IRI Report No. 2014

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HMX: 14 Day Toxicity in Mice by Dietary Administration

Final Report by: R.J. Greenough P. McDonald

> *30* July, 1985

Supported by:

U.S. Army Medical Research and Development Command Fort Detrick Frederick, Maryland 21701

> Contract No. DAMD-17-80-C-0053 IRI Project 415669 SM

Inveresk Research International Limited Musselburgh, EH21 7UB, Scotland

Contracting Officer's Technical Representative:

Jesse J. Barkley, Jr. U.S. Army Medical Bioengineering Research and Development Laboratory Fort Detrick, Frederick, Maryland 21701-5010

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AUTHOR(#)	415669 SM/2014 8. CONTRACT OR GRANT NUMBER(*)
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PERFORMING ORGANIZATION NAME AND ADDRESS Inveresk Research International Lin Musselburgh, EH21 7UB, Scotland	nited 62720A.3E162720A835.00
CONTROLLING OFFICE NAME AND ADDRESS Jesse J. Barkley, Jr., U.S. Army Mo Research and Development Command,	edical 12. REPORT DATE 30 July 1985
Ft Detrick, Maryland, U.S.A.	97
. MONITORING AGENCY NAME & ADDRESS(II different from Control	ling Office) 15. SECURITY CLASS. (of this report) Non classified
	15. DECLASSIFICATION/DOWNGRADING SCHEDULE
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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. E. hill.

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



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Project No. 415669SM

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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:

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dvav Waddel Quality Assurance Manager)

Date: 141h 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 6d and 6? B6C3F<sub>1</sub> 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				Fe	males	<u>,</u>	
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.

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### 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 d and 30 9) 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  $20^{\circ}$ C + 2°C with extreme limits of 20°C and 24°C, and humidity <u>ca</u> 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

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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 colourcoded according to the treatment group.

The treatment groups were as follows:

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

### 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.

Concentration (ppm, w/w) =	Dose level (mg/kg/day) x predicted mid-week body weight (g) predicted daily food consumption (g)
Amount of test substance _ required (g)	ppm x weight of diet required 1000

After drying to a constant weight HMX was sieved through a plastic 100  $\mu$ m 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 SpectrophotometerColumn:Hypersil ODS (10 cm x 0.5 cm)Solvent:Acetonitrile:water (20:30 v/v)Flow:1 ml/minWavelength:228 nmRecorder:Servoscribe 1 s-10 mVChart 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

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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  $-20^{\circ}$ C for analysis at a later date.

### <u>Gross\_Necropsy</u>

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  $\mu m$  thickness and stained with haem-atoxylin 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.

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### 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 al	bnoi	cmalities were observed.
Group 2 - (100 mg/ kg/day)			hyperkinesia/excitability observed in all animals when aroused.
Group 3 - (300 mg/ kg/day)	Day 2	2:	4143 found dead in cage. Hyper- kinesia and sensitivity to audio stimuli observed in all animals when aroused. One animal (4153) observed having a convulsion.
	Day 3	3:	surviving animals extremely sensi- tive to external stimuli, erect peni observed in 2 animals. When aroused the animals held their tails horizontally, producing a quivering effect. Animal 4155 had an emaci- ated, hunched appearance with pilo- erection - killed in extremis.
	Day 4	4:	416d penis erect, piloerection, hunched/emaciated appearance - killed in extremis.
	Day 5	5 <del>-</del> 7:	hyperkinesia, tail quivering when
			surviving animals appeared emaciated, 4175 observed having a convulsion - died 1½ h later. Blood observed at animal's mouth, cage also heavily blood stained.
	Day 9	9:	4135 found dead in cage.
Group 4 - (900 mg/	Day 1	1:	4245 found dead in cage, remaining animals had a hunched appearance.
kg/day)	Day 2	2:	4233 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 420d and 421d observed to have piloerection, erect peni and a hunched emaciated appearance. Number 421d unable to maintain upright posture - later found dead in cage. Number 420d killed in extremis.
- Day 4: 4193, 4223 piloerection, hunched/ emaciated appearance, 4193 hyperkinetic when aroused. Number 4223 had difficulty in standing - killed in extremis.
- Day 5: 4198 found dead in cage.
- Group 5 Day 1: 429° found dead in cage, others (2700 mg/ appeared subdued with hunched kg/day) Day 2: 426°, 428° and 430° found dead in their cages. Surving animals
  - sensitive to audio stimuli. Day 3: 4253 and 4273 subdued, piloerection, hunched/emaciated appearance, both animals sensitive to external stimuli when aroused, tails quivering and held horizontally. Killed <u>in</u> extremis.

### Females

Group 1 - (Control)	No a	abnoi	rmalities were observed.
Group 2 -			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	10:	4489 found dead in cage. 4439 bald patches on abdomen, fore legs and right hind leg.
	Day	14:	4479 found dead in cage.
<b>Group 4 -</b> (2000 mg/ kg/dav)	Day	1:	all animals appeared slightly sub- dued.

Day 3: from day 3, and for most of the remainder of the dosing period, all animals showed hyperkinesia when aroused. 4549 found dead in cage. Day 4: 4499, 4509 and 4539 all found dead Day 6: in their cages. Day 7: surviving animals had a hunched appearance and piloerection. Group 5 - Day 1: all animals subdued. (5000 mg/ Day 3: 457 and 459 subdued, emaciated/ kg/day) hunched appearance, hypokinetic when aroused. Remaining animals hyperkinetic when aroused. Day 4: all animals had an emaciated/ hunched appearance, 4559 hyper-Number 4599 killed in kinetic. extremis. Day 5: 4559 and 4589 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, 4579 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

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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

			Dos	Dose Group/Dose Level (mg HMX/kg/day)	Dose Lev	el (mg F	IMX/kg/d	ay)		
Day of Dosing	1.5 0	2.5 100	3.5 300	4 <i>3</i> 900	5.f 2700	1 0	29 320	39 800	49 2000	59 5000
1	1	-	-	la	la	1	-	ŧ	1	1
2	ł	ı	la	la	3а	ı	ı	ı	١	I
e	1	ı	qI	la, lb	2b	ı	ı	1	I	ı
4	'	ı	1b	115	ı	I	1	ı	la	1b
5	1	ı	1	la	ł	1	ı	1	I	2a
9	ı	I	ı	1	1	1	1	1	3а	2a, 1b
7	ł	ı	1	I	ı	1	ı	1	ł	ı
80	ł	ı	la	1	1	ı	I	la	1	1
6	I	ı	la	ı	ı	ł	ı	ı	I	ı
10	ı	,	I	ı	I	ı	ı	•	ı	ı
11	ł	ł	ı	1	ı	ı	ı	1	ł	ı
12	ı	ı	1	ı	ı	J	ı	1	I	ı
13	ı	ı	ı	ı	ı	1	ı	1	ı	ı
14	1	I	ł	1	I	ı	1	la	I	I
Total	0	0	5	9	6	ο	0	2	4	6
Number commencing treatment	6	9	9	9	ę	9	9	و	9	6
a = Found b = Kille	<pre>= Found dead in cage = Killed in extremis</pre>	n cage cremis							•	

