70% RH). Maximum and minimum temperature and relative humidity were recorded daily; these records indicate no significant variation from target values.

Temperature and airflow sensors were connected to an audible and visible 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 husbandry

The mice were housed four males per cage, unless this number was reduced by mortality, in high-density polypropylene cages measuring 33 x 15 x 13 cms (type M2 from North Kent Plastics Limited, Dartford, Kent, England) with stainless steel mesh lid. Wood shavings, used as bedding, were sterilised by autoclaving and changed twice weekly. Cages, food hoppers and water bottles were changed at intervals of approximately two weeks. Cages comprising the different treatment groups, described below, were distributed in such a way as to equalise, as far as possible, the effect of any spatially variable component of the environment. The cage arrangement is recorded in Figure 1.

4.1.6 Diet and water supply

Drinking water was supplied to each cage via polyethylene bottles with chromium plated sipper-tubes. The water was taken from the public supply, controlled by the East Anglia Water Company, Lowestoft, Suffolk, England.

A commercially available powdered rodent diet, Laboratory Animal Diet No. 2 (Biosure, Manea, Cambridgeshire, England), was offered *ad libitum*. This was an expanded diet subsequently ground by the supplier. It was supplied in a discardable outer paper sack and sealed inner sterilisable polythene bag and contained no added antibiotic or other chemotherapeutic or prophylactic agent.

Diet and water were available *ad libitum* except for brief intervals due to husbandry considerations.

4.1.7 Contaminants control

A sample of each batch of Lignocel Type 3/4 wood shaving bedding (J. Rattenmaier and Söhne GmbH, Ellwangen-Holzühle, Federal Republic of Germany) were taken on receipt and retained. At approximately six-month intervals additional samples were taken from the then current batch and examined for selected chlorinated pesticides and polychlorinated biphenyl contaminants. In addition, certificates of analysis were received from the supplier.

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

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

Results of these various 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 to treatment groups

On arrival, the mice 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.

4.1.9 Treatment groups and animal numbers

Cage and animal numbers related to treatment as follows:

<u>Group</u>	<u>Treatment</u>	<u>Dietary Concentration (ppm)</u>	<u>Cage numbers</u>	<u>Animal numbers (males)</u>
1	Negative control	0	1-3	1-12
2	M&B 46030 (positive control)	5	4-6	13-24
3	M&B 46030 (positive control)	150	7-9	25-36
4		5	10-12	37-48
5		20	13-15	49-60
6		50	16-18	61-72
7		5	19-21	73-84
8		20	22-24	85-96
9		50	25-27	97-108
10		5	28-30	109-120
11		20	31-33	121-132
12		50	34-36	133-144
13		20	37-39	145-156
14		50	40-42	157-168
15		150	43-45	169-180
16		20	46-48	181-192
17		50	49-51	193-204
18		150	52-54	205-216

Cage labels, identifying the occupants by experiment, animal number and treatment group were colour-coded to match similar labels, attached to the formulation container. White labels denoted animals not assigned to study groups before commencement of treatment. These animals were discarded without necropsy at the start of the treatment period.

4.2 Treatment

4.2.1 Formulation

The M&B 46030, as appropriate, were incorporated into ground diet at constant concentrations for each group by initial preparation of a premix, followed by dilution with further quantities of diet. Initially the appropriate test substance was mixed manually with small measured quantities of diet of increasing weight and the resulting premix milled in an ultracentrifugal mill fitted with a 2 mm screen. The final amount of diet required was added to give the required high concentration and mixing was continued for ten minutes in a small planetary mixer. This diet was divided for treatment of the high dose group and for preparation of the remaining groups, using a small planetary mixer, by a serial dilution process.

On each occasion of diet preparation, a 100 g aliquot of each treatment diet was taken into sealed aluminium foil laminated sachets and stored in a deep-freeze pending possible future analytical requirements. They were discarded after three months unless used for dietary analysis (Section 4.2.3).

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 at approximately -20°C pending possible future analytical requirement.

After formulation, diets were sealed in transparent polyethylene bags bearing a colour-coded label similar to that used to identify the cages of the appropriate group.

4.2.2 Test substance balance

Detailed records of compound usage were maintained. On each occasion that quantities of test and control substances were taken for weekly preparation of the test formulations, the stock container for each was weighed before and after removal of part of its contents. The reduction in weight of each stock container was documented as an independent check that the correct amount of the appropriate test compound had been used.

