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HMX: 14 Day Toxicity in Mice by Dietary Administration

Final Report by:

R.J. Greenough
P. McDonald

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U.S. Army Medical Research and Development Command
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Abstract

Male and female mice were fed diets containing up to 500 mg HMX/kg/day for 14 days with the object of selecting dose levels for a 13 week study. Deaths occurred in males at 300 mg/kg and above and in females at 800 mg/kg and above. Clinical signs included hyperkinesia. Histopathology of premature decedents revealed some hepatocellular hyperplasia, cytoplasmic eosinophilia and cellular depletion of splenic red and white pulp. Cause of death was not determined.

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FOREWORD

"I, the undersigned, hereby declare that this work was performed under my supervision, according to the procedures herein described and that this report represents a true and accurate record of the results obtained."

A.B. Wilson, B.V.Sc., M.R.C.V.S.
Principal Investigator

Project No. 415669SM

Report No. 2014

QUALITY ASSURANCE AUTHENTICATION

The execution of this type of short-term study is not individually inspected. The processes involved are inspected at intervals according to a pre-determined schedule.

This report has been audited by IRI Quality Assurance Personnel according to the appropriate Standard Operating Procedure and is considered to describe the methods and procedures used in the study. The reported results accurately reflect the original data of the study.

IRI Project No. 415669SM

Report No. 2014

Signed: Andrew Waddell
(Quality Assurance Manager)

Date: 14th January 1986

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SUMMARY

The object of this study was to provide information on the toxic effects of the test substance and to give an indication of suitable dose levels for subsequent studies.

Groups of 6♂ and 6♀ B6C3F$_1$ mice were fed diets containing Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX) for 14 days at nominal dose levels of 0, 100, 300, 900 and 2700 mg HMX/kg/day for males and 0, 320, 800, 2000 and 5000 mg HMX/kg/day for females. At the end of this period all the surviving mice were killed and subjected to necropsy. Subsequent histopathological examination of selected target organs was carried out on all control animals together with all the premature decendents from groups 3, 4 and 5.

The results obtained are summarised below:

Mortality

There were 29 premature decendents distributed as follows:

	Males					Females				
Dose Group	1	2	3	4	5	1	2	3	4	5
Nominal Dose Level mg HMX/kg/day	0	100	300	900	2700	0	320	800	2000	5000
% Mortality	0	0	83	100	100	0	0	33	67	100

Clinical Signs

HMX treated animals exhibited piloerection, hunched posture and a subdued/emaciated appearance. Hyperkinesia was observed when the animals were aroused, increased sensitivity to audio stimuli was also noted. Two convulsions were observed among the group 3 males (300 mg HMX/kg/day).

Body Weight

Depressed body weight gain/weight loss was observed for the HMX treated groups during week 1. Surviving animals regained the weight lost during the second week of dosing.

Food Consumption

Dose related reductions in food consumption were observed during the first week of dosing. During week 2 food consumption values for surviving animals were only slightly less than those of controls.

Water Consumption

No obvious treatment related differences in water consumption were observed.

Terminal Studies

Organ Weights

Absolute organ weights were found to be similar for control and HMX treated animals. Slight differences observed for relative weight profiles were attributed to the reduced body weight gain shown by the HMX treated animals.

Gross Pathology and Histopathology

Histopathological examination of the premature decedents in the groups receiving HMX, showed a dose related increase in incidence of hepatocellular hyperplasia and cytoplasmic eosinophilia, splenic red and white pulp cellular depletion and thymic cellular depletion.

INTRODUCTION

Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX) is an explosive and is found in the water effluent from the manufacturing processes for RDX and HMX.

This report describes a 14 day dietary study in mice conducted to set dose levels for a proposed 90 day study.

The study was undertaken at the Elphinstone Research Centre of Inveresk Research International Limited over the period 13 October-4 November 1980.

MATERIALS AND METHODS

Test Substance

The HMX (Lot No. HMX-IRI-001) was manufactured by the Royal Ordnance Factory, Somerset. The bulk of the material (5 kg wetted with 15.25% water and packaged in individual 50 g lots) was stored at Nobel's Explosive Company, Muirside, Dunfermline. Small amounts of HMX were transported in an approved container, to the IRI laboratories as required. The samples used in this study were obtained on 4 August, 16 September and 7 October 1980. The test compound was stored in a Ministry of Defence approved container under ambient conditions in the company dispensary. Prior to use the required amount of HMX was removed from this container and dried at approximately 90°C overnight. The dried HMX was then stored in a glass desiccator until used.

Animals

Thirty five male and 35 female B6C3F$_1$ mice (18 g body weight) were obtained from Charles River (U.S.A.) Limited, Wilmington, Mass. on 1 October 1980. Sixty mice (30 ♂ and 30 ♀) were allowed to acclimatise to their new environment for 12 days before treatment commenced.

Pre-experiment Acceptance Testing

All animals were examined on arrival for signs of disease. Five animals of each sex were selected, firstly on the basis of a clinical examination and secondly in a random choice manner, and subjected to a microbial examination and histopathological evaluation of main organs. The results of these tests showed that the delivery of animals was of an acceptable standard for use on this study.

Animal Management

The mice were housed in an animal room dedicated to this experiment with a light intensity of approximately 200 lux, a 12 h light-dark cycle, temperatures automatically maintained at 20°C ± 2°C with extreme limits of 20°C and 24°C, and humidity ca 50% with extreme limits of 34% and 65%.

Caging

The mice were housed one per cage in polypropylene cages (overall dimensions 12 cm x 11.5 cm x 42 cm) with a stainless steel wire grid top. Cages were changed once each week.

Diet

Food and tap water were freely available to the mice at all times. The diet used was BP Nutrition Expanded Maintenance Diet, a ground diet adequate for all stages of growth in mice.

Typical analyses of both water and diet are presented in Appendix 1.

Allocation of Mice to Cages and Treatment Groups

Empty cages were placed on racks, then upon receipt, starting first with male mice, a transporting box was opened and a mouse placed in the first cage at the top left hand corner of the rack. A second mouse was removed from the same transporting box and placed in the next cage and so on until 35 cages each contained one male mouse.

This process was repeated using new cages and female mice.

Following a 2 day transportation recovery period animals were allocated to specific treatment groups using a stratified body weight sequenced randomisation procedure.

Four body weight ranges were selected for each sex. Starting first with the males, the animals were removed from their cages, weighed and then placed in one of 4 large stainless steel holding cages according to their body weight. Six rows of cages, each row containing 5 cages, were then arranged on racks. Two sets of computer generated random number permutations were obtained, the first set gave 5 random sets of numbers from 1-6 corresponding to the number of sequences of cages and the second gave 6 random sets of numbers from 1-5 corresponding to the number of treatment groups.

Starting with the lowest weight range of male mice, one animal was placed in a cage according to the sequence position indicated by the first number in the first set of random numbers. The cage was then assigned to a treatment group using the second random number set. This process was repeated until all the male mice from the 4 different weight ranges had been assigned to cages and treatment groups.

This complete process was repeated for the female mice.

Animal Identification, Treatment Groups and Dose Levels

Each animal received a unique ear punch which identified it individually within the study and which corresponded to that animal's number. Each mouse was ascribed a cage card which identified that animal by project number, cage number, animal number, sex and treatment group. Each cage card was colour-coded according to the treatment group.

The treatment groups were as follows:

Dose Group	Dose Level mg HMX/kg/day		Colour Code	Animal Numbers	
	♂	♀		♂	♀
1	0	0	Green	401-406	431-436
2	100	320	Blue	407-412	437-442
3	300	800	Yellow	413-418	443-448
4	900	2000	Buff	419-424	449-454
5	2700	5000	Red	425-430	455-460

Animal Room Sanitation

Floors were mopped each morning, using a mop impregnated with Tego, an ampholytic detergent (A.J. Beveridge, Edinburgh) before other work in the room had begun. In the afternoon, floors were swept and then mopped with Tego disinfectant solution after work in the room was finished.

Diet Preparation

Diets containing HMX were prepared fresh at the beginning of each study week. The concentration of test compound in the diet was calculated weekly after predicting the mid-week body weight and food consumption for the forthcoming week.

$$\text{Concentration (ppm, w/w)} = \frac{\text{Dose level (mg/kg/day) x predicted mid-week body weight (g)}}{\text{predicted daily food consumption (g)}}$$

$$\text{Amount of test substance required (g)} = \frac{\text{ppm x weight of diet required}}{1000}$$

After drying to a constant weight HMX was sieved through a plastic 100 μm mesh sieve immediately before use. The requisite

amounts of HMX and powdered diet were measured out, transferred to plastic containers, sealed and mixed for 20 min using a Winkworth change drum tumble mixer.

Dietary Sampling

Ten gram samples were taken from the top, middle and bottom of the container holding the freshly mixed diet to confirm stability and homogeneity of mixing of HMX. These samples, along with a 100 g sample taken for Archives, were taken from all diet mixes including controls.

Analysis of HMX in Diets

Analytical Method

HMX was analysed by high performance liquid chromatography (HPLC).

Three samples (of an appropriate size depending on the nominal concentration of HMX in the diet) were weighed into 3 x 8 oz glass jars. To this was added an appropriate volume of internal standard solution (1,3-dinitrobenzene in acetonitrile) and sufficient acetonitrile for complete extraction. The glass jars were then capped and shaken mechanically for one hour after which the jars were removed and the contents allowed to settle. An aliquot of the liquid fraction was injected into the HPLC and analysed either directly or after suitable dilution using acetonitrile:water (20:30 v/v).