TABLE 2a

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

Dose Level	Number of				Treatment	Treatment Week/Day of Dosing	Dosing		
/XMH 6m)	Animals			Pre-trial		Week		Week	2
kg/day)			7	4	0	3	7	10	14
c	v	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
-	, v	Mean	21.3	22.8	23.0	21.8	22.7	23.8	24.8
2	)	+ s.D.	1.0	1.5	1.7	1.7	1.9	2.1	1.8
UOR	4	Mean	19.8	21.2	22.5	17.8(a)	21.3(c)	24.0(e)	24.0(e)
200	5	± s.D.	0.8	1.3	1.4	1.9	2.9	0.0	0.0
000	×	Mean	20.2	21.5	22.7	1 <sup>***</sup> (b)	+	+	+
	)	+ S.D.	1.2	1.5	1.8	2.2	-		-
0020	4	Mean	20.3	22.5	23.7	16.0 (d)	+	+	+
2	>	+ S.D.	0.8	1.5	1.6	1.4	-		
(a) n =	5	* Sign	ifficantly di	Significantly different from controls, P<0.05	controls,	P<0.05			
= u (q)	4	** Sign	ifficantly di	** Significantly different from controls, P<0.01	controls, 1	P<0.01			

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\*\*\* Significantly different from controls, P<0.001

t All animals dead

(c) n = 3 (d) n = 2 (e) n = 1

TABLE 2b

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

Dose Level	Number of				Treatment	Treatment Week/Day of Dosing	Dosing		
(mg HMX/	Animals			Pre-trial		Week	k 1	Week	2
kg/day)			7	4	0	Э	7	10	14
c	v	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
120	Ŷ	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	و	Mean	18.3	19. <sup>*</sup>	20.5	19.5	20.0	20.4(a)	22.0(b)
	)	<u>+</u> s.D.	1.4	0.5	0.5	1.2	2.2	1.1	0.8
2000	ي. د	Mean	18.8	20.**	21.0	19,3	18.0(d)	20.5(d)	21.5(d)
	,	<u>+</u> s.D.	0.8	0.4	0.9	0.8	0.0	0.7	0.7
5000	ÿ	Mean	18.8	20.0	21.2	17.2	+	+	÷
		+ S.D.	0.8	0.6	1.0	1.7	-		
(a) n = 5	5	* Sign	ificantly di	* Significantly different from controls, P<0.05	n controls, 1	P<0.05			

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

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

TABLE 3

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

			Dose Gro	dno10/dnc	Mean Food	Dose Group/Group Mean Food Consumption (g/mouse/day)	snow/ɓ) u	(/day)		
Treatment Week	1 <del>3</del> (0)	2đ (100)	3ð 3ð	4 <i>3</i> (900)	43 53 (900) (2700)	1 م 1 م	29 (320)	39 (800)	49 (2000)	59 (5000)
Pre-trial	5.0	4.8	4.6		4.3 5.1	1.2	5.0	5.1	5.1 5.4	5.1
1	5.3	4.7	3.5	1.9 1.9	1.9	5.5	4.5	3.6	3.6 3.1	2.8
2	6.0	5.9	5.4	1	I	5.8	5.1	5.0	5.1	I

### TABLE 4

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

			Dose G	roup/Ach	Dose Group/Achieved Dosage (mg HMX/kg/day)	sage (mo	HMX/kg	/day)		
Treatment Week	1đ (0)	2đ (100)	3đ (300)	4ð (900)	45 53 (900) (2700)	14 (0)	2 <i>q</i> 3 <i>q</i> (320) (800)	32 (800)	49 (2000)	59 (5000)
1	0	111.8	111.8 297.5	ł	1	0	297.0	297.0 581.9 1316.1	1316.1	۱
2	0	127.1 468.5	468.5	I	1	0	391.8	391.8 1183.4 2775.0	2775.0	1
Average achieved dosage	0	119.5	119.5 383.0	I	I	0	344.4	344.4 882.7 2045.6	2045.6	1

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

TABLE 5a

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## HMX: 14 Day Dietary Toxicity Study in Mice Absolute Organ Weights (g)

Group Mean Values of Animals Surviving 14 Days Dosing

	R	0.24 1.38 0.03 0.09	0.23 1.35 0.02 0.19	0.23 1.38 0.0 0.0	0.17 1.25 0.01 0.04	0.15 1.25 0.02 0.08	0.16 1.33 0.01 0.09	0.15 1.27 0.01 0.25
Kidneys	L	0.23 0.03	0.21	0.21 0.0	0.15 0.004	0.13 0.04	0.15 0.02	0.14 0.01
		Mean + S.D.	Mean + S.D.	Mean + S.D.	Mean + S.D.	Mean + S.D.	Mean + s.D.	Mean + S.D.
Number of	Animals/Sex	63	6đ	ام	69	69	49	29
Dose Level	(mg HMX/kg/day)	0	100	300	0	320	800	2000

\* 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

(mg HMX/kg/day) An				•	
	Animals/Sex		L	R	Liver
0	63	Mean + S.D.	0.898 0.065	0.957 0.079	5.548 0.390
100	وئ	Mean + S.D.	0.886 0.057	0.947 0.045	5.590 0.355
300	1ð	Mean <u>-</u> S.D.	0.840 0.0	0.920 0.0	5.520 0.0
0	69	Mean + S.D.	0.701 0.019	0.775 0.022	5.801 0.248
320	69	Mean + S.D.	0.662 0.173	0.749 0.053	6.267 0.255
800	4 5	Mean + S.D.	0.717 0.047	0.753 0.020	6.23 <sup>2</sup> 0.237
2000	29	Mean + S.D.	0.660 0.023	0.714 0.019	5.998 0.774