0 0 2 6

4.2.3 Analysis of test diets

Before commencement of treatment the suitability of the mixing procedure was determined by a trial preparation. Diet samples were obtained from the highest and lowest dietary concentrations for the control and each test compound. These samples were retained deep frozen (approximately -20°C) against possible future requirements for homogeneity and stability assays.

Samples of each test and control diet prepared for Weeks 1 and 6 were retained deep frozen (approximately 20°C) against possible future requirements for achieved concentration assays.

4.2.4 Administration

Mice received the test and control substances, as appropriate, continuously, via the diet, throughout the treatment period. The dietary concentration was maintained at a constant level for each treated group. Negative control mice received untreated diet at the same frequency, and from the same batch, as treated animals.

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 mice were killed after completing at least six weeks of treatment. Necropsies took two days to complete.

4.3 Serial observations

4.3.1 Signs

All mice were inspected at least twice daily for signs of ill-health or reaction to treatment. Any deviations from normal were recorded at the time in respect of nature and severity, date and time of onset, duration and progress of the observed condition.

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

One or two daily checks for deaths, 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 in the cages was also noted.

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

The observations were 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.

4.3.2 Mortality

A complete necropsy was performed, as described in Section 4.4, on all animals that died during the study.

4.3.3 Food consumption

The quantity of food eaten by each cage of mice was calculated for each week of treatment by measurement of the amount of food given and that remaining in the food hopper. The quantity of food scattered from the food hopper was weighed or estimated twice each week and included in the food residue for calculation of food consumption.

4.3.4 Bodyweight

Each mouse was weighed on the day that treatment commenced, at twice 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, expressed as mg/kg/day, were calculated weekly.

4.4 Terminal observations

4.4.1 Euthanasia

After completion of the scheduled treatment period all surviving mice were killed by carbon dioxide inhalation. The sequence in which the animals were killed was selected to allow satisfactory inter-group comparison.

All mice killed and those which died during the study were subjected to a detailed necropsy as described below, with the minimum delay.

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 organs and tissues were examined as appropriate. Abnormalities, interactions and changes were noted, the requisite organs weighed, and the required tissues preserved in fixative.

Before disposing of the carcass the tissues retained were checked against the protocol and a senior prosector reviewed the necropsy report.

4.4.3 Organ weight analysis

The organs specified below, taken from all animals, were dissected free of adjacent fat and other contiguous tissue and the weights recorded:

Brain
Kidneys
Liver.

4.4.4 Tissues preserved for histopathology

Samples of liver were preserved for histological processing and microscopic examination in buffered 4% formaldehyde saline.

4.4.5 Other tissues preserved

Samples of the tissues listed below, together with macroscopic abnormalities, were not processed histologically, but are held in buffered 4% formaldehyde saline against possible future requirement for microscopic evaluation.

Brain
Kidneys
Sciatic nerves
Spinal cord
Thyroid with parathyroids.

4.4.6 Histological processing

After dehydration and embedding in paraffin wax, sections of liver were cut at approximately five micron thickness and stained with haematoxylin and eosin.

4.4.7 Microscopic examination

Samples of two lobes of liver, taken from all mice killed at the end of the treatment period, and from all animals which died during the study, were subjected to microscopic examination.

4.5 Data processing

4.5.1 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 where appropriate using the sample statistic. Group means and standard deviations are presented to the same level of accuracy as the individual values.

4.5.2 Food consumption

Total food intake values presented in Table 2 were generated from unrounded mean weekly values.

4.5.3 Bodyweight

Bodyweight change was calculated from the weight changes of individual mice.

4.5.4 Food conversion ratio

Food conversion ratios were calculated from unrounded group mean food consumption and bodyweight values.

4.5.5 Organ weights

The weights of kidneys were separately recorded for left and right sides. These were summed for reporting and before calculation of individual relative organ weight values as a percentage of bodyweight.

4.5.6 Pathology

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

4.5.7 Statistical evaluation

Tests for the significance of difference between each treatment group and the corresponding controls were conducted as follows:

For bodyweight gain a series of Student's t-tests was performed using a pooled within-group error variance.

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

For macroscopic and microscopic changes, inter-group differences in incidences were evaluated by Fisher's Exact Test (two-tailed).