Standard solutions of HMX were prepared by adding known amounts of HMX to samples of untreated diets. These were treated with internal standard solution and extracting solvent as described above for the formulated diet samples. Further details are reported under project DAMD 17-80-C-0053.

Stability and Homogeneity of HMX in Diets

Before commencement of the study experiments were performed to determine homogeneity and stability of HMX treated diets. Accordingly diets containing 1,250, 10,000 and 25,000 ppm (w/w) of HMX were formulated. Ten representative samples from each diet mixture were analysed immediately after preparation. Ten samples from each diet were subjected to accelerated ageing by storage at 40°C in an environmental cabinet and analysed after 14 days. The remainder of each diet was stored at room temperature and analysed after 21 days.

Results of these analyses showed that mixing procedures and stability were deemed satisfactory (see Appendix 2).

HPLC Conditions

HPLC:	Altex pump, Pye Unicam LC3 UV Spectrophotometer
Column:	Hypersil ODS (10 cm x 0.5 cm)
Solvent:	Acetonitrile:water (20:30 v/v)
Flow:	1 ml/min
Wavelength:	228 nm
Recorder:	Servoscribe 1 s-10 mV
Chart Speed:	300 mm/h

Observations

Mortality

All animals were inspected for any deaths at the start of each working day and again during the afternoon clinical signs check.

Clinical Signs

The mice were observed at intervals throughout the working day for any signs of ill health or reaction to treatment.

Physical Examination

Each animal was given a detailed physical examination for external lesions or palpable masses.

Body Weights

The weight of each mouse was recorded on the day dosing commenced and twice each week thereafter. Animals were also weighed twice in the week prior to the start of treatment.

Food Consumption

Food consumption was recorded on a weekly basis. The quantity of food eaten by each mouse was calculated by measurement of the amount of food given at the beginning of each week and deducting that remaining in the food hopper at the end of each week and any that may have been scattered on the cage floor during that week.

Water Consumption

The quantity of water consumed by each mouse was assessed each week by visual assessment of the calibrated water bottle.

Terminal Studies

On day 15 of dosing all the surviving mice were sacrificed by nitrogen asphyxiation. Blood samples of ca 1 ml were taken into heparin via the posterior vena cava from all animals. Plasma was separated by centrifugation and stored deep frozen at -20°C for analysis at a later date.

Gross Necropsy

A full necropsy was performed as detailed below. Each mouse was examined externally including the body orifices along with examination of internal organs and tissues.

The following organs were taken at necropsy:

Brain
Heart
*Kidneys
*Liver
Spleen
Thymus

The fresh weights of the organs marked * were recorded before preservation.

All organs were examined in situ, then dissected from the carcass, re-examined, including cut surfaces, and then preserved in 10% neutral buffered formalin.

Tissues were fixed after slicing to a thickness not exceeding 0.5 cm.

Liver lobes were sliced, the kidneys longitudinally bisected and the cut surfaces examined before fixation.

All gross lesions were recorded in narrative, descriptive terms, including size (in mm), number, shape, colour and texture.

Carcasses of animals were discarded immediately following autopsy and the placing of all tissues listed above in fixative.

Processing of Fixed Tissues

The fixation time was 7 days.

Tissues were trimmed to a maximum thickness of 0.3 cm for processing.

Parenchymal organs, e.g. liver, were trimmed to allow the largest surface area possible for examination.

Multi-longitudinal sections through the entire cortex and medulla of each kidney were submitted.

Three cross sections of brain including (a) frontal cortex and basal ganglia, (b) parietal cortex and thalamus and (c) cerebellum and pons were submitted.

Histological Technique

Tissue were cut to 4-6 μm thickness and stained with haematoxylin and eosin (H & E).

All staining methods used are described in "Histological Laboratory Methods" by Disbrey and Rack (E.S. Livingstone Limited, Edinburgh, 1970).

Histopathological Examination

Histopathological examination of the tissues listed above was carried out on all control animals together with all the premature decedents. Tissues from other animals were preserved but not examined.

Statistical Analysis

Whenever considered necessary, numerical data were subjected to statistical analysis using Student's 't' test.

The levels of significance as indicated in the report are:

* Significantly different from controls, $P<0.05$
** Significantly different from controls, $P<0.01$
*** Significantly different from controls, $P<0.001$

Archiving

On completion of all practical work the biological material and data generated during the study was stored, together with samples of the diet formulations and a sample of the test

compound used, in the Scientific Archives of Inveresk Research International Limited. All materials relating to this study will be retained for a minimum period of 5 years.

RESULTS

Dosing period: 23 October 1980-3 November 1980
Necropsy: 4 November 1980

Observations

Mortality

There were 29 premature decedents during the course of this study. The time of death and mortality distribution is presented in Table 1.

Clinical Signs

Males

Group 1 - (Control)	No abnormalities were observed.	
Group 2 - (100 mg/kg/day)	Day 5, 6, 7:	hyperkinesia/excitability observed in all animals when aroused.
Group 3 - (300 mg/kg/day)	Day 2:	414♂ found dead in cage. Hyperkinesia and sensitivity to audio stimuli observed in all animals when aroused. One animal (415♂) observed having a convulsion.
	Day 3:	surviving animals extremely sensitive to external stimuli, erect peni observed in 2 animals. When aroused the animals held their tails horizontally, producing a quivering effect. Animal 415♂ had an emaciated, hunched appearance with piloerection - killed *in extremis*.
	Day 4:	416♂ penis erect, piloerection, hunched/emaciated appearance - killed *in extremis*.
	Day 5-7:	hyperkinesia, tail quivering when aroused.
	Day 8:	surviving animals appeared emaciated, 417♂ observed having a convulsion - died 1½ h later. Blood observed at animal's mouth, cage also heavily blood stained.
	Day 9:	413♂ found dead in cage.
Group 4 - (900 mg/kg/day)	Day 1:	424♂ found dead in cage, remaining animals had a hunched appearance.
	Day 2:	423♂ found dead in cage, others appeared to be sensitive to audio stimuli.

	Day 3:	all animals sensitive to external stimuli, tails quivering and held horizontally when aroused. Numbers 420♂ and 421♂ observed to have piloerection, erect peni and a hunched emaciated appearance. Number 421♂ unable to maintain upright posture - later found dead in cage. Number 420♂ killed in extremis.
	Day 4:	419♂, 422♂ piloerection, hunched/emaciated appearance, 419♂ hyperkinetic when aroused. Number 422♂ had difficulty in standing - killed in extremis.
	Day 5:	419♂ found dead in cage.
Group 5 - (2700 mg/kg/day)	Day 1:	429♂ found dead in cage, others appeared subdued with hunched appearance.
	Day 2:	426♂, 428♂ and 430♂ found dead in their cages. Surving animals sensitive to audio stimuli.
	Day 3:	425♂ and 427♂ subdued, piloerection, hunched/emaciated appearance, both animals sensitive to external stimuli when aroused, tails quivering and held horizontally. Killed in extremis.

Females

Group 1 - (Control)	No abnormalities were observed.	
Group 2 - (320 mg/kg/day)	Day 6, 7:	hyperkinesia observed when animals aroused.
Group 3 - (800 mg/kg/day)	Day 3:	from day 3, and for most of the remainder of the dosing period, all animals showed hyperkinesia when aroused.
	Day 8:	448♀ found dead in cage.
	Day 10:	443♀ bald patches on abdomen, fore legs and right hind leg.
	Day 14:	447♀ found dead in cage.
Group 4 - (2000 mg/kg/day)	Day 1:	all animals appeared slightly subdued.

	Day 3:	from day 3, and for most of the remainder of the dosing period, all animals showed hyperkinesia when aroused.
	Day 4:	454♀ found dead in cage.
	Day 6:	449♀, 450♀ and 453♀ all found dead in their cages.
	Day 7:	surviving animals had a hunched appearance and piloerection.
Group 5 - (5000 mg/ kg/day)	Day 1:	all animals subdued.
	Day 3:	457♀ and 459♀ subdued, emaciated/ hunched appearance, hypokinetic when aroused. Remaining animals hyperkinetic when aroused.
	Day 4:	all animals had an emaciated/ hunched appearance, 455♀ hyperkinetic. Number 459♀ killed in extremis.
	Day 5:	455♀ and 458♀ found dead in their cages, surviving animals were subdued with an emaciated hunched appearance, hyperkinetic when aroused.
	Day 6:	456♀ and 460♀ found dead in their cages, 457♀ killed in extremis.

Body Weight

Group mean body weights are presented numerically in Tables 2a and 2b and graphically in Figures 1 and 2. Individual values are given in Appendix 3.

Males

By day 3 of dosing most of the surviving animals receiving HMX treated diet had shown a significant loss of body weight. All animals in groups 4 and 5 died during the first week. After an initial weight loss the surviving mouse in group 3 showed a marked increase in weight gain from day 3 onwards. Following a slight loss in body weight at the start of dosing group 2 mice showed a steady body weight gain. By the end of the 14 day dosing period the group 2 mean body weight was only slightly less than that of the control group.

