

The BFGoodrich Company
3925 Embassy Parkway
Akron, Ohio 44333-1799



8EHQ-95-13499
SP001 03/12/96

Carl A. Mattia
Vice President
Environmental Health and
Safety Management Systems

8EHQ-0396-13499

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March 8, 1996

ORIGINAL

Control No GBI

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Document Control Officer
Chemical Information Division
Office of Toxic Substances
Room E-108
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Re: Notice of Substantial Risk Under TSCA Section 8(e) -
Supplemental Submission.

Dear Sir/Madam:

The B.F. Goodrich Company (BFG) submits this supplemental information in accordance with Section 8(e) of the Toxic Substances Control Act (TSCA) and EPA's numerous interpretive statements. This submission does not contain confidential business information.

We are providing the EPA with a copy of the final report on a 28-day subacute oral toxicity study in the rat with allyl sucrose (CAS No. 68784-14-5). This final report supplements the unaudited rangefinding results that were submitted to the Agency on August 31, 1995. Although we are making this submission to ensure compliance with the latest expressed indications of the EPA for reporting such information, BFG believes that these test results do not demonstrate a human risk from the manufacture or use of this product.

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Akron, Ohio 44333-1799
February 12, 1996
Page 2

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Vice President
Environmental Health and
Safety Management Systems

Background

Allyl Sucrose is a crosslinking agent that is manufactured and used to make high molecular weight polymers of acrylic acid. Our August 31, 1995 submission to the EPA regarding this chemical identifies additional neurotoxic findings in rats (via oral gavage) which appear to be consistent with earlier findings in mice (intraperitoneal injection) that were reported to EPA under TSCA 8(e) on September 1, 1992. However, in the 28-day study there is no evidence of neurotoxicity. Clinical signs are very limited and sporadic. Furthermore, toxicologically significant effects (liver toxicity) occur only at the highest dose (650 mg/kg/day).

Significance/Assessment of the Data

An assessment of the relevant information on this chemical and its end-use products indicates that it does not pose any significant risk of neurotoxicity to worker or consumers for the following reasons:

- 1) allyl sucrose has a low volatility,
- 2) workers wear protective equipment and follow work practices designed to minimize exposure,
- 3) In the 28-day gavage study with allyl sucrose no neurotoxicity was observed at any dose level, and 150 mg/kg/day was the no observed adverse effect level (NOAEL).
- 4) no neurotoxic effects have been observed in any of the numerous 30-day and 90-day, rat and dog feeding studies that have been conducted with various crosslinked polyacrylic acid polymers, and

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The BFGoodrich Company
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Akron, Ohio 44333-1799
March 4, 1996
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Carl A. Mattia
Vice President
Environmental Health and
Safety Management Systems

- 5) no evidence of neurotoxicity has been observed or reported in our workers.

If you have any questions regarding this submission, please contact Dr. Robert K. Hinderer at (216) 447-5181.

Sincerely,

THE BFGOODRICH COMPANY



Carl A. Mattia
Vice President
Environmental, Health and Safety
Management Systems

CAM/rh

CONFIDENTIAL

**SafePharm
Laboratories**

DERBY U.K.

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ALLYL SUCROSE:
TWENTY-EIGHT DAY SUB-ACUTE
ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
SPL PROJECT NUMBER: 826/009

AUTHORS: M.S. Wragg
A.J. Bartlett
P.N. Brooks

STUDY SPONSOR:

BF Goodrich Company
Specialty Polymers & Chemicals
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Cleveland
OHIO 44141-3247
UNITED STATES OF AMERICA

ISSUED BY:

Safeparm Laboratories Limited
P.O. Box No. 45
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DE1 2BT
U.K.

Telephone: DERBY (01332) 792896

Facsimile: (01332) 799018

QUALITY ASSURANCE REPORT

The conduct of this study has been subjected to periodic inspections by Safeparm Laboratories Quality Assurance Unit. The dates of inspection and reporting are given below:

01, 22 August 1995

07, 21 September 1995

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

Date of Report Audit:

23 January 1996

J.R. Pateman C. Biol., M.I. Biol.
For Safeparm Quality Assurance Unit



.....

14. FEB. 1996

DATE:

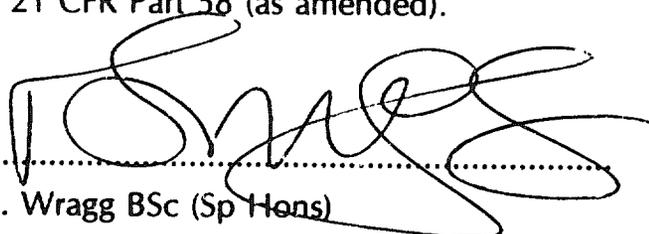
.....

GLP COMPLIANCE STATEMENT

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

The work described was performed in compliance with the UK Principles of Good Laboratory Practice (The United Kingdom Compliance Programme, Department of Health 1989). These Principles are in accordance with GLP standards published as OECD