4.6 Archives

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

5. RESULTS

5.1 Signs (Appendix 2)

Signs of reaction to treatment were seen in animals receiving M&B 46030 at 150 ppm, at 50 ppm, at 20 or 50 ppm, at 150 ppm, at 50 or 150 ppm. The signs observed consisted of hyperactivity, irritability, convulsions, piloerection, irregular respiration, hunched posture and dark eyes.

There were no signs of reaction to treatment recorded for animals receiving M&B 46030 at 5 ppm, at 5 or 20 ppm, at 5 ppm or at 20 or 50 ppm. One animal receiving at 20 ppm was considered to be irritable in the final stages of the study; this single observation was not clearly attributable to treatment however.

5.2 Mortality (Table 1; Appendix 2)

Eighty three animals died or were killed during the study period. These were distributed amongst the groups as follows:

Compound	Dietary concentration (ppm)			
	5	20	50	150
M&B 46030	0	*	*	12
	1	2	12	*
	0	0	7	*
	0	6	12	*
	*	0	1	12
	*	2	4	12

* Not applicable

Most of the decedents were found dead without previous indications of ill-health. Others were found in a moribund condition with signs including irregular respiration, hunched posture and dark eyes. Most of these animals died before they could be humanely killed. The decline in health and subsequent death were rapid and usually without warning. All deaths were attributed to treatment.

5.3 Food consumption (Table 2; Appendix 2)

The interpretation of food consumption data after the first week of treatment was complicated by the reduced group size caused by treatment-related deaths (Section 5.2).

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Examination of weekly values indicates that the amount of food consumed during the first week of treatment by animals receiving M&B 46030 at 150 ppm or at 150 ppm was slightly lower than that eaten by the controls during the same period. Thereafter, the amount of food eaten by these animals and by other groups in which all of the animals died prematurely (Group 6 receiving at 50 ppm, Group 12 receiving at 50 ppm and Group 18 receiving at 150 ppm) generally increased to values higher than those evident for the controls.

Clearly low food consumption, when compared with values for the controls during the same period, were recorded during Weeks 2 and 3 of treatment for animals receiving at 20 or 50 ppm respectively.

Overall food consumption of treated animals in groups with survivors after six weeks of treatment was generally similar or slightly lower than that of the controls although higher values were recorded for Week 6 for animals receiving at 50 ppm, at 20 or 50 ppm or at 20 ppm. Similarly high food consumption was also evident during Week 5 of treatment for animals receiving at 50 ppm.

5.4 Bodyweight (Figure 2; Table 3; Appendix 4)

When expressed as percentages relative to controls, overall bodyweight gains (Weeks 0-6) were as follows:

Compound	Dietary concentration (ppm)			
	5	20	50	150
M&B 46030	96	*	*	-
	100	80	-	*
	121	93	75	*
	102	76	-	*
	*	99	104	-
	*	89	68	-

* Not applicable
- No survivors in Week 6

During the first week of treatment bodyweight stasis or loss was evident for animals receiving M&B 46030 at 150 ppm. Subsequently surviving animals in this group gained bodyweight at a reduced rate when compared to the controls. Animals receiving at 50 ppm, at 50 ppm or at 150 ppm gained bodyweight more slowly than the controls and periods of bodyweight stasis or loss were evident for most animals before death.

Bodyweight gains for most of the animals receiving at 20 ppm, at 50 ppm, at 20 ppm or at 20 or 50 ppm were similar to those of the controls during the first eleven days of the treatment period. Thereafter gains for these animals were generally lower than for the controls with periods of bodyweight stasis evident for many individuals. Loss or stasis of bodyweight were seen before death for decedents in these groups.

Animals receiving at 20 ppm gained weight at a similar rate to the controls during the first two weeks of treatment. After this time bodyweight gains for these animals were consistently slightly inferior to those of the controls.

Animals receiving at 5 ppm had slightly superior bodyweight gains throughout the treatment period when compared to the controls. Overall weight gain for these animals was clearly higher than that of the controls but this was considered in part due to lower than expected weight gains for many of the controls during the last week of the treatment period.

The overall bodyweight gains of animals receiving at 5 ppm, at 5 ppm or those receiving at 20 or 50 ppm were unaffected by treatment.