Females

Groups 3, 4 and 5 showed a loss in body weight at the start of dosing. All of the group 5 animals died during the first week - a significant weight loss was

observed prior to death. During week 2 of dosing the surviving animals in groups 3 and 4 recovered the weight they had previously lost. Group 2 animals showed a slightly depressed body weight gain when compared to controls.

Food Consumption

Group mean food consumption values are presented numerically in Table 3.

Dose related reductions in food consumption were observed during the first week of treatment. During the second week, group mean food consumption values for the HMX treated animals were only slightly less than those of the control animals.

Water Consumption

No differences were detected between control and HMX treated animals.

Achieved Dosage

The actual amounts of HMX consumed by each dose group are presented in Table 4.

Results obtained from analysis of the freshly prepared diets are presented in Appendix 4.

Terminal Studies

Organ Weights

Group mean values for kidney and liver weights, expressed in absolute terms and as a percentage of body weight, are presented in Tables 5a and 5b whilst individual values are given in Appendix 5.

Absolute organ weights for both the control and HMX treated animals surviving the 14 day feeding period were considered to be similar.

Slight differences observed in the relative organ weights, of animals receiving HMX treated diet, can probably be attributed to the reduced body weight gain exhibited by the treated animals.

Gross Pathology and Histopathology

Gross and histopathological findings for individual animals are presented in Appendix 6. Histopathological findings are summarised in Table 6, the evaluation of the limited range of sample types show a dose related increase in incidence of hepatocellular hyperplasia and cytoplasmic eosinophilia, splenic red and white pulp cellular depletion and thymic cellular depletion. Equal effects were found in both sexes.

The hepatocellular eosinophilia could be caused to some degree by autolysis, but in most animals it probably represents an early stage in the hyperplastic process which was invariably present in the same animal.

DISCUSSION

The early onset of mortality observed among male mice receiving nominal concentrations of 900 and 2700 mg HMX/kg/day is indicative of potent toxicity at these levels. Subsequent mortalities may have been due to nutritional deficiences caused by unpalatability of the treated diet, probably as a result of the high levels of HMX. This assumption is based upon the marked reduction in food consumption, resulting in a significant body weight loss. However, those animals which survived appeared to develop a tolerance to the HMX treated diet. Increased food consumption and a resumption of body weight gain were observed by the end of the 14 day dosing period. Similar results were obtained with female rats although generally at somewhat higher dose levels.

The histopathological findings in the liver, spleen and thymus of HMX treated animals would indicate a requirement for a detailed histopathological evaluation of these organs in subsequent subchronic studies.

Dose levels selected for the 90 day study were 0, 5, 12, 30, 75 and 200 mg HMX/kg/day for males and 0, 10, 30, 90, 250 and 750 mg HMX/kg/day for females.

TABLE 1

HMX: 14 Day Dietary Toxicity Study in Mice
Incidence of Mortality

Day of Dosing	Dose Group/Dose Level (mg HMX/kg/day)									
	1♂ 0	2♂ 100	3♂ 300	4♂ 900	5♂ 2700	1♀ 0	2♀ 320	3♀ 800	4♀ 2000	5♀ 5000
1	-	-	-	1a	1a	-	-	-	-	-
2	-	-	1a	1a	3a	-	-	-	-	-
3	-	-	1b	1a, 1b	2b	-	-	-	-	-
4	-	-	1b	1b	-	-	-	-	1a	1b
5	-	-	-	1a	-	-	-	-	-	2a
6	-	-	-	-	-	-	-	-	3a	2a, 1b
7	-	-	-	-	-	-	-	-	-	-
8	-	-	1a	-	-	-	-	1a	-	-
9	-	-	1a	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-
13	-	-	-	-	-	-	-	-	-	-
14	-	-	-	-	-	-	-	1a	-	-
Total	0	0	5	6	6	0	0	2	4	6
Number commencing treatment	6	6	6	6	6	6	6	6	6	6

a = Found dead in cage

b = Killed in extremis

TABLE 2a

HMX: 14 Day Dietary Toxicity Study in Mice
Group Mean Body Weights (g) - Males

Dose Level (mg HMX/ kg/day)	Number of Animals		Treatment Week/Day of Dosing						
			Pre-trial			Week 1		Week 2	
			7	4	0	3	7	10	14
0	6	Mean	22.0	23.5	24.3	24.3	24.8	25.5	25.7
		± S.D.	1.4	1.5	1.4	1.4	1.7	2.1	2.1
100	6	Mean	21.3	22.8	23.0	21.8*	22.7***	23.8	24.8
		± S.D.	1.0	1.5	1.7	1.7	1.9	2.1	1.8
300	6	Mean	19.8**	21.2*	22.5*	17.8***(a)	21.3(c)	24.0(e)	24.0(e)
		± S.D.	0.8	1.3	1.4	1.9	2.9	0.0	0.0
900	6	Mean	20.2*	21.5*	22.7	17.3***(b)	†	†	†
		± S.D.	1.2	1.5	1.8	2.2			
2700	6	Mean	20.3*	22.5	23.7	16.0***(d)	†	†	†
		± S.D.	0.8	1.5	1.6	1.4			

(a) n = 5
(b) n = 4
(c) n = 3
(d) n = 2
(e) n = 1

* Significantly different from controls, P<0.05
** Significantly different from controls, P<0.01
*** Significantly different from controls, P<0.001
† All animals dead

TABLE 2b

HMX: 14 Day Dietary Toxicity Study in Mice
Group Mean Body Weights (g) - Females

Dose Level (mg HMX/ kg/day)	Number of Animals		Treatment Week/Day of Dosing						
			Pre-trial			Week 1		Week 2	
			7	4	0	3	7	10	14
0	6	Mean	17.5	18.5	20.2	21.2	21.2	21.3	22.8
		± S.D.	0.5	0.8	0.8	1.0	0.8	0.5	0.8
320	6	Mean	17.2	18.2	19.5	20.0*	20.0	19.7*	21.0*
		± S.D.	1.0	1.0	1.2	0.6	1.3	1.5	1.4
800	6	Mean	18.3	19.7*	20.5	19.5*	20.0	20.4(a)	22.0(b)
		± S.D.	1.4	0.5	0.5	1.2	2.2	1.1	0.8
2000	6	Mean	18.8**	20.2**	21.0	19.3**	18.0**(d)	20.5(d)	21.5(d)
		± S.D.	0.8	0.4	0.9	0.8	0.0	0.7	0.7
5000	6	Mean	18.8**	20.0**	21.2	17.2***	†	†	†
		± S.D.	0.8	0.6	1.0	1.7			

(a) n = 5
(b) n = 4
(d) n = 2

* Significantly different from controls, P<0.05
** Significantly different from controls, P<0.01
*** Significantly different from controls, P<0.001
† All animals dead

TABLE 3

HMX: 14 Day Dietary Toxicity Study in Mice
Group Mean Food Consumption

Treatment Week	Dose Group/Group Mean Food Consumption (g/mouse/day)									
	1♂ (0)	2♂ (100)	3♂ (300)	4♂ (900)	5♂ (2700)	1♀ (0)	2♀ (320)	3♀ (800)	4♀ (2000)	5♀ (5000)
Pre-trial	5.0	4.8	4.6	4.3	5.1	5.1	5.0	5.1	5.4	5.1
1	5.3	4.7	3.5	1.9	1.9	5.5	4.5	3.6	3.1	2.8
2	6.0	5.9	5.4	-	-	5.8	5.1	5.0	5.1	-

TABLE 4

HMX: 14 Day Dietary Toxicity Study in Mice
Achieved Dosage: Group Mean Values (mg HMX/kg/day)

Treatment Week	Dose Group/Achieved Dosage (mg HMX/kg/day)									
	1♂ (0)	2♂ (100)	3♂ (300)	4♂ (900)	5♂ (2700)	1♀ (0)	2♀ (320)	3♀ (800)	4♀ (2000)	5♀ (5000)
1	0	111.8	297.5	-	-	0	297.0	581.9	1316.1	-
2	0	127.1	468.5	-	-	0	391.8	1183.4	2775.0	-
Average achieved dosage	0	119.5	383.0	-	-	0	344.4	882.7	2045.6	-

Values in parenthesis indicate nominal concentration (mg HMX/kg/day)
Achieved dosage based on actual concentration of HMX analysed in diet

TABLE 5a

HMX: 14 Day Dietary Toxicity Study in Mice
Absolute Organ Weights (g)
Group Mean Values of Animals Surviving 14 Days Dosing

Dose Level (mg HMX/kg/day)	Number of Animals/Sex		Kidneys		Liver
			L	R	
0	6♂	Mean	0.23	0.24	1.38
		± S.D.	0.03	0.03	0.09
100	6♂	Mean	0.21	0.23	1.35
		± S.D.	0.01	0.02	0.19
300	1♂	Mean	0.21	0.23	1.38
		± S.D.	0.0	0.0	0.0
0	6♀	Mean	0.15	0.17	1.25
		± S.D.	0.004	0.01	0.04
320	6♀	Mean	0.13	0.15*	1.25
		± S.D.	0.04	0.02	0.08
800	4♀	Mean	0.15	0.16	1.33
		± S.D.	0.02	0.01	0.09
2000	2♀	Mean	0.14	0.15	1.27
		± S.D.	0.01	0.01	0.25