\* Significantly different from controls, P<0.05

\*\* Significantly different from controls, P<0.01

TABLE 6

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

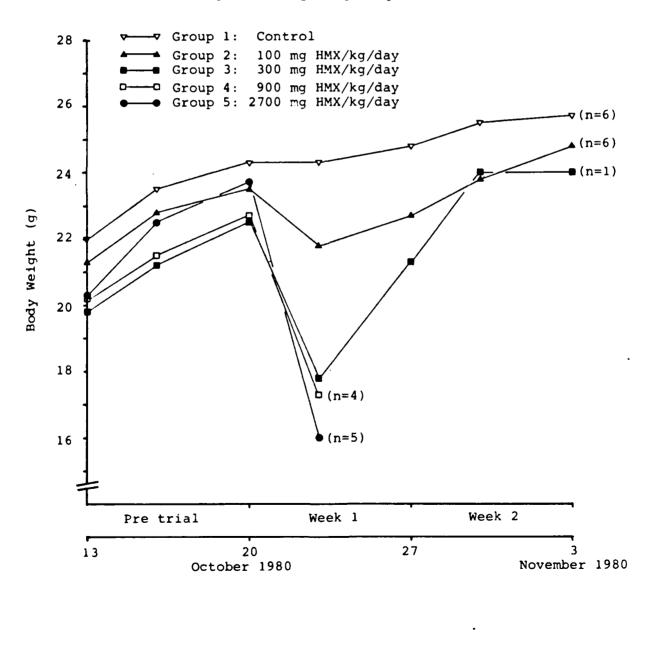
		(5000) \$	6/6 6/6	4/4	5/5 5/5
	5 (a)	(2700) (5000) 3 9	5/6 5/6	4/5	5/6 6/6
	a)	(2000) (2 ?	3/4 4/4	4/4	4/4 4/4
	4 (a)	(00 P	5/5 5/6	4/4	5/5 5/5
scidence	(1	5) (008)	0/2 0/2	1/2	1/2 1/2
Group Incidence	3 (a)	(300) ð	3/5 2/5	4/5	2/5 1/5
	2	(320) 9		ı	1 1
	2	(100) J		•	• •
	1	ა (0)	0/6 0/6	0/6	0/6 0/6
		(0) ع	0/6 0/6	0/6	9/U 9/0
Dose Group/Nominal Dose Level	(mg HMS/KG/ dav)	Lesion	Eosinophilic cytoplasm Increased cellularity	Lymphocyte depletion	White pulp depletion Red pulp depletion
	Organ		Liver	Thymus	Spleen

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

no histopathology undertaken

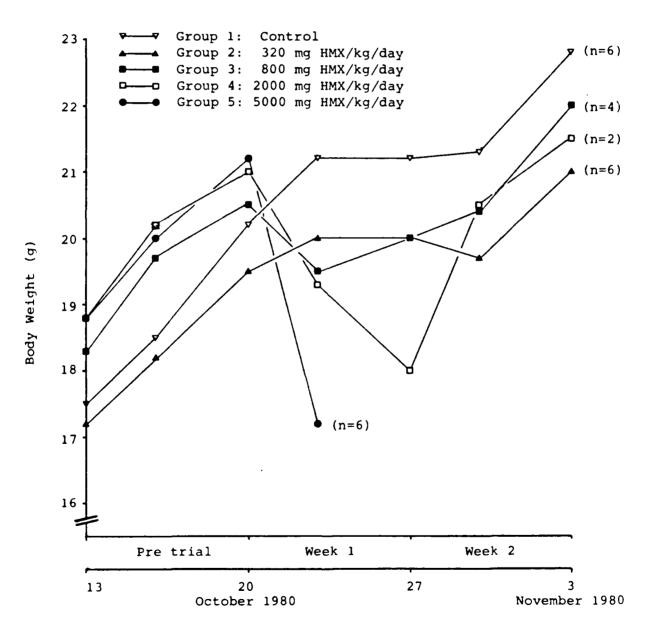
### FIGURE 1

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

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	%	Nitrile as NaNO2	<b>٤ 1.</b> 0	mg/kg	1.0 mg/kg
Crude Fibre	2.2	%	Lead	<b>٤ 1.</b> 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	۷.01 د	mg/kg	0.01 mg/kg
odium	0.22	%	Selenium	0.12	mg/kg	0.02 mg/kg
Chiorine	0.34	%				
Potassium	1.10	%				ľ
Magnesium	0.13	%	Total Aflatoxins NON	E DETECTEL	ug/kg	1 ug/kg
Iron	231	mg/kg				each of B1,82,G1,G2
Copper	٦	mgikg				{
Manganese	55	mg/kg	NONE			
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

Vitamin A	7000	iu/kg
fitamin E	60	mg/kg
Vitamin C		mg/kg

\*repeat 3.4

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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
Total Viable Organisms	1.13 x 10 <sup>3</sup>	per grm	1000/g
Mesophilic Spores	17.5 x 10 <sup>2</sup>	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	I NONE DETECTED	per grm	Absent in 10 grm
Fungal Units	NONE DETECTED	per grm	Absent in
Antibiotic Activity		Ì	10 grm

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

C Topplistons Signed 1012 September 1980 Dated

C P POPPIESTONEMS - PHD C Chem MRIC

### APPENDIX 15

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

	s of a of Water :							
Received					Your Ref			
-				_	Our Ref	G/B/3882	2	
From Labelled	Inveresk Rese Mains Water S		rnation	1				
Lovened	MAILS WALEF 5	appry			Date	4.45 pm	13	/8/
Taken by	M. Scott	Witness	D. Bro	wa	Signed	M. Scott	-	
	Bright with a			Odour				
Electrical C		7.8		Colour (Ha		<u> </u>		
Chlorine in	Chloride	15C		Turbidity/	Formazin			
Hardness a	Is Ca CO1 Total	75		<u>APHA</u> Nitrogen i			LT	
	Carbonate	60		Nitrogen i	n Nitrite		LT	с
	Non-carbonate	15		Ammonia	ical Nitrogen			_0
Alkalinitya	sCaCO)	60	<u>)                                    </u>	Albumino	nd Nitrogen		LT	
				Permanga 4943 at 27 C	enate value			c
Free Carbo	n Dioxide	2	2	Residual	Chlorine		LT	C
		105	<u>;</u>	Iron(Fe) ]	LT 0.03	Zinc(Zn)	LT	c
Dissolved S dried at 180						uminium (A	ND .	c
dried at 180	) LT 0.03 Lead(P	b)LT 0.03	Manga	nese(Mn) (	0.04 A		,	

(mill		· <u>-</u> · · ·	litre and		opl <b>y</b> equivalent:	s per litre)		
	Catio	ons		Anio	ns			
	mg ′	l me∕t		mg ′l	me/i		mg∕I	me/i
Ca	16	0.80	•CO3	36	1.20	Calcium Carbonate	40	0.80
Mg	9	0.70	so.	20	0.42	Magnesium Carbonate	17	0.40
Na	8	0.33	CI	9	0.26	Magnesium Sulphate	18	0.30
к	2	0.05	NO3	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
Com This noti neut soli and Thes	ment ceabl ralit ds. is of	e colour y and th The wate a satis nults ind	actica - The wate factor icate,	reac ris ree f y star from	tion is si soft in cl rom metals ndard of c the aspec	bright in appearance and i lightly on the alkaline si baracter with a low conter s apart from a minute trac organic quality. ct of the chemical and min ag and domestic purposes.	ide of at of di ce of me	.ssolved Inganese