5.5 Food conversion ratios (Table 4)

The efficiency of food utilisation, as indicated by the food conversion ratio, in animals receiving at 20 or 50 ppm, at 50 ppm, at 20 or 50 ppm or at 50 ppm was inferior to that of the controls.

Food utilisation efficiency for animals receiving at 5 ppm was slightly superior to that evident for the controls. Overall food conversion ratios for other treated groups were similar to those for the controls.

5.6 Achieved dosage (Table 5)

The following overall dosages (mg/kg/day) were achieved:

Compound	Dietary concentration (ppm)			
	5	20	50	150
M&B 46030	0.73	*	*	33.36
	0.73	2.98	10.14	*
	0.74	2.61	10.14	*
	0.70	3.13	8.51	*
	*	3.03	6.58	25.78
	*	2.57	6.90	24.72

* Not applicable

5.7 Organ weight (Table 6; Appendix 5)

Inter-group differences, after six weeks of treatment, in absolute and bodyweight-relative liver weights which were clearly attributable to treatment were confined to animals which received [redacted] at 20 or 50 ppm or those which received [redacted] at 50 ppm. High liver weights were seen for all animals in these groups with dosage-relationship evident for animals that received [redacted]. The most marked increases in liver weight were seen for animals which had received [redacted] at 20 or 50 ppm but there was no evidence of dosage-relationship in the magnitude of the effect for these animals. Liver weights for premature decedents were consistently much higher than expected.

Slightly lower bodyweight-relative kidney weights were evident for animals that received [redacted] at 50 or 150 ppm when compared to the controls. The differences from control kidney weights did not attain statistical significance but in view of the apparent dosage-relationship they were attributed to treatment. The kidney weights for all other treatment groups were considered to be unaffected by treatment.

Apparent effects on bodyweight-relative brain weight were considered to have arisen as a result of the low terminal bodyweight of some treated animals.

5.8 Macroscopic pathology (Table 7; Appendix 6)

Treatment-related changes for animals which survived the scheduled six weeks of treatment were evident only among animals that received [redacted]. Enlarged and pale livers were present in two animals that received 20 ppm and in four animals that received 50 ppm. The livers of a further four animals that received 20 ppm appeared enlarged.

Among animals that died during the study there were enlarged livers in: three animals given M&B 46030 at 150 ppm; one animal given [redacted] at 20 ppm; four animals given 50 ppm; two animals [redacted] at 50 ppm and in seven given 150 ppm. Additional, probable treatment related findings for premature decedents that received [redacted] included: hepatic pallor in one animal given 50 ppm and two given 150 ppm and a swollen appearance to the liver for one animal that had received 50 ppm.

5.9 Microscopic pathology (Table 8; Appendix 6)

Findings considered to be related to treatment were seen in the livers of animals treated with each of the test materials. The main features consisted of hypertrophy/vesiculation and fatty vacuolation of hepatocytes. Perivascular coagulative necrosis and apoptosis were seen in occasional animals.

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No no-effect-level was identified for which received at 5 ppm effects were confined to peri-acinar hypertrophy/cytoplasmic vesiculation in seven of the eleven animals examined. For at 5 or 20 ppm there were no changes attributed to treatment. No-effect-levels for (5 ppm) and (20 ppm) were identified.

There were no treatment-related changes in animals which received M&B 46030 at 5 ppm.

Other findings were those commonly seen in mice of this age and strain at these laboratories.

There were a large number of decedent animals which makes interpretation of data difficult. The majority of the decedents did exhibit some signs of liver toxicity.

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6. DISCUSSION

Evidence of toxicity was observed with all of the test materials and with the reference material M&B 46030. The principle targets of toxicity for all of the test compounds identified by this study were the nervous system and the liver.

Changes in behaviour considered attributable to treatment were evident for animals receiving each of the test substances and included hyperactivity, irritability and convulsions.

Effects of treatment on food consumption, bodyweight and the efficiency of food utilisation were variable but there was a clear trend toward higher food consumption, lower bodyweight gains and poor efficiency of food utilisation by animals in groups in which 100 percent mortality occurred. This observation was probably associated with the increased levels of activity and irritability evident for many of these animals before death. In groups with survivors, lower overall food consumption and inferior bodyweight gains could not be associated with clear changes in behaviour. There were no clear differences from control values for the food consumption and bodyweight gains of animals receiving at 5 ppm or at 20 ppm.