* Significantly different from controls, $P<0.05$

TABLE 5b

HMX: 14 Day Dietary Toxicity Study in Mice
Organ Weights as a % of Body Weight
Group Mean Values of Animals Surviving 14 Days Dosing

Dose Level (mg HMX/kg/day)	Number of Animals/Sex		Kidneys		Liver
			L	R	
0	6♂	Mean	0.898	0.957	5.548
		± S.D.	0.065	0.079	0.390
100	6♂	Mean	0.886	0.947	5.590
		± S.D.	0.057	0.045	0.355
300	1♂	Mean	0.840	0.920	5.520
		± S.D.	0.0	0.0	0.0
0	6♀	Mean	0.701	0.775	5.801
		± S.D.	0.019	0.022	0.248
320	6♀	Mean	0.662	0.749	6.267**
		± S.D.	0.173	0.053	0.255
800	4♀	Mean	0.717	0.753	6.232*
		± S.D.	0.047	0.020	0.237
2000	2♀	Mean	0.660*	0.714*	5.998
		± S.D.	0.023	0.019	0.774

* Significantly different from controls, P<0.05

** Significantly different from controls, P<0.01

TABLE 6

HMX: 14 Day Dietary Toxicity Study in Mice
Incidence of Histopathological Findings

Organ	Dose Group/Nominal Dose Level (mg HMS/KG/day) / Lesion	Group Incidence									
		1		2		3(a)		4(a)		5(a)	
		(0) ♂	(0) ♀	(100) ♂	(320) ♀	(300) ♂	(800) ♀	(900) ♂	(2000) ♀	(2700) ♂	(5000) ♀
Liver	Eosinophilic cytoplasm	0/6	0/6	-	-	3/5	0/2	5/5	3/4	5/6	6/6
	Increased cellularity	0/6	0/6	-	-	2/5	0/2	5/6	4/4	5/6	6/6
Thymus	Lymphocyte depletion	0/6	0/6	-	-	4/5	1/2	4/4	4/4	4/5	4/4
Spleen	White pulp depletion	0/6	0/6	-	-	2/5	1/2	5/5	4/4	5/6	5/5
	Red pulp depletion	0/6	0/6	-	-	1/5	1/2	5/5	4/4	6/6	5/5

(a) premature decedents observed in groups 3, 4 and 5

\- no histopathology undertaken

FIGURE 1

HMX: 14 Day Dietary Toxicity Study in Mice
Group Mean Body Weight (g) - Males

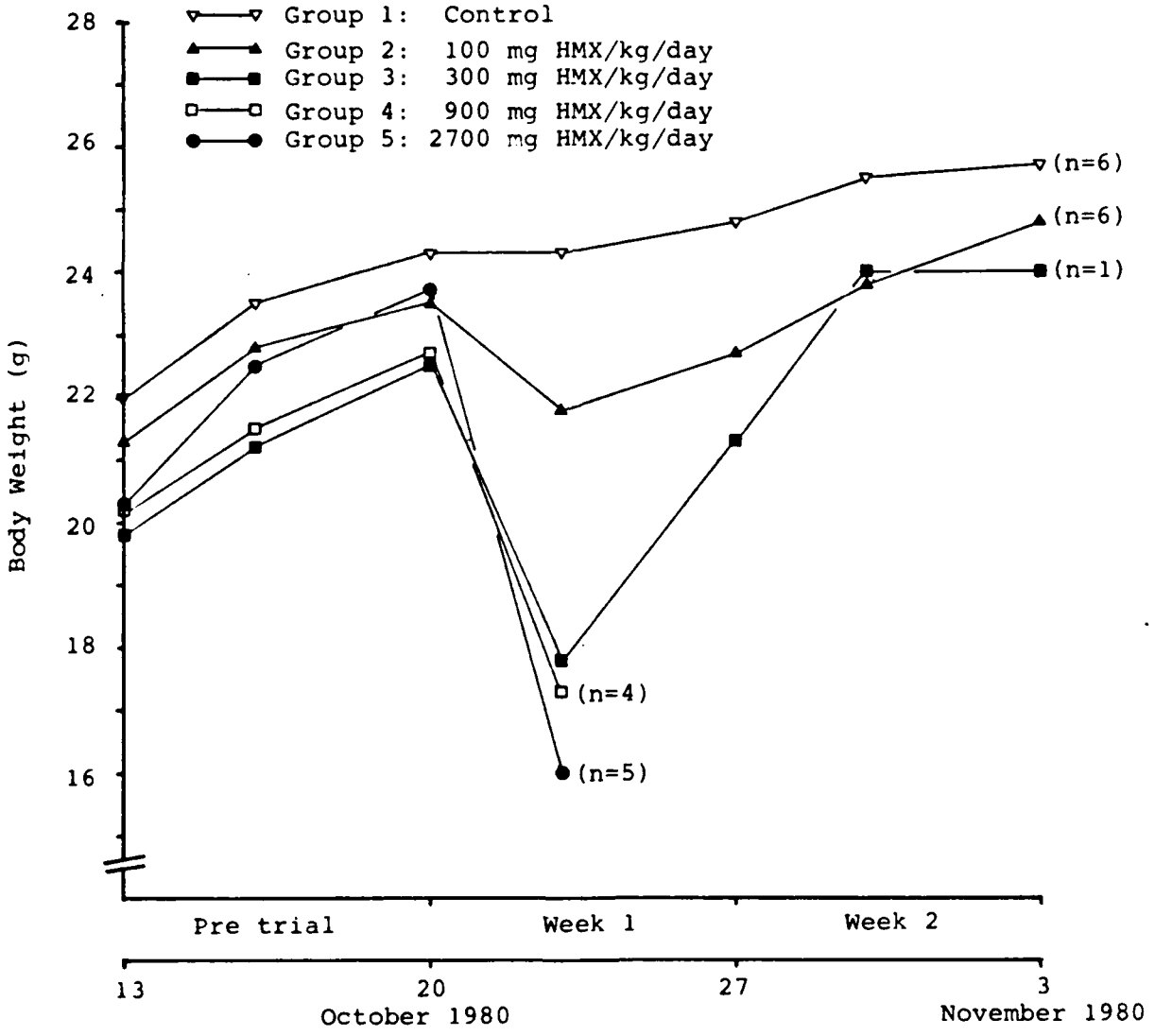
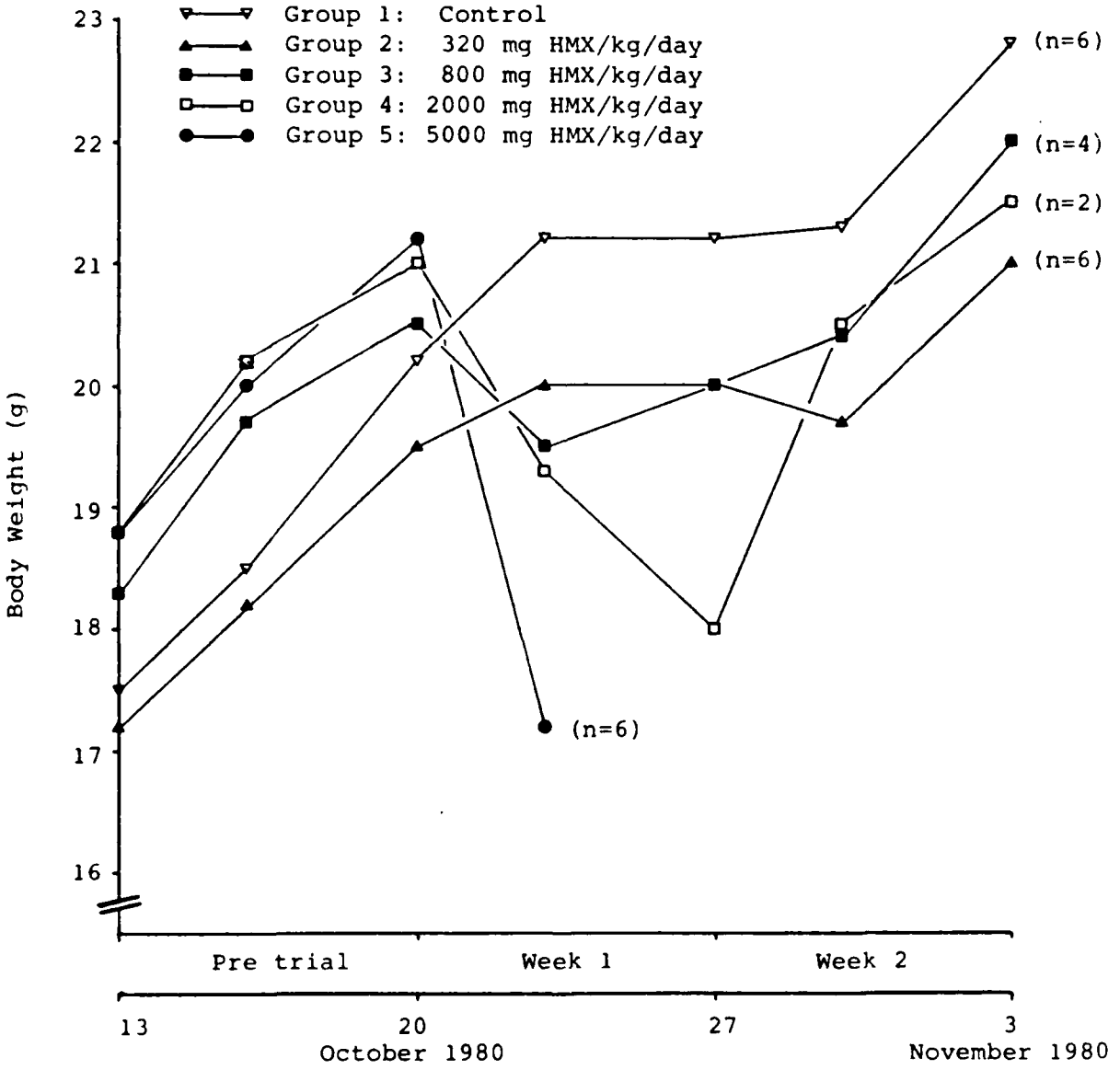