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### <u>G/B/3882</u>

### Polynuclear Aromatic Hydrocarbons

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

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

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APPENDIX 2

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

		Nomina	Nominal Concentration (ppm)	tration	(mdd)	
	1,250 ppm	ppm	19000 ppm	mdd	25,000 ppm	mdd
nac vilatysed	Mean	*Coeff Var %	Mean	*Coeff Var %	Mean	*Coeff Var %
Immediately after preparation 1177	1177	5.3	10198		5.4 24817	2.5
After 14 d at 40 <sup>0</sup> C	1234	3.8	10130 3.6 25004	3.6	25004	4.4
After 21 d at Ambient	1291	3.9	10311	3.0	3.0 25598	3.5

\* coefficient of variation (%)

APPENDIX 3a

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

_	_	-	-	_	_				_	
	2	14	28	28	25	26	23	24	25.7	2.1
	Week 2	10	28	28	25	25	23	24	25.5	2.1
Dosing	k 1	2	26	27	24	26	23	23	24.8	1.7
Treatment Week/Day of Dosing	Week ]	~	25	26	24	25	22	24	24.3	1.4
Treatment		С	26	25	24	25	22	24	24.3	1.4
	<b>Pre-trial</b>	4	25	25	24	23	21	23	23.5	1.5
		2	24	23	21	22	20	22	22.0	1.4
Animal	Number/Sex		4018	402	403	404	405	406		
Dose Level	kg/dav)		0						Mean	+ s.D.

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Dose Level	Animal			Treatment	Treatment Week/Day of Dosing	Dosing		
(mg HmA/ kg/dav)	Number/Sex		Pre-trial		Week	k 1	Week 2	k 2
(Inn )fru		7	4	0	3	7	10	1 14
100	4073	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

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Dose Level	Animal			Treatment	Treatment week/Day of Dosing	t Dosing		
(md HMX/	Number/Sex		<b>Pre-trial</b>		Wee	Week I	Wee	Week 2
/ Apn / Ay		7	4	Ú	3	7	10	14
300	4138	20	20	22	18	18	+	1
	414	19	20	21	+	1	1	1
	415	19	20	21	15	+	ı	'
	416	20	22	23	17	+	1	1
	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	o	0

† = Animal dead

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Dose Level	Animal			Treatment	Treatment Week/Day of Dosing	Dosing		
(WE AMX/	Number/Sex		<b>Pre-trial</b>		Week 1	1	Wee	Week 2
/Inn/fw		7	4	0	٣	6	10	14
006	4193	22	24	26	20	+		1
	420	20	21	22	15	+	,	1
	421	21	22	23	16	+	•	۱
	422	20	22	22	18	+	ı	1
	423	19	20	21	+	1	1	۱
	424	19	20	22	+-	ı	ı	1
Mean		20.2	21.5	22.7	17.3			
+ s.D.		1.2	1.5	1.8	2.2	•	ł	۱ 

t = Animal dead

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Dose Level	Animal			Treatment	Treatment Week/Day of Dosing	t Dosing		
(Net/DA	Number/Sex		<b>Pre-trial</b>		Week	× 1	Week 2	< 2 2
/Inn/fw		7	4	0	e	7	10	14
2700	<b>4</b> 25ð	21	24	26	17	+	1	1
	426	20	22	23	+	۰ 	1	1
	427	20	22	22	15	+	•	1
	428	19	20	22	+	,	1	•
	429	21	24	25	+	1	1	ı
	430	21	23	24	+	,	1	1
Mean	. <u> </u>	20.3	22.5	23.7	16.0			
+ s.D.		0.8	1.5	1.6	1.4	I	I	1

t = Animal dead

APPENDIX 3b

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

Dose Level	Animal			Treatment	Treatment Week/Day of Dosing	Dosing		
(VED/24)	Number/Sex		<b>Pre-trial</b>		Week	k 1	Week 2	k 2
/ Inn /6v		7	4	0	£	7	10	14
0	4319	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

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Dose Level	Animal			Treatment	Treatment Week/Day of Dosing	Dosing		
(mg HMX/	Number/Sex		<b>Pre-trial</b>		Week	k 1	Week	K 2
/ Apn / hy		7	4	0		7	10	14
320	4379	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
<u>+</u> s.b.		1.0	1.0	1.2	0.6	1.3	1.5	1.4

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Dose Level	Animal			Treatme	Treatment Week/Day of Dosing	of Dosing		
(mg HMX/	Number/Sex		Pre-trial		Week	¢ 1	Week 2	×
ryb/udy i		7	4	0	e N	7	10	14
800	4439	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

t = Animal dead

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ose Level	Animal			Treatment	Treatment Week/Day of Dosing	Dosing		
(mg HMX/	Number/Sex		<b>Pre-trial</b>		Week ]	t 1	Wee	Week 2
Ay/uay/		2	4	0	3	7	10	14
2000	4492	18	20	20	18	+	I	1
	450	18	20	20	19	+-	1	1
	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	+	1	1
Mean		18.8	20.2	21.0	19.3	18.0	20.5	21.5
<u>+</u> s.D.		0.8	0.4	6.0	0.8	0.0	0.7	0.7

t = Animal dead

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Zex Zex	7 Pre-trial		TTCHCHICH LCCV/ NOT NOSING	I DOSING		
4559 456 457 458	7 4		Week ]	k 1	Wee	Week 2
4554 456 458		0	ſ		01	VI
	19 20	21	16	+		;
	20 21	23	20	• +	1	•••
	18 20	21	18	· +-	1	1
-	19 20	21	17	· +-	ı	I
459	18 19	20	15	+	1	1
460	19 20	21	17	+	1	ł
Mean 16	18.8 20.0	21.2	17.2			
+ s.D.	0.8 0.6	1.0	1.7	1	t	ı

t = Animal dead

APPENDIX 4

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HMX: 14 Day Dietary Toxicity Study in Mice

Formulated Diet Analysis

Treatment		Dose Level		Observed (	Observed Concentration (PPM)	(Mdd) uo	Mean	Standard Deviation	Deviation (8) from Mean
Week	Group/ Sex	(mg HMX/ kg/day)	(bbm)	Sample 1	Sample 2	Sample 3	(bbm)	(ppm)	Concentration
	13	0	0	0	0	0	0	D	0
	2	100	483	527	478	559	521	+ 41	+ 7.9
	~	300	1513	1534	1515	1593	1547	+ 41	+ 2.2
	4	006	4856	4833	4562	6439	5278	<u>+</u> 1015	+ 8.7
-	5	2700	12547	11852	12904	13705	12820	+ 929	+ 2.2
	19	0	0	0	0	0	0	0	0
_	2	320	1331	1295	1293	1371	1320	+ 44	- 0.8
	~	800	3325	3088	3115	3253	3152	+ 89	- 5.2
	4	2000	7926	7878	7835	8614	8109	+ 438	+ 2.3
	2	5000	21078	22237	22115	22328	22227	+ 107	+ 5.5
	13	0	0	0	0	0	0	0	0
	2	100	500	548	505	493	515	+ 29	+ 3.0
	~	300	2014	2026	2127	2093	2082	+ 51	+ 3.4
	4	006	1	1	1	,	ł	ı	1
, ,	5	2700	-	1	1	1	ł	•	-
۷	19	0	0	0	0	0	0	0	0
	2	320	1458	1463	1547	1553	1521	+ 50	+ 4.3
	m	800	4556	4698	4916	4941	4852	<u>+</u> 134	+ 6.5
	4	2000	11613	11221	11256	11151	11209	+ 53	- 3.5
	Ś	2000	I	1	٠	1	3	I	ł
Theoretical conc food consumption	cal concer sumption	Theoretical concentration (ppm) food consumption	pm) calculated from predicted group mean mid-week body weight and predicted group mean	om predict	ed group m	ean mid-we	ek body welght	and predicte	ed group mean

rood consumption All animals in groups 43, 53 and 59 dead during treatment week 2