Effects of treatment on the liver were identified for all of the test materials and for M&B 46030. These comprised high liver weights, macroscopic changes in size or shape and histopathological observations.

Hepatocytic fatty vacuolation in the periacinar, centriacinar and midzonal regions indicates an effect of treatment on the production or metabolism of fats within the liver. The hepatocytic hypertrophy may represent an adaptation to the changes in fat metabolism, or possibly enzyme induction in response to a xenobiotic.

The presence of fatty vacuolation and hepatocytic hypertrophy were probably significant factors in the increased liver weights. Dosage-relationship for the liver weight changes was evident only for animals which received , however findings for animals that received other test substances were probably disturbed by the high levels of mortality in many groups.

Based on the observed effects of treatment including mortality, liver weight, macropathology and histopathology the five test substances and the reference material M&B 46030 were ranked according to their relative toxicities at each dietary concentration.

At 150 ppm animals receiving died more quickly and showed more treatment-associated liver weight and histopathological changes than animals that received M&B 46030 or ; findings for the latter two materials were similar.

At 50 ppm all of the animals that received [redacted] 186 died during the treatment period and showed similar incidences of histopathological changes; however, for [redacted] there was no evidence of increased liver weight. More of the animals receiving [redacted] died as a result of treatment (7) than did those receiving [redacted] (4) but the incidence of histopathological change and liver weight increase were similar for the two materials. Mortality at 50 ppm for [redacted] was the lowest for any of the test substances at this treatment level and there were no liver weight changes and only a low incidence of liver histopathological findings for this material.

At 20 ppm treatment with [redacted] resulted in fewer deaths than for [redacted]; however, liver weight increases were evident among animals receiving all of these substances. The incidence of microscopic changes in the liver was highest for animals that received [redacted]. These compounds were therefore considered of similar toxicity at this dietary concentration. There were no deaths, liver weight changes or microscopic findings for animals receiving [redacted] at this treatment level.

At 5 ppm death was seen in only one animal, receiving [redacted]; liver weight increases were also evident for some of these animals after six weeks. Histopathological examination of the livers for these animals revealed a higher incidence of hepatic hypertrophy than for any other group. There were no findings of toxicological significance for animals that received M&B 46030, [redacted] at 5 ppm

No-effect-levels in respect of affected parameters were considered to be at the following dietary concentrations (ppm);

	Lowest ppm	Signs	Mortality	Food consumption	Growth	Liver weight	Liver histopathology
M&B 46030	5	5	5	5	5	5	5
	5	-	-	20	5	-	-
	5	20	20	50	-	20	20
	5	5	5	20	5	50	5
	20	50	20	50	50	20	20
	20	-	-	50	-	-	-

- = No no-effect level

Based on these observations the test substances were ranked according to the relative toxicities seen in this study.

Assessment of the comparative toxicity of M&B 46030 was complicated by the absence of an intermediate treatment level, but in view of effects seen it probably has comparable toxicity to