FIGURE 2

HMX: 14 Day Dietary Toxicity Study in Mice
Group Mean Body Weight (g) - Females



APPENDIX 1a

HMX: 14 Day Dietary Toxicity Study in Mice
Analysis of Diet

B.P. NUTRITION (U.K.) LTD.
SPECIAL QUALITY CONTROL OF LABORATORY ANIMAL DIETS

CERTIFICATE OF ANALYSIS

PRODUCT: RAT & MOUSE NO.1 (MODIFIED) EXPANDED FINE GROUND

BATCH NO: 919 PREMIX BATCH NO: P110

DATE OF MANUFACTURE: 15TH AUGUST 1980

Nutrient	Found Analysis		Contaminant	Found Analysis		Limit of Detection
Moisture	7.1	%	Fluorine	7.6	mg/kg	10.0 mg/kg
Crude Fat	3.5*	%	Nitrate as NaNO3	11.0	mg/kg	1.0 mg/kg
Crude Protein	14.9	%	Nitrite as NaNO2	< 1.0	mg/kg	1.0 mg/kg
Crude Fibre	2.2	%	Lead	< 1.0	mg/kg	1.0 mg/kg
Ash	4.8	%	Arsenic	0.23	mg/kg	0.2 mg/kg
Calcium	0.69	%	Cadmium	0.13	mg/kg	0.2 mg/kg
Phosphorus	0.53	%	Mercury	< 0.01	mg/kg	0.01 mg/kg
Sodium	0.22	%	Selenium	0.12	mg/kg	0.02 mg/kg
Chlorine	0.34	%				
Potassium	1.10	%				
Magnesium	0.13	%	Total Aflatoxins	NONE DETECTED	ug/kg	1 ug/kg each of B1,B2,G1,G2
Iron	231	mg/kg				
Copper	7	mg/kg				
Manganese	55	mg/kg				
Zinc	40	mg/kg	Total P.C.B.	NONE DETECTED	mg/kg	0.001 mg/kg
			Total D.D.T.	0.003	mg/kg	0.001 mg/kg
			Dieldrin	0.001	mg/kg	0.001 mg/kg
			Lindane	0.005	mg/kg	0.001 mg/kg
			Heptachlor	NONE DETECTED	mg/kg	0.001 mg/kg
			Malathion	NONE DETECTED	mg/kg	0.02 mg/kg
Vitamin A	7000	iu/kg	Total Viable Organisms	1.13×10^3	per grm	1000/g
Vitamin E	60	mg/kg				
Vitamin C		mg/kg	Mesophilic Spores	17.5×10^2	per grm	100/g
			Salmonellae Species	NONE DETECTED	per grm	Absent in 20 grm
			Presumptive E. Coli	NONE DETECTED	per grm	Absent in 10 grm
			E Coli Type 1	NONE DETECTED	per grm	Absent in 10 grm
			Fungal Units	NONE DETECTED	per grm	Absent in 10 grm
			Antibiotic Activity			

*repeat 3.4

RECEIVED
17 SEP 1980

Signed C L Poppleston

Dated 10th September 1980

C. R. POPPLESTONE M.Sc. Ph.D. C.Chem. M.R.I.C.

B P Nutrition (U K.) Limited
Stepfield,
Witham,
Essex CM8 3AB

APPENDIX 1b

HMX: 14 Day Dietary Toxicity Study in Mice
Analysis of Water

ICLS

International Consulting and Laboratory Services

Analysis of a Sample of Water:

Received

Your Ref

Our Ref G/B/3882

From **Inveresk Research International**

Labelled **Mains Water Supply**

Date 4.45 pm 13/8/80

Taken by **M. Scott** Witness **D. Brown** Signed **M. Scott**

Results *(in milligrammes per litre)*

Appearance

Bright with a few particles

pH	7.8		Odour		NIL
Electrical Conductivity (Reciprocal Megohms, Micro Siemens per cm at 25°C)	150		Colour (Hazen)		3
Chlorine in Chloride	9		Turbidity (Formazin, A P H A. units)		0.5
Hardness as $CaCO_3$ Total	75		Nitrogen in Nitrate	LT	0.1
Carbonate	60		Nitrogen in Nitrite	LT	0.01
Non-carbonate	15		Ammoniacal Nitrogen		0.10
Alkalinity as $CaCO_3$	60		Albuminoid Nitrogen	LT	.01
			Permanganate value 4hrs at 27°C		0.55
Free Carbon Dioxide	2		Residual Chlorine	LT	0.02
Dissolved Solids dried at 180°C	105		Iron (Fe) LT 0.03	Zinc (Zn) LT	0.03

Copper (Cu) LT 0.03 Lead (Pb) LT 0.03 Manganese (Mn) 0.04 Aluminium (Al) 0.03

Cadmium (Cd) LT 0.001 Fluorine in Fluoride LT 0.1 Silica (SiO_2) 4

("Absent" refers to a detection limit of 0.03mg/l of each metal unless otherwise stated)

Comment

Volatile Total Dissolved Solids		10
Mercury expressed as Hg	LT	0.0005
Selenium expressed as Se	LT	0.001
Dissolved Oxygen		8.8

PSW/SL 23rd September, 1980 Signed

APPENDIX 1b (continued)

ICLS

International Consulting and Laboratory Services

Mineral Analysis of a Sample of Water: *(after filtration if necessary)* G/B/3882

Labelled

Mains Water Supply

(milligrammes per litre and millequivalents per litre)

Cations			Anions					
	mg/l	me/l		mg/l	me/l		mg/l	me/l
Ca	16	0.80	$^{*}CO_3$	36	1.20	Calcium Carbonate	40	0.80
Mg	9	0.70	SO_4	20	0.42	Magnesium Carbonate	17	0.40
Na	8	0.33	Cl	9	0.26	Magnesium Sulphate	18	0.30
K	2	0.05	NO_3	0	-	Sodium Sulphate	9	0.12
						Sodium Chloride	12	0.21
						Potassium Chloride	4	0.05
						Silica	4	
Total		1.88	Total		1.88	Total	104	1.88

(usually present as bicarbonate)

Comment

This sample is practically clear and bright in appearance and is free from noticeable colour. The reaction is slightly on the alkaline side of neutrality and the water is soft in character with a low content of dissolved solids. The water is free from metals apart from a minute trace of manganese and is of a satisfactory standard of organic quality.

These results indicate, from the aspect of the chemical and mineral analysis, a wholesome water suitable for drinking and domestic purposes.

PSW/SHL 23rd September, 1980

Signed

APPENDIX 1b (continued)

ICLS

G/B/3882

Polynuclear Aromatic Hydrocarbons

Fluoranthene	NDLT 20 ng/litre
Benzo (ghi) perylene	NDLT 4 ng/litre
Benzo (k) fluoranthene	NDLT 4 ng/litre
2, 3 C - phenylene pyrene	NDLT 4 ng/litre
Benzo (b) fluoranthene	NDLT 4 ng/litre
Benzo (a) pyrene	NDLT 4 ng/litre

Total P.A.H. NDLT 40 ng/litre

Organochlorine Pesticides

alpha B.H.C.	NDLT 10 ng/litre
gamma B.H.C.	NDLT 10 ng/litre
Heptachlor	NDLT 20 ng/litre
Aldrin	NDLT 20 ng/litre
Dieldrin	NDLT 40 ng/litre
p.p. D.D.T.	NDLT 20 ng/litre

Polychlorinated biphenyls

NDLT 400 ng/litre (expressed as AROCHLOR 1248)

NDLT = Not Detected, Less Than

APPENDIX 2

HMX: 14 Day Dietary Toxicity Study in Mice
Pre-experimental Analysis of Formulated Diets For
Stability and Homogeneity

Time Analysed	Nominal Concentration (ppm)					
	1,250 ppm		10,000 ppm		25,000 ppm	
	Mean	*Coeff Var %	Mean	*Coeff Var %	Mean	*Coeff Var %
Immediately after preparation	1177	5.3	10198	5.4	24817	2.5
After 14 d at 40°C	1234	3.8	10130	3.6	25004	4.4
After 21 d at Ambient	1291	3.9	10311	3.0	25598	3.5

* coefficient of variation (%)

APPENDIX 3a

HMX: 14 Day Dietary Toxicity Study in Mice
Individual Body Weights (g) - Males

Dose Level (mg HMX/ kg/day)	Animal Number/Sex	Treatment Week/Day of Dosing						
		Pre-trial			Week 1		Week 2	
		7	4	0	3	7	10	14
0	401♂	24	25	26	25	26	28	28
	402	23	25	25	26	27	28	28
	403	21	24	24	24	24	25	25
	404	22	23	25	25	26	25	26
	405	20	21	22	22	23	23	23
	406	22	23	24	24	23	24	24
Mean		22.0	23.5	24.3	24.3	24.8	25.5	25.7
± S.D.		1.4	1.5	1.4	1.4	1.7	2.1	2.1