APPENDIX 5.1

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

1.1 ver	15417	1.32	1.46	1.44	1.50	1.27	1.31	1.38	60.0	1.29	1.14	1.59	1.27	1.20	1.58	1.35	0.19	1.38
eys	R	0.25	0.27	0.26	0.26	0.18	0.23	0.24	0.03	0.22	0.21	0.25	0.23	0.21	0.24	0.23	0.02	0.23
 Kidneys	Г	0.24	0.25	0.23	0.25	0.17	0.22	0.23	0.03	0.21	0.20	0.22	0.21	0.20	0.23	0.21	0.01	0.21
rodmil [emics		401	402	403	404	405	406	Mean	+ s.D.	407	408	409	410	411	412	Mean	+ s.D.	418
Dose Level	(mg HMX/kg/day)	o								100								300

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Individual Values - Females Surviving 14 Days Dosing

Dose Level	And milling	Kidneys	ski	1.1 ver
(mg HMX/kg/day)		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.b.	0.04	0.02	0.08

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Dose Level	rodmiiN I am tak	Kidneys	ys	1.1 ver
(mg HMX/kg/day)		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
	<u>+</u> 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
	<u>+</u> s.D.	0.01	0.01	0.25

APPENDIX 5b

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

	Liver	4.889	5.407	5.760	6.000	5.773	5.458	5.548	0.390	5.864	5.182	5.679	5.522	5.217	6.077	5.590	0.355	5.520
:ys	R	0.926	1.000	1.040	1.000	0.818	0.958	0.957	0.079	1.000	0.955	0.893	1.000	0.913	0.923	0.947	0.045	0.920
Kidneys	L	0.889	0.926	0.920	0.362	0.773	0.917	0.898	0.065	0.955	606.0	0.786	0.913	0.870	0.885	0.886	0.057	0.840
Body	Weight (g)	27	27	25	26	22	24			22	22	28	23	23	26			25
	Animal Number	401	402	403	404	405	406	Mean	± s.D.	407	408	409	410	411	412	Mean	+ S.D.	418
Dose Level	(mg HMX/kg/day)	0								100						•		300

Individual Values - Females Surviving 14 Days Dosing

Dose Level	Antmul Lumbor	Body	Kidneys	ska		
(mg HMX/kg/day)		(d)	L	R	12417	
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	·· 1
	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	

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Dose Level		Body	Kldneys	sys	
(mg HMX/kg/day)	ANIMAL NUMDER	Weight (g)	Г	R	r1ver
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	866.2
	+ s.D.		0.023	0.019	0.774

APPENDIX 5c

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

Dose Level	Antmal Number	Kidneys	ys.	Liver
(mg HMX/kg/day)		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
006	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

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Individual Values - Females

Dose Level	rodmin lemind	Kidneys	ys	Li ver
(mg HMX/kg/day) (mg HMX/kg/day)		г	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

e = 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		Body	Kidneys	ieys	
(mq HMX/kg/day)	Animal Number	Weight (g)	Г	æ	LIVER
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
006	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

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B = Organ weights not recorded
 NDA = No data available

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# Individual Values - Females

	IANIT	7.826	NDA	4.500	4.385	5.353	5.632	4.583	4.692	4.154	4.539	4.333	4.000
eys	R	0.913	NDA	1.000	0.923	0.941	0.789	1.000	1.000	0.846	1.077	0.917	0.923
Kidneys	L	0.826	NDA	1.000	0.923	0.882	0.684	0.917	1.000	0.769	0.923	0.917	0.846
Body	weight (g)	23	17	12	13	17	19	12	13	13	13	12	13
and the second	JAGWINN TPWTUM	447	448	449	450	453	454	455	456	457	458	159	460
Dose Level	(mg HMX/kg/đay)	800		2000				5000					

• = 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:

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

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	<b>.</b>		SS		Ι	Ι	Γ				Ι		Ι		$\prod$		Ţ																
	Number of	Sections Examined	HE		_	Z Kidney	1 Spleen	Thymus	<b>J</b> Brain	Ţ	Ţ	I	Γ	1		T		1		1		Γ	1	Γ	I	I		]	T	Ī	Γ	Γ	Γ
				ology																													
Death	ΤK			Histopathology		NAD																											
he on Study	2 weeks																		 -		<u> </u>				 		 						
ka/day Time		J		Organ																													
415669SM	Animal No: 401 Sex: ð			Internal and External Necropsy Findings		NAD																											

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	Number of Sections Examired	SS		kidney Heart Spleen	Brain	Π		TI		Π					I
		HE				11			<u>1</u> 1	II		<u>I</u>			
Death	тĸ		Histopathologv	NAD											
Time on Study	2 weeks									 	 		 	 	
			Organ				 			 			 	 	
WS699	Animal No: 402 Sex: d		Internal and External Necropsy Findings	NAD											

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	Number of Sections Examined			Liver	Heart	Spleen	Thymus	Brain		••••		<b>•</b>																							
	°.	ΗE		Ŀ		-				Γ			Ι	Ţ			Ι				Ι	Ι	Γ				$\prod$		Ι			Ι			
—-1			thology		9																														
Death	TK		<b>Histopathology</b>		NAD																														
Time on Study	2 weeks							-									-	 		-															
Ē			Organ																																
415669SM	Animal No: 403 Sex: d		Internal and External Necropsy Findings		NAD																														

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	Numier of	LesiDEX3 SUCT LA			Kidney   Heart	ГТ	_				<del>т -</del> т		<del>1 1</del>		- <b>-</b> -	<del>7 - 1</del>	- <b>-</b>		<b>T</b> - <b>T</b> -		1 <b>- 1</b>	<b>--</b>		<b></b>	<b>T</b>				
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		-	ologv																										
Death	ТК		Histopathology		NAD																								
Time on Study	2 weeks																						 						
Tin			Organ																										
Project No. 4]56695M Group No. ] Animal No. 404 Sov. 4			Internal and External Necropsy Findings		NAU																								