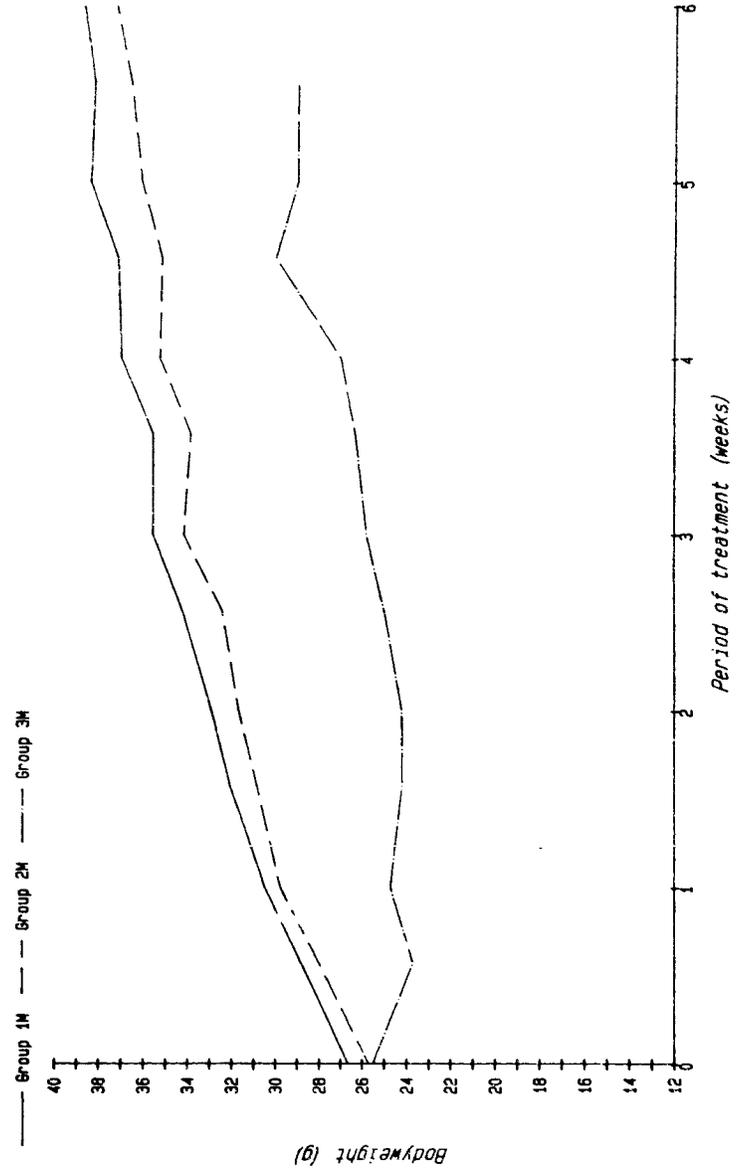
7. CONCLUSION

It was concluded that the relative toxicities of each of the test substances were:

M&B 46030 was considered to have comparable toxicity to

FIGURE 2A
Group mean bodyweight versus period of treatment - males

Group : 1 2 3
Compound : Control
Level (ppm) : 0 5 150



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FIGURE 2B
Group mean bodyweight versus period of treatment - males

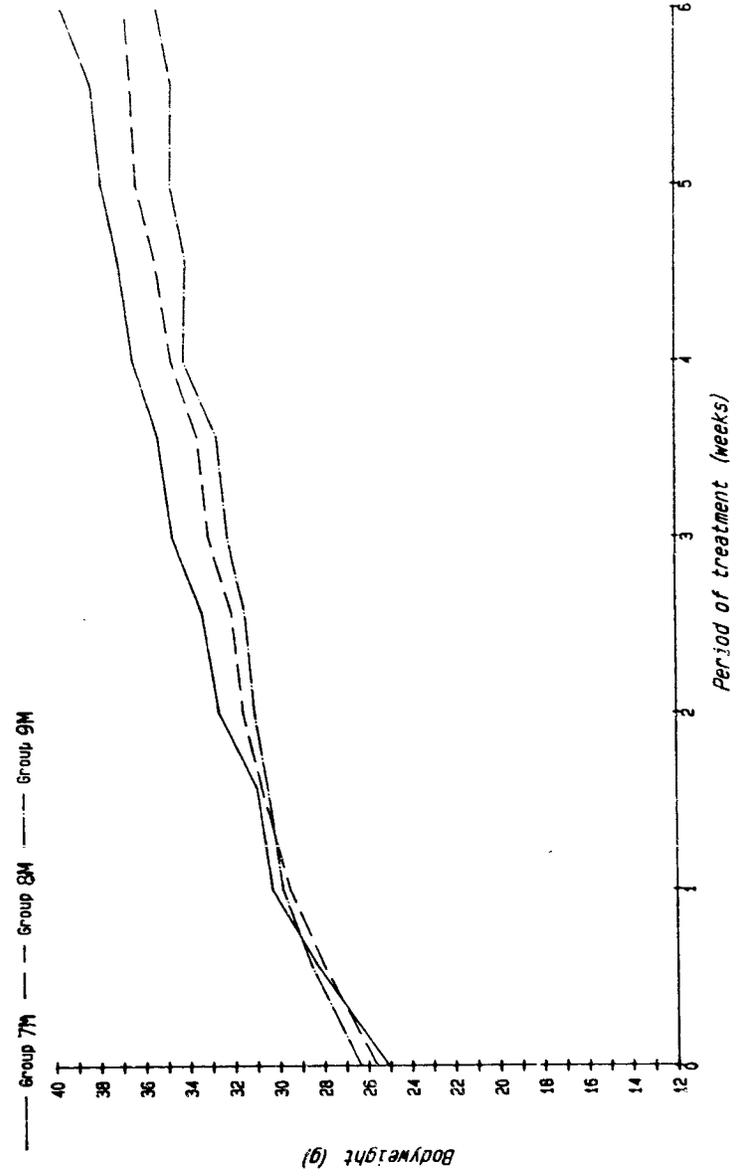
Group	:	4	5	6
Compound	:	5	20	50
Level (ppm)	:			