APPENDIX 3a (continued)

Dose Level (mg HMX/ kg/day)	Animal Number/Sex	Treatment Week/Day of Dosing						
		Pre-trial			Week 1		Week 2	
		7	4	0	3	7	10	14
100	407♂	21	21	22	21	21	22	23
	408	20	22	21	20	21	22	23
	409	23	25	25	24	25	27	27
	410	21	22	22	21	22	23	24
	411	21	23	23	21	22	23	25
	412	22	24	25	24	25	26	27
Mean		21.3	22.8	23.0	21.8	22.7	23.8	24.8
± S.D.		1.0	1.5	1.7	1.7	1.9	2.1	1.8

APPENDIX 3a (continued)

Dose Level (mg HMX/ kg/day)	Animal Number/Sex	Treatment Week/Day of Dosing						
		Pre-trial			Week 1		Week 2	
		7	4	0	3	7	10	14
300	413♂	20	20	22	18	18	†	-
	414	19	20	21	†	-	-	-
	415	19	20	21	15	†	-	-
	416	20	22	23	17	†	-	-
	417	20	22	24	20	23	†	-
	418	21	23	24	19	23	24	24
Mean		19.8	21.2	22.5	17.8	21.3	24.0	24.0
± S.D.		0.8	1.3	1.4	1.9	2.9	0	0

† = Animal dead

APPENDIX 3a (continued)

Dose Level (mg HMX/ kg/day)	Animal Number/Sex	Treatment Week/Day of Dosing						
		Pre-trial			Week 1		Week 2	
		7	4	0	3	7	10	14
900	419♂	22	24	26	20	†	-	-
	420	20	21	22	15	†	-	-
	421	21	22	23	16	†	-	-
	422	20	22	22	18	†	-	-
	423	19	20	21	†	-	-	-
	424	19	20	22	†	-	-	-
Mean		20.2	21.5	22.7	17.3	-	-	-
± S.D.		1.2	1.5	1.8	2.2			

† = Animal dead

APPENDIX 3a (continued)

Dose Level (mg HMX/ kg/day)	Animal Number/Sex	Treatment Week/Day of Dosing						
		Pre-trial			Week 1		Week 2	
		7	4	0	3	7	10	14
2700	425♂	21	24	26	17	†	-	-
	426	20	22	23	†	-	-	-
	427	20	22	22	15	†	-	-
	428	19	20	22	†	-	-	-
	429	21	24	25	†	-	-	-
	430	21	23	24	†	-	-	-
Mean		20.3	22.5	23.7	16.0	-	-	-
± S.D.		0.8	1.5	1.6	1.4			

† = Animal dead

APPENDIX 3b

HMX: 14 Day Dietary Toxicity Study in Mice
Individual Body Weights (g) - Females

Dose Level (mg HMX/ kg/day)	Animal Number/Sex	Treatment Week/Day of Dosing						
		Pre-trial			Week 1		Week 2	
		7	4	0	3	7	10	14
0	431♀	18	19	20	21	22	22	23
	432	17	18	19	20	20	21	23
	433	18	18	21	21	21	21	22
	434	17	18	20	21	21	21	23
	435	18	20	21	23	22	22	24
	436	17	18	20	21	21	21	22
Mean		17.5	18.5	20.2	21.2	21.2	21.3	22.8
± S.D.		0.5	0.8	0.8	1.0	0.8	0.5	0.8

APPENDIX 3b (continued)

Dose Level (mg HMX/ kg/day)	Animal Number/Sex	Treatment Week/Day of Dosing						
		Pre-trial			Week 1		Week 2	
		7	4	0	3	7	10	14
320	437♀	17	17	18	20	20	19	21
	438	18	19	20	20	20	20	22
	439	18	19	21	21	22	21	23
	440	18	19	20	20	20	21	21
	441	16	17	18	19	18	17	19
	442	16	18	20	20	20	20	20
Mean		17.2	18.2	19.5	20.0	20.0	19.7	21.0
± S.D.		1.0	1.0	1.2	0.6	1.3	1.5	1.4

APPENDIX 3b (continued)

Dose Level (mg HMX/ kg/day)	Animal Number/Sex	Treatment Week/Day of Dosing						
		Pre-trial			Week 1		Week 2	
		7	4	0	3	7	10	14
800	443♀	18	20	20	20	21	20	22
	444	16	19	20	18	18	19	21
	445	19	20	21	20	21	21	23
	446	19	20	21	20	20	20	22
	447	20	20	21	21	23	22	†
	448	18	19	20	18	17	†	-
Mean		18.3	19.7	20.5	19.5	20.0	20.4	22.0
± S.D.		1.4	0.5	0.5	1.2	2.2	1.1	0.8

† = Animal dead

APPENDIX 3b (continued)

Dose Level (mg HMX/ kg/day)	Animal Number/Sex	Treatment Week/Day of Dosing						
		Pre-trial			Week 1		Week 2	
		7	4	0	3	7	10	14
2000	449♀	18	20	20	18	†	-	-
	450	18	20	20	19	†	-	-
	451	19	20	21	19	18	21	21
	452	19	20	21	20	18	20	22
	453	19	20	22	20	†	-	-
	454	20	21	22	20	†	-	-
Mean		18.8	20.2	21.0	19.3	18.0	20.5	21.5
± S.D.		0.8	0.4	0.9	0.8	0.0	0.7	0.7

† = Animal dead

APPENDIX 3b (continued)

Dose Level (mg HMX/ kg/day)	Animal Number/Sex	Treatment Week/Day of Dosing						
		Pre-trial			Week 1		Week 2	
		7	4	0	3	7	10	14
5000	455♀	19	20	21	16	†	-	-
	456	20	21	23	20	†	-	-
	457	18	20	21	18	†	-	-
	458	19	20	21	17	†	-	-
	459	18	19	20	15	†	-	-
	460	19	20	21	17	†	-	-
Mean ± S.D.		18.8 0.8	20.0 0.6	21.2 1.0	17.2 1.7	-	-	-

† = Animal dead

APPENDIX 4

HMX: 14 Day Dietary Toxicity Study in Mice
Formulated Diet Analysis

Treatment Week	Dose Group/ Sex	Dose Level (mg HMX/ kg/day)	Theoretical Concentration (ppm)	Observed Concentration (PPM)			Mean Concentration (ppm)	Standard Deviation (ppm)	Deviation (%) from Mean Concentration
				Sample 1	Sample 2	Sample 3			
1	1♂	0	0	0	0	0	0	0	0
	2	100	483	527	478	559	521	± 41	+ 7.9
	3	300	1513	1534	1515	1593	1547	± 41	+ 2.2
	4	900	4856	4833	4562	6439	5278	± 1015	+ 8.7
	5	2700	12547	11852	12904	13705	12820	± 929	+ 2.2
	1♀	0	0	0	0	0	0	0	0
	2	320	1331	1295	1293	1371	1320	± 44	- 0.8
	3	800	3325	3088	3115	3253	3152	± 89	- 5.2
	4	2000	7926	7878	7835	8614	8109	± 438	+ 2.3
	5	5000	21078	22237	22115	22328	22227	± 107	+ 5.5
2	1♂	0	0	0	0	0	0	0	0
	2	100	500	548	505	493	515	± 29	+ 3.0
	3	300	2014	2026	2127	2093	2082	± 51	+ 3.4
	4	900	-	-	-	-	-	-	-
	5	2700	-	-	-	-	-	-	-
	1♀	0	0	0	0	0	0	0	0
	2	320	1458	1463	1547	1553	1521	± 50	+ 4.3
	3	800	4556	4698	4916	4941	4852	± 134	+ 6.5
	4	2000	11613	11221	11256	11151	11209	± 53	- 3.5
	5	5000	-	-	-	-	-	-	-

Theoretical concentration (ppm) calculated from predicted group mean mid-week body weight and predicted group mean food consumption

All animals in groups 4♂, 5♂ and 5♀ dead during treatment week 2

APPENDIX 5a

HMX: 14 Day Dietary Toxicity Study in Mice
Absolute Organ Weights (g)
Individual Values - Males Surviving 14 Days Dosing

Dose Level (mg HMX/kg/day)	Animal Number	Kidneys		Liver
		L	R	
0	401	0.24	0.25	1.32
	402	0.25	0.27	1.46
	403	0.23	0.26	1.44
	404	0.25	0.26	1.50
	405	0.17	0.18	1.27
	406	0.22	0.23	1.31
	Mean	0.23	0.24	1.38
	± S.D.	0.03	0.03	0.09
100	407	0.21	0.22	1.29
	408	0.20	0.21	1.14
	409	0.22	0.25	1.59
	410	0.21	0.23	1.27
	411	0.20	0.21	1.20
	412	0.23	0.24	1.58
	Mean	0.21	0.23	1.35
	+ S.D.	0.01	0.02	0.19
300	418	0.21	0.23	1.38

APPENDIX 5a (continued)