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	Number of	Sections Examined			Liver	Z Kidney	Heart	Spleen	sumyhi	Brain																								
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4				Histopathology		NAD	1																											
Death	¥ t			HIS																														
Time on Study	) weeks					_							 					<u>.</u>	 	 									-		 			
Ē				Organ																														
415669SM	Animal No: 405 Sex: u			Internal and External Necropsy Findings		NAD																												

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	Г		SS			Т	Т	Т	Т	Т	Г	Π	1	T	Т	Т	Т	Τ	T	Γ	T	Τ	Т	T	Γ	Π	T	Т	Τ		Π	Τ	Τ	T	Τ		
	Number of	Sections Examired			Liver	Kidney	Heart	Spleen	enatur da antes da		<b>.</b>			-		~ 4 -			<u>.</u>		 •					•				<u> </u>							
		Se	ΗE			~	Т	-	Т	Т		$\prod$		Ι		Ţ	Ι		Ι				Γ	I	Ι			Τ	Ι				Ι		Ι	Ι	Π
				ology																																	
Death	4	I.K		Histopathology		NAD																															
Time on Study		Z WEEKS																						_			 			<u>.</u>	 						
<u> </u>				Organ																									-		 			-			
669SM	Animal No: 406 Sex: of			Internal and External Necropsy Findings		NAD																															

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SS Number of Sections Examined Liver Z Kidney Heart Spleen J Brain ΗE Areas tubular dilation, tubular atrophy. Cytoplasm of hepatocytes eosinophilic. Areas focal necrosis. Histopathologv Lymphocyte depletion. Death FD Time on Study 9 days Organ Group No: 3 300 mg HMX/kg/day Kidneys Thymus Liver Internal and External Necropsy Findings Sex: ð Project No: 415669SM Pale and mottled. Pale and mottled. Animal No: 413

APPENDIX 6 (continued)

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ŝ Number of Sections Examined 2 Kidney 1 Heart 1 Spleen 1 Thymus 3 Brain 1 Liver HΕ Cytoplasm of hepatocytes vacuolated. Histopathology Red and white pulp depletion. Lymphocyte depletion. Death FD Time on Study 2 days Organ Thymus Spleen Liver Internal and External Necropsy Findings Group No: 3 Sex: ð Very small and pale. Project No: 4156695M 414 Animal No:

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	Number of Sertions Examined			T tuor	13417	Aldney		mande		ulbid									_										_							
	Ů		ž	ŀ		- -	ŀ	Т	ŀ	Т			Ι			Ţ	Ι			Ι		Ι	L	$\Box$				Π	Ι	Γ		Ι	Γ			
		•		Aboro		eosinophilic,	v		on.																											
Death	KIE		Histonathe	Histopathologv		asm of hepatocyti		Cytoplasm of hepatocytes eosinophilic, increased cellularity.		Some white pulp depletion.		Lymphocyte depletion.																								
Time on Study	3 days					Cytople	increas		Some wh		Lymphoc								 <u> </u>													 		 		
<b>I</b>		J	Ordan	110610		Liver			Spleen		Thymus			_																				 _		
669SM	Animal No: 415 Sex: d		Internal Puternal Nacronev Findinge	TURELUAL AND EXCEINAL WELLOPSY FINATIOS					Small.			Darte restriction	furnation for the second states of the second state																							

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APPENDIX 6 (continued) APPENDIX 6 (C

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SS Number of Sections Examined 1 Liver 2 Kidney 1 Heart 1 Spleen 1 Thymus 3 Brain ΗE Cytoplasm of hepatocytes eosinophilic. Increased cellularity. Histopathology Lymphocyte depletion. Death KIE Time on Study 4 days Organ Thymus Liver Internal and External Necropsy Findings Group No: 3 Sex: ð Penis red and protruding. Project No: 415669SM Animal No: 416

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Number of Sections Examined Z Kidney Heart Spleen Thymus Brain Stomach Liver 1 ΗE Histopathologv NAD NAD Death FD Autolytic. Time on Study 8 days Duodenum Organ Stomach Heart Red encrustations round mouth, nose and feet. Internal and External Necropsy Findings Group No: 3 One side brown the other red. Sex: ð Contents dark brown liquid. Contents dark brown. Project No: 4156695M Animal No: 417

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	5	Ľ	3		Π			Γ	Π	Π		Π	1			Π		$\prod$					Ц		
	Number of Sections Examined					Spleen		Brain	<b>1</b> -1	 - <b>-</b>	 	1-1		- <b>-</b>	- <b>-</b>	ŦŦ	-	<b>•</b> •	-	· •	i T	 T	 T		
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				Ab010	Cytoplasm of hepatocytes eosinophillc,		letion.																		
Death	FD			histopatioudy	asm of hepatocyt	sed cellularity.	White and red pulp depletion.	•																	
Time on Study	5 days				Cytople	Increa	White a													 			 		
Time																									
		J		upb 10	Liver		Spleen						_												
415669SM	Animal No: 419 Sex: ð			Internal and External vecropsy ringings			Small and pale.																		

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č Number of Sections Examined Liver Kidney Heart Spleen Brain НЕ Cytoplasm of hepatocytes eosinophilic, increased cellularity. White and red pulp depletion. Histopathologv Lymphocyte depletion. Death KIE Time on Study 3 days Organ Spleen Thymus Liver Internal and External Necropsy Findings Group No: 4 Sex: d Penis erect and red. Project No: 415669SM Animal No: 420 Very small.

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	Number of Sections Examined			Liver Kidney	Heart Soleen	Thymus				 	 		<b></b> -	- <b>-</b>	<del></del>	 <del>.</del>	- <b>-</b>		- <b>-</b>	-	·	<b>-T</b> -	-	<b>•</b> •	_	
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			oloqy	s eosinophilic.		letion.																				
Death	FD		Histopathology	asm of hepatocyte	increased cellularity.	White and red pulp depletion.	Lymphocyte depletion.																			
Time on Study	3 days			Cytopla	Increas	White a	Lymphod			 	 			_		 										
71 <u>7</u>			Organ	Liver		Spleen	Thymus																			
5669SM	Animal No: 42] Sex: d		Internal and External Necropsy Findings			Very small.		Denis erort and rod																		

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SS Number of Sections Examined Litver2Kidney1Heart1Spleen1Thymus3Brain ΞH Some degree white and red pulp depletion. Cytoplasm of hepatocytes eosinophilic, increased cellularity. Histopathology Lymphocyte depletion. Death KIE Time on Study 4 days Organ Spleen Thymus Liver Internal and External Necropsy Findings Group No: 4 Sex: ð Project No: 415669SM Animal No: 422

Death

Time on Study

4

Group No:

Project No: 415669SM

ŝ Number of Sections Examined kidney Heart Spleen Thymus Brain Liver -1 L -3 -4 Some degree red and white pulp depletion. Cytoplasm of hepatocytes eosinophilic, slight increase in cellularity. Slight degree lymphocyte depletion. Histopathology FD 2 days Organ Thymus Spleen Liver Internal and External Necropsy Findings Sex: ð Small and pale. Animal No: 423

Service Contraction

2

Number of Sections Examined Lilver 2 Kidney 1 Heart L Spleen 1 Thymus 1 Brain H Histopathology Sections autolytic. Death FD Time on Study l day Organ Internal and External Necropsy Findings Group No: Sex: ð Project No: 4156695M Animal No: 424 Spleen pale. Liver pale.