0042

FIGURE 2C
Group mean bodyweight versus period of treatment - males

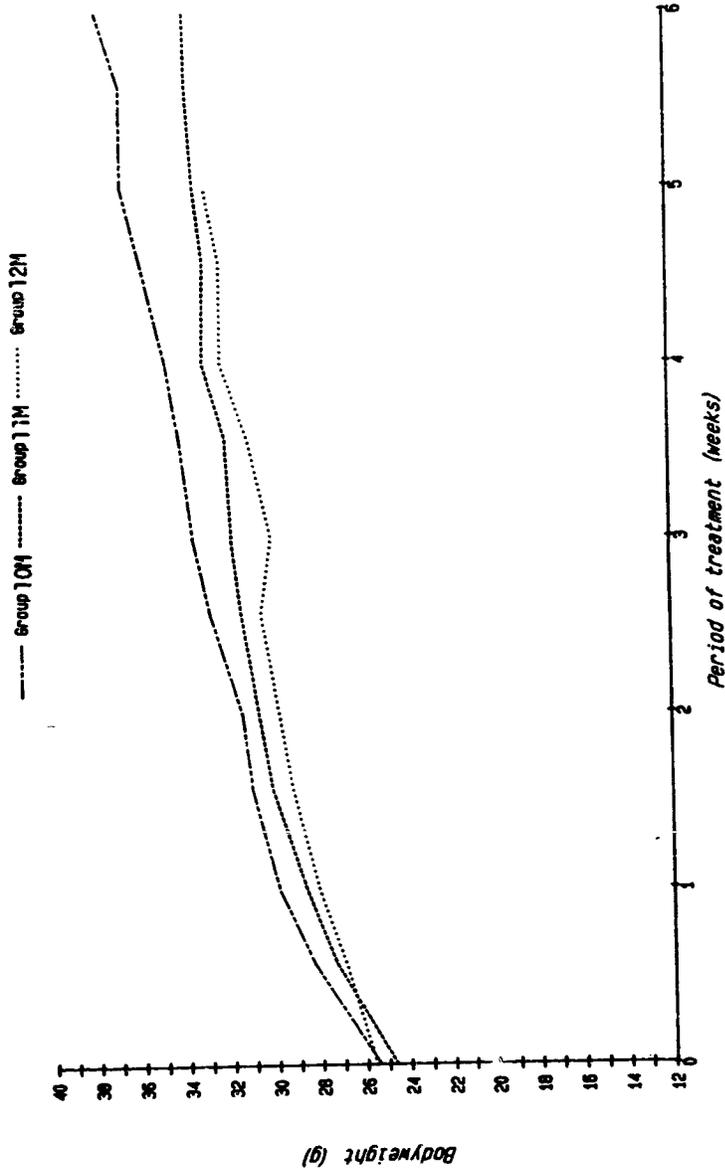
Group : : 7 8 9
Compound : : 5 20 50
Level (ppm) : : 5 20 50