Individual Values - Females Surviving 14 Days Dosing

Dose Level (mg HMX/kg/day)	Animal Number	Kidneys		Liver
		L	R	
0	431	0.15	0.17	1.26
	432	0.15	0.16	1.19
	433	0.15	0.16	1.32
	434	0.15	0.18	1.26
	435	0.16	0.17	1.23
	436	0.15	0.16	1.22
	Mean	0.15	0.17	1.25
	± S.D.	0.004	0.01	0.04
320	437	0.14	0.16	1.18
	438	0.16	0.16	1.34
	439	0.16	0.16	1.34
	440	0.15	0.16	1.24
	441	0.13	0.13	1.16
	442	0.06	0.13	1.26
	Mean	0.13	0.15	1.25
	± S.D.	0.04	0.02	0.08

APPENDIX 5a (continued)

Dose Level (mg HMX/kg/day)	Animal Number	Kidneys		Liver
		L	R	
800	443	0.16	0.16	1.37
	444	0.13	0.15	1.19
	445	0.16	0.17	1.36
	446	0.16	0.16	1.38
	Mean	0.15	0.16	1.33
	± S.D.	0.02	0.01	0.09
2000	451	0.13	0.14	1.09
	452	0.15	0.16	1.44
	Mean	0.14	0.15	1.27
	± S.D.	0.01	0.01	0.25

APPENDIX 5b

HMX: 14 Day Dietary Toxicity Study in Mice
Organ Weights as a % of Body Weight
Individual Values - Males Surviving 14 Days Dosing

Dose Level (mg HMX/kg/day)	Animal Number	Body Weight (g)	Kidneys		Liver
			L	R	
0	401	27	0.889	0.926	4.889
	402	27	0.926	1.000	5.407
	403	25	0.920	1.040	5.760
	404	26	0.962	1.000	6.000
	405	22	0.773	0.818	5.773
	406	24	0.917	0.958	5.458
	Mean		0.898	0.957	5.548
	± S.D.		0.065	0.079	0.390
100	407	22	0.955	1.000	5.864
	408	22	0.909	0.955	5.182
	409	28	0.786	0.893	5.679
	410	23	0.913	1.000	5.522
	411	23	0.870	0.913	5.217
	412	26	0.885	0.923	6.077
	Mean		0.886	0.947	5.590
	± S.D.		0.057	0.045	0.355
300	418	25	0.840	0.920	5.520

APPENDIX 5b (continued)

Individual Values - Females Surviving 14 Days Dosing

Dose Level (mg HMX/kg/day)	Animal Number	Body Weight (g)	Kidneys		Liver
			L	R	
0	431	22	0.682	0.773	5.727
	432	21	0.714	0.762	5.667
	433	21	0.714	0.762	6.286
	434	22	0.682	0.818	5.727
	435	22	0.727	0.773	5.591
	436	21	0.714	0.762	5.810
	Mean		0.701	0.775	5.801
	± S.D.		0.019	0.022	0.248
320	437	20	0.700	0.800	5.900
	438	21	0.762	0.762	6.381
	439	21	0.762	0.762	6.381
	440	20	0.750	0.800	6.200
	441	19	0.684	0.684	6.105
	442	19	0.316	0.684	6.632
	Mean		0.662	0.749	6.267
	± S.D.		0.173	0.053	0.255

APPENDIX 5b (continued)

Dose Level (mg HMX/kg/day)	Animal Number	Body Weight (g)	Kidneys		Liver
			L	R	
800	443	21	0.762	0.762	6.524
	444	20	0.650	0.750	5.950
	445	22	0.727	0.773	6.182
	446	22	0.727	0.727	6.273
	Mean		0.717	0.753	6.232
	± S.D.		0.047	0.020	0.237
2000	451	20	0.650	0.700	5.450
	452	22	0.682	0.727	6.545
	Mean		0.660	0.714	5.998
	± S.D.		0.023	0.019	0.774

APPENDIX 5c

HMX: 14 Day Dietary Toxicity Study in Mice
Premature Decedents - Absolute Organ Weights (g)
Individual Values - Males

Dose Level (mg HMX/kg/day)	Animal Number	Kidneys		Liver
		L	R	
300	413	0.25	0.20	1.75
	414	0.17	0.17	1.39
	415	0.13	0.14	0.53
	416	0.14	0.14	0.61
	417●	NDA	NDA	NDA
900	419	0.15	0.17	0.79
	420	0.13	0.14	0.59
	421	0.17	0.18	0.78
	422	0.14	0.14	0.57
	423	0.16	0.17	1.02
	424	0.15	0.16	1.27
2700	425	0.15	0.18	0.71
	426	0.16	0.17	1.03
	427	0.13	0.14	0.55
	428	0.15	0.15	0.83
	429	0.18	0.19	1.46
	430	0.18	0.19	1.11

● = Organ weights not recorded

NDA = No data available

APPENDIX 5c (continued)

Individual Values - Females

Dose Level (mg HMX/kg/day)	Animal Number	Kidneys		Liver
		L	R	
800	447	0.19	0.21	1.80
	448●	NDA	NDA	NDA
2000	449	0.12	0.12	0.54
	450	0.12	0.12	0.57
	453	0.15	0.16	0.91
	454	0.13	0.15	1.07
5000	455	0.11	0.12	0.55
	456	0.13	0.13	0.61
	457	0.10	0.11	0.54
	458	0.12	0.14	0.59
	459	0.11	0.11	0.52
	460	0.11	0.12	0.52

● = Organ weights not recorded

NDA = No data available

APPENDIX 5d

HMX: 14 Day Dietary Toxicity Study in Mice
Premature Decedents - Organ Weights as % of Body Weight
Individual Values - Males

Dose Level (mg HMX/kg/day)	Animal Number	Body Weight (g)	Kidneys		Liver
			L	R	
300	413	21	1.190	0.952	8.333
	414	19	0.895	0.895	7.316
	415	15	0.867	0.933	3.533
	416	15	0.933	0.933	4.067
	417●	24	NDA	NDA	NDA
900	419	17	0.882	1.000	4.647
	420	15	0.867	0.933	3.933
	421	16	1.063	1.125	4.875
	422	15	0.933	0.933	3.800
	423	17	0.941	1.000	6.000
	424	19	0.789	0.842	6.684
2700	425	17	0.882	1.059	4.176
	426	19	0.842	0.895	5.421
	427	15	0.867	0.933	3.667
	428	17	0.882	0.882	4.882
	429	23	0.783	0.826	6.348
	430	19	0.947	1.000	5.842

● = Organ weights not recorded
NDA = No data available

APPENDIX 5d (continued)

Individual Values - Females

Dose Level (mg HMX/kg/day)	Animal Number	Body Weight (g)	Kidneys		Liver
			L	R	
800	447	23	0.826	0.913	7.826
	448●	17	NDA	NDA	NDA
2000	449	12	1.000	1.000	4.500
	450	13	0.923	0.923	4.385
	453	17	0.882	0.941	5.353
	454	19	0.684	0.789	5.632
5000	455	12	0.917	1.000	4.583
	456	13	1.000	1.000	4.692
	457	13	0.769	0.846	4.154
	458	13	0.923	1.077	4.539
	159	12	0.917	0.917	4.333
	460	13	0.846	0.923	4.000

● = Organ weights not recorded

NDA = No data available

APPENDIX 6

HMX: 14 Day Dietary Toxicity Study in Mice
Gross Pathology and Histopathological Findings in Individual Animals

Abbreviations used:

TK	Terminal kill
KIE	Killed *in extremis*
FD	Found dead
NAD	No abnormality detected
HE	Haematoxylin and Eosin
SS	Special stain

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1 0 mg HMX/kg/day
Animal No: 401 Sex: ♂

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1
Animal No: 402 Sex: ♂

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1
Animal No: 403 Sex: ♂

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1
Animal No: 404 Sex: ♂

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined: HE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1
Animal No: 405 Sex: ♂

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1
Animal No: 406 Sex: ♂

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 3 300 mg HMX/kg/day
Animal No: 413 Sex: ♂

Time on Study	Death
9 days	FD

Internal and External Necropsy Findings	Organ	Histopathology
Pale and mottled.	Kidneys	Areas tubular dilation, tubular atrophy.
Pale and mottled.	Liver	Cytoplasm of hepatocytes eosinophilic. Areas focal necrosis.
	Thymus	Lymphocyte depletion.

Number of Sections Examined		
HE		SS
1	Liver	
2	Kidney	
1	Heart	
1	Spleen	
1	Thymus	
1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 3
Animal No: 414 Sex: ♂

Time on Study	Death
2 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
			1	Liver	
	Liver	Cytoplasm of hepatocytes vacuolated.	2	Kidney	
			1	Heart	
Very small and pale.	Spleen	Red and white pulp depletion.	1	Spleen	
			1	Thymus	
	Thymus	Lymphocyte depletion.	3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 3
Animal No: 415 Sex: ♂

Time on Study	Death
3 days	KIE

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.	1	Liver	
Small.	Spleen	Some white pulp depletion.	2	Kidney	
	Thymus	Lymphocyte depletion.	1	Heart	
Penis protruding.			1	Spleen	
			1	Thymus	
			3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 3
Animal No: 416 Sex: ♂

Time on Study	Death
4 days	KIE

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic. Increased cellularity.	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
	Thymus	Lymphocyte depletion.	1	Thymus	
			1	Brain	
Penis red and protruding.					