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APPENDIX 6 (continued)

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	Number of	Sections Examined			Liver	Kidney	riedir C Solgen	Thymus	Brain																				-			
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				oloqv		of hepatocytes eosinophilic,				Some degree white and red pulp depletion.	e depletion.																					
Death		AIE		Histopathologv				NAD		egree white and r	Slight dearee lymphocyte depletion.	landal - and																				
Time on Study		J days				Cytoplasm	Increased			Some d	Slight			;						 												
2,700 mg HMX/kg/dav				Organ		Liver		Kidnevs		Spleen	Thymus															 					 -	
415669SM Group No:5	Animal No: 425 Sex: d			Internal and External Necropsy Findings				Left smaller than right.		Very small.																						

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ŝ Number of Sections Examined 1 Liver 2 Kidney 1 Heart 1 Spleen 1 Rymus 3 Brain ΗE Ecsinophilic, some increased cellularity. Some degree lymphocyte depletion. White and red pulp depletion. Histopathology Death FD Time on Study 2 days Organ Spleen Thymus Liver Internal and External Necropsy Findings Group No: 5 Sex: d Very small and thin. Project No: 415669SM Animal No: 426

Number of Sections Examired Liver Kidney Heart Spleen Thymus Brain -~ - - 0 ~ H Cytoplasm of hepatocytes eosinophilic, increased cellularity. Some degree of red and white pulp depletion. Histopathologv Death KIE Time on Study 3 days Organ Spleen Liver Internal and External Necropsy Findings Group No: 5 Sex: ð Project No: 415469SM Animal No: 427 Small.

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APPENDIX 6 (continued)

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20 Number of Sections Examired 2 Kidney 1 Heart 1 Spleen 1 Thymus 3 Brain Liver ΞE Cytoplasm of hepatocytes eosinophilic, increased cellularity. Some red and white pulp depletion. Histopathology Some lymphocyte depletion. Sections fairly autolytic. FD Time on Study 2 days Organ Spleen Thymus Liver Internal and External Necropsy Findings Group No. 5 Sex: ð Project No. 4156695M Small and pale. Animal No: 428

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Death		FD		Histopathology		NAD		Some red pulp depletion.		Sections fairly autolytic.	•																							
Time on Study		l day						Some rec		Section												 	-										<u>.</u>	
Ē				Organ		Liver		Spleen	•																									
669SM	Animal No: 429 Sex: d			Internal and External Necropsy Findings		Pale.		Pale.																										

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ŝ Number of Sections Examined Kidney Heart Spleen Thymus Brain Liver 1 HΕ Cytoplasm of hepatocytes eosinophilic, increased cellularity. Red and white pulp depletion. Histopathologv Lymphocyte depletion. FD 2 days Organ Spleen Thymus Liver Internal and External Necropsy Findings Group No: 5 Sex: ð Project No: 415669SM Small and pale. Animal No: 430

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APPENDIX 6 (continued)

Death

Time on Study

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ŝ Number of Certions Examined Kidney Heart Spleen Thymus Brain Liver 2-1-1-7 Ŧ Histopathology NAD Death ЧK Time on Study 2 weeks Ordan 0 ma HMX/ka/day Internal and External Necropsy Findings ч Group No: (+ Sex: NAD Project No. 4156695M Animal No: 431

APPENDIX 6 (continued)

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v Number of Sections Examined 2 Kidney L Heart Spleen Thymus Brain Liver -ΞH Histopathology NAD Death ТК Time on Study 2 weeks Organ Internal and External Necropsy Findings Group No: 1 0+ Sex: NAD Project No: 415669SM Animal No: 432

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		Number of Sections Examined		1										-4	4	 	<b>.</b>	•	•	·	•			<u> </u>												_					
	Number of	ions F.			Liver	Kidney	Heart	Spleen	Thymus	Brain																															
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Vo: 4	o: 43			al ar																																					
Project No: 415669SM	Animal No: 433			Internal and External Necropsy Findings																																					
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Animal No: 434 Sex: V		2 weeks	ТК	L	Number of	.
	L			<u></u>	Sections Examined	ۍ ۲
Internal and External Necropsy Findings	Organ		Histopathologv		1 1	
					Liver	
KIGNT KIDNEY LARGER THAN LEFT.	Kidneys		NAD	<u>-1</u> -	-	
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				<u></u>	Brain	L
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ŝ Number of Sections Examined Llver 2 Kidney 1 Heart 1 Spleen 3 Brain 핖 Histopathologv NAD Death ΤX Time on Study 2 weeks Organ Internal and External Necropsy Findings Group No: 1 0 Sex: NAD Project No: 415669SM Animal No: 435

APPENDIX 6 (continued)

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	Number of	Sections Examined			<b>_</b>	~	-т	T	Thymus	$-\mathbf{r}$	-1-	T	- -	T	<b>F</b> - <b>T</b>			- <b>-</b>	- <b>-</b>	<b>T</b>	<b>r</b>	r – 1			<b>1</b> -1		<b>-</b>	11	-1			Ŧ	- -	r T	<b>-</b>	-
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				Histopathology		NAD																														
Death	ТК			Histo		-	•																													
Time on Study	2 weeks																	-					 					_								
11		ſ		Organ																																
415669SM Group A	Animal No: 436 Sex: F			Internal and External Necropsy Findings		NAD																														

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	Number of Sections Examired	HE		2 Kidney	Т	Т		1-	İ	]	]	Ţ	Ţ		I			Ι			Ţ	Τ			11	T		T	]_]	I	T
Death	FD		Histopathology	NAD																											
Time on Study	2 weeks																	 									 				
mq HMX/kq/dav Ti			Organ																												
5669SM Group No: 3 800	Animal NO: 44/ Sex: *		Internal and External Necropsy Findings	NAD																											

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Project No: 4156695M Group No: 3 Animal No: 448 Sex: ?

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Time on Study Death 8 days FD

Animal No: 448 Sex: 2		8 days	FD		L	Number of	Γ
	ل				S	Sections Examined	~
					ΗE		55
Internal and External Necropsy Findings	Organ		Histopathologv	oloqv			
					-ŀ I	Liver	
Very pale.	Spleen	Red pull	p and some white	Red pulp and some white pulp depletion.	~ -	Kidney Heart	Τ
	Thymus	Lymphoc	Lymphocyte depletion.			Spleen	Π
Darkor red that return					-	Brain	Ι
Daiver ich chan putmat.	Lungs	Congest	Congested and autolytic.	•	-	Lung	
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Number of Sections Examined Kidney Heart Spleen Thymus Brain Liver -----Ŧ Cytoplasm of hepatocytes eosinophilic, increased cellularity. Section fairly autolytic. Red and white pulp depletion. Histopathologv Lymphocyte depletion. FD 6 days Organ Thymus Spleen Liver Internal and External Necropsy Findings C+ Sex: Animal No: 449 Small.