0043

FIGURE 20
Group mean bodyweight versus period of treatment - males

Group : : 10 11 12
Compound : : 5 20 50
Level (ppm) : : 5 20 50



0044

FIGURE 2E
Group mean bodyweight versus period of treatment - males

Group	:	13	14	15
Compound	:	--		
Level (ppm)	:	20	50	150



0045

FIGURE 2F
Group mean bodyweight versus period of treatment - males

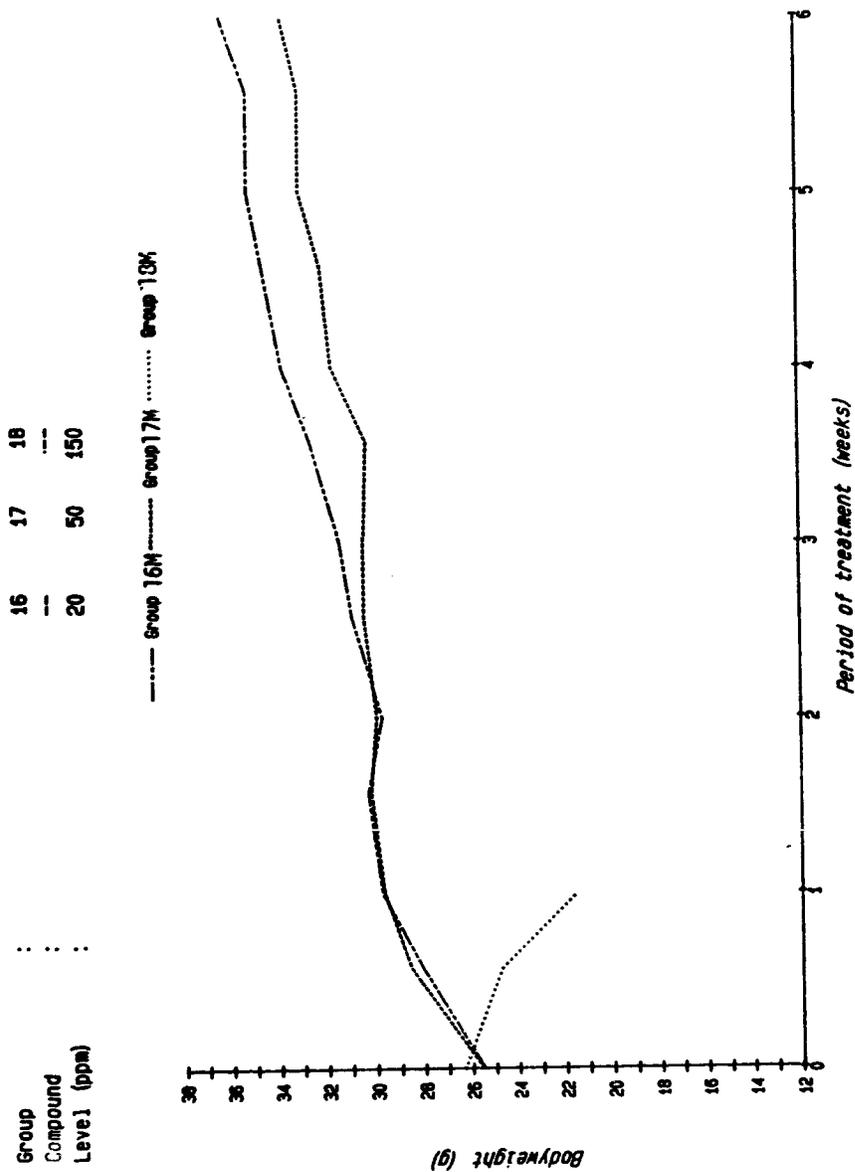


TABLE 1
Weekly incidence of mortality

Group	1	2	3	4	5	6
Compound	M&B 46030					
Level (ppm)	0	5	150	5	20	50
Week number	Group and sex					
	1M	2M	3M	4M	5M	6M
1	0	0	5	0	0	0
2	0	0	2	1	0	3
3	0	0	0	0	0	6
4	0	0	3	0	1	3
5	0	0	2	0	0	0
6	0	0		0	0	0
7	0	0		0	1	1
Total	0	0	12	1	2	12

0 0 4 7

TABLE 1 - continued

Weekly incidence of mortality

Group	7	8	9	10	11	12
Compound	---					
Level (ppm)	5	10	50	5	20	50
Week number	Group and sex					
	7M	8M	9M	10M	11M	12M
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	0	0	1	0	0	3
4	0	0	1	0	0	3
5	0	0	0	0	0	4
6	0	0	4	0	6	2
7	0	0	1	0	0	0
Total	0	0	7	0	6	12

TABLE 1 - continued

Weekly incidence of mortality

Group	13	14	15	16	17	18
Compound	20	50	150	20	50	150
Level (ppm)	14M	15M	16M	17M	18M	
Week number	Group and sex					
	13M	14M	15M	16M	17M	18M
1	0	0	0	0	0	10
2	0	0	1	2	0	2
3	0	0	3	0	0	
4	0	0	6	0	2	
5	0	1	2	0	2	
6	0	0	0	0	0	
7	0	0	0	0	0	
Total	0	1	12	2	4	12