APPENDIX 6 (continued)

Project No: 415669SM Group No: 3
Animal No: 417 Sex: ♂

Time on Study	Death
8 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
One side brown the other red.	Heart	NAD	1	Liver	
Contents dark brown.	Stomach	NAD	2	Kidney	
Contents dark brown liquid.	Duodenum	Autolytic.	1	Heart	
Red encrustations round mouth, nose and feet.			1	Spleen	
			1	Thymus	
			1	Brain	
			1	Stomach	
			1	Duodenum	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 4 900 mg HMX/kg/day
Animal No: 419 Sex: ♂

Time on Study	Death
5 days	FD

Internal and External Necropsy Findings	Organ	Histopathology
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.
Small and pale.	Spleen	White and red pulp depletion.

Number of Sections Examined		
HE		SS
1	Liver	
2	Kidney	
1	Heart	
1	Spleen	
0	Thymus	
1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 4
Animal No: 420 Sex: ♂

Time on Study	Death
3 days	KIE

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.	1	Liver	
Very small.	Spleen	White and red pulp depletion.	2	Kidney	
	Thymus	Lymphocyte depletion.	1	Heart	
Penis erect and red.			1	Spleen	
			1	Thymus	
			3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 4
Animal No: 421 Sex: ♂

Time on Study	Death
3 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.	1	Liver	
Very small.	Spleen	White and red pulp depletion.	2	Kidney	
	Thymus	Lymphocyte depletion.	1	Heart	
Penis erect and red.			1	Spleen	
			1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 4
Animal No: 422 Sex: ♂

Time on Study	Death
4 days	KIE

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.	1	Liver	
	Spleen	Some degree white and red pulp depletion.	2	Kidney	
	Thymus	Lymphocyte depletion.	1	Heart	
			1	Spleen	
			1	Thymus	
			3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 4
Animal No: 423 Sex: ♂

Time on Study	Death
2 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic, slight increase in cellularity.	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
Small and pale.	Spleen	Some degree red and white pulp depletion.	1	Thymus	
	Thymus	Slight degree lymphocyte depletion.	3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 4
Animal No: 424 Sex: ♂

Time on Study	Death
1 day	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
Liver pale.		Sections autolytic.	1	Liver	
Spleen pale.			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No:5 2,700 mg HMX/kg/day
Animal No: 425 Sex: ♂

Time on Study	Death
3 days	KIE

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.	1	Liver	
Left smaller than right.	Kidneys	NAD	2	Kidney	
Very small.	Spleen	Some degree white and red pulp depletion.	1	Heart	
	Thymus	Slight degree lymphocyte depletion.	1	Spleen	
			1	Thymus	
			3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 5
Animal No: 426 Sex: ♂

Time on Study	Death
2 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Eosinophilic, some increased cellularity.	1	Liver	
			2	Kidney	
Very small and thin.			1	Heart	
	Spleen	White and red pulp depletion.	1	Spleen	
			1	Thymus	
	Thymus	Some degree lymphocyte depletion.	1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 5
Animal No: 427 Sex: ♂

Time on Study	Death
3 days	KIE

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.	1	Liver	
Small.	Spleen	Some degree of red and white pulp depletion.	2	Kidney	
			1	Heart	
			1	Spleen	
			0	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 5
Animal No: 428 Sex: ♂

Time on Study	Death
2 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined NE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.	1	Liver	
			2	Kidney	
Small and pale.	Spleen	Some red and white pulp depletion.	1	Heart	
			1	Spleen	
	Thymus	Some lymphocyte depletion.	1	Thymus	
			1	Brain	
		Sections fairly autolytic.			

APPENDIX 6 (continued)

Project No: 415669SM Group No: 5
Animal No: 429 Sex: ♂

Time on Study	Death
1 day	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
Pale.	Liver	NAD	1	Liver	
Pale.	Spleen	Some red pulp depletion.	2	Kidney	
		Sections fairly autolytic.	1	Heart	
			1	Spleen	
			1	Thymus	
			3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 5
Animal No: 430 Sex: ♂

Time on Study	Death
2 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.	1	Liver	
Small and pale.	Spleen	Red and white pulp depletion.	2	Kidney	
	Thymus	Lymphocyte depletion.	1	Heart	
			1	Spleen	
			1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1 0 mg HMX/kg/day
Animal No: 431 Sex: ♀

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined NE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1
Animal No: 432 Sex: ♀

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1
Animal No: 433 Sex: ♀

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1
Animal No: 434 Sex: ♀

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology
Right kidney larger than left.	Kidneys	NAD

Number of Sections Examined		
HE		SS
1	Liver	
2	Kidney	
1	Heart	
1	Spleen	
1	Thymus	
1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1
Animal No: 435 Sex: ♀

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 1
Animal No: 436 Sex: ♀

Time on Study	Death
2 weeks	TK

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 3 800 mg HMX/kg/day
Animal No: 447 Sex: ♀

Time on Study	Death
2 weeks	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
NAD		NAD	1	Liver	
			2	Kidney	
			1	Heart	
			1	Spleen	
			1	Thymus	
			3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 3
Animal No: 448 Sex: ♀

Time on Study	Death
8 days	FD

Internal and External Necropsy Findings	Organ	Histopathology
Very pale.	Spleen	Red pulp and some white pulp depletion.
	Thymus	Lymphocyte depletion.
Darker red than normal.	Lungs	Congested and autolytic.

Number of Sections Examined		
HE		SS
1	Liver	
2	Kidney	
1	Heart	
1	Spleen	
1	Thymus	
3	Brain	
1	Lung	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 4 2,000 mg HMX/kg/day
Animal No: 449 Sex: ♀

Time on Study	Death
6 days	FD

Internal and External Necropsy Findings	Organ	Histopathology
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity. Section fairly autolytic.
Small.	Spleen	Red and white pulp depletion.
	Thymus	Lymphocyte depletion.

Number of Sections Examined		
HE		SS
1	Liver	
2	Kidney	
1	Heart	
1	Spleen	
1	Thymus	
3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 4
Animal No: 450 Sex: ♀

Time on Study	Death
6 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
			1	Liver	
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity. Section fairly autolytic.	2	Kidney	
			1	Heart	
Small.	Spleen	Red and white pulp depletion.	1	Spleen	
	Thymus	Lymphocyte depletion.	1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 4
Animal No: 453 Sex: ♀

Time on Study	Death
6 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
			1	Liver	
	Liver	Cytoplasm of hepatocytes eosinophilic. Some degree increased cellularity.	2	Kidney	
			1	Heart	
Small and pale.	Spleen	Red and white pulp depletion.	1	Spleen	
	Thymus	Some lymphocyte depletion.	1	Thymus	
		Sections fairly autolytic.	3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 4
Animal No: 454 Sex: ♀

Time on Study	Death
4 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Slight increase in cellularity.	1	Liver	
			2	Kidney	
Small.	Spleen	Red pulp and some white pulp depletion.	1	Heart	
			1	Spleen	
	Thymus	Lymphocyte depletion.	1	Thymus	
			3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No:5 5,000 mg HMX/kg/day
Animal No: 455 Sex: ♀

Time on Study	Death
5 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.	1	Liver	
			2	Kidney	
			1	Heart	
Small.	Spleen	Slight degree red and white pulp depletion.	1	Spleen	
			1	Thymus	
	Thymus	Lymphocyte depletion.	3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 5
Animal No: 456 Sex: ♀

Time on Study	Death
6 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic. Some increase in cellularity.	1	Liver	
			2	Kidney	
			1	Heart	
Small.	Spleen	Red and white pulp depletion.	1	Spleen	
			1	Thymus	
	Thymus	Lymphocyte depletion.	1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 5
Animal No: 457 Sex: ♀

Time on Study	Death
6 days	KIE

Internal and External Necropsy Findings	Organ	Histopathology
Small.	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.
	Spleen	Red and white pulp depletion.

Number of Sections Examined		
HE		SS
1	Liver	
2	Kidney	
1	Heart	
1	Spleen	
0	Thymus	
3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No:5
Animal No: 458 Sex: ♀

Time on Study	Death
5 days	FD

Internal and External Necropsy Findings	Organ	Histopathology
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.
Very small.	Spleen	Red and white pulp depletion.
	Thymus	Lymphocyte depletion.
Left kidney smaller than right.		Sections fairly autolytic.

Number of Sections Examined		
HE		SS
1	Liver	
2	Kidney	
1	Heart	
1	Spleen	
1	Thymus	
3	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 5
Animal No: 459 Sex: ♀

Time on Study	Death
4 days	KIE

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Cytoplasm of hepatocytes eosinophilic, increased cellularity.	1	Liver	
	Spleen	Red and white pulp depletion.	2	Kidney	
	Thymus	Lymphocyte depletion.	1	Heart	
			1	Spleen	
			1	Thymus	
			1	Brain	

APPENDIX 6 (continued)

Project No: 415669SM Group No: 5
Animal No: 460 Sex: ♀

Time on Study	Death
6 days	FD

Internal and External Necropsy Findings	Organ	Histopathology	Number of Sections Examined HE		SS
	Liver	Eosinophilic cytoplasm. Increased cellularity.	1	Liver	
Small.	Spleen	Too autolytic.	2	Kidney	
		Sections autolytic.	1	Heart	
			1	Spleen	
			1	Thymus	
			1	Brain	

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