APPENDIX 6 (continued)

Death

Group No: 4 2,000 mg HMX/kg/day Time on Study

Project No: 4156695M

Death

Time on Study

Group No: 4

Project No: 415669SM

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С Ľ Number of Sections Examined Kidney Heart Spleen Thymus Brain Liver ч ~---~ HΕ Cytoplasm of hepatocytes eosinophilic, increased cellularity. Section fairly autolytic. Red and white pulp depletion. Histopathology Lymphocyte depletion. FD 6 days Organ Thymus Spleen Liver Internal and External Necropsy Findings (× Sex: Animal No: 450 Small.

Death

Time on Study

Group No 4

Project No: 4156695M

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č Number of Sections Examined Liver Z Kidney Heart Spleen J Brain HΕ Cytoplasm of hepatocytes eosinophilic. Some degree increased cellularity. Red and white pulp depletion. Histopathologv Some lymphocyte depletion. Sections fairly autolytic. FD 6 days Organ Thymus Spleen Liver Internal and External Necropsy Findings 0• Sex: Small and pale. Animal No: 453

SS Number of Sections Examined Liver Kidney Heart Spleen Thymus Brain -1 ~----HE Red pulp and some white pulp depletion. Slight increase in cellularity. Histopathology Lymphocyte depletion. Death FD Time on Study 4 days Organ Spleen Thymus Liver Internal and External Necropsy Findings Group No: 4 0+ Sex: Project No: 415669SM Animal No: 454 Small.

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APPENDIX 6 (continued)

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Death

Group No:5 5,000 mg HMX/kg/dav Time on Study

Project No: 415669SM

		5 days	FD		Section	Number of Sections Examined	bec
					Эн		SS
Internal and External Necropsy Findings	Organ		Histopathology	loqy	_		
	Liver	Cytopla increas	Cytoplasm of hepatocytes eosinophilic, increased cellularity.	s eosinophilic,	L Liver 2 Kidney 1 Heart	r ev	Ш
Small.	Spleen	Slight depleti	Slight degree red and white pulp depletion.	hite pulp	Spleen Thymus Brain	een Ins	
	Thymus	Lymphoc	Lymphocyte depletion.				
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		Number of Sections Examined			er	ney	Heart	een	Thymus	In																										
	ľ	sect i			Liver	Kidney	Hea	Sp1	Ê,	Brain			-	<b>-</b>	 	-	<b>_</b>	•			-				<b>-</b>	-	,- <b>-</b> -	_		_	•	_	<b>_</b>	-		┛
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				ology		es ensincohilic.	larttv.		letion.																											
Death		ΓD		Histopathology		asm of hepatocyte	Some increase in cellularity.		Red and white pulp depletion.		Lymphocyte depletion.																									
Study		aays				Cvtopl	Some 11	•	Red and		Lymphoe																									
Time on Study		o o					-						-		 																					
				Organ		Liver			Spleen		Thymus	•								_																
669SM Group N	Animal No: 456 Sex: <sup>2</sup>			Internal and External Necropsy Findings					Small.																							-				

	Number of Sections Examined	HE		[-] 	ophilic, 2 Kidney	-	<b>T</b>	-	-			1	Ţ		T					T	I		T	I	L		
Death	KIE		Histopathology		Cytoplasm of hepatocytes eosinophilic,	sed cellularity.	d white mula dealetier	ked and white pulp depletion.																			
Time on Study	6 days		Organ		Liver Cytop1		Sulean Dod an	_			 			 			 	 	 								
e693M Group M	Animal No: 457 Sex: 9		Internal and External Necropsy Findings				Small.																				

Death

Time on Study

Group No:5

Project No: 415669SM

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SS Number of Sections Examined Liver Kidney Heart Spleen Brain НЕ Cytoplasm of hepatocytes eosinophilic, increased cellularity. Red and white pulp depletion. Histopathology Sections fairly autolytic. Lymphocyte depletion. PD 5 days Organ Spleen Thymus Liver Internal and External Necropsy Findings Left kidney smaller than right. (4 Sex: Animal No: 458 Very small.

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Death

Time on Study

Group No: 5

Project No: 4156695M

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and External Necrop	Animal No. 459 Sex: ?	1_				L		
aid External Necropay Findines Ordan: Histopatholouv Liver Cytoplasm of hepatocytes eosinophilic, Spleen Red and white pulp depletion. Thymus Lymphocyte depletion.		]		KIE		Ň	Number of ections Examir	<b>F</b> a
and External Necropsy Findines Organ. Histopathology Liver Cytoplasm of hepatocytes eosimophilic.						ΗE		SS
Cytoplasm of hepatocytes eosinophilic, increased cellularity. Red and white pulp depletion. Lymphocyte depletion.	and External Necropsy Find	Organ		Histopatho	oloqv	ŀ	:	
Cytoplasm of hepatocytes eosinophilic, increased cellularity. Red and white pulp depletion. Lymphocyte depletion.							Liver	
Itymphocyte depletion.		Liver	Cytopla	sm of hepatocyte	s eosinophilic,		Kidn <b>ey</b> Heart	
Red and white pulp depletion.			THOTOGRA	en certantattcy.			Spleen	
Lymphocyte depletion.		Spleen	Red and	white pulp depl	etion.	-[~	Thymus Brain	
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		Thymus	Lymphoc	yte depletion.				1.
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Death

Time on Study

Group No: 5

Project No: 4156695M

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Internal and External Mecropay Findings     Oran:     Histopatholowy     Inver     Science       Liver     Essinophilic cytoplasm. Increased     1 kiver     Science       Shall.     Spleen     Too autolytic.     1 kiver       Shall.     Spleen     Too autolytic.     1 kiver	Animal No: 460 Sex: 9		6 days	FD			Number of Sections Examined	<b>Г</b> ,
and External Necropsy Findings Oraxin Histopathology International Sections autolytic.						Ξ		SS
Liver Essinophilic cytoplasm. Increased	Internal and External Necropsy Findings	Organ		Histopatho	ologv			
Liver Essinophilic cytoplasm. Increased Liver cellularity. Spleen Too autolytic. Sections autolytic.						- <u> </u> 	Liver	
Spleen cellutarity. Sections autolytic.		Liver	Eosinop	hilic cytoplasm.		~ -	Kidney	Τ
Spleen Too autolytic. Sections autolytic.			cellula	rity.		1-	Soleen	Γ
Spleen Too autolytic.						1-	Thimite	Ι
	Small.	spieen	TOO AUT	olytic.			Brain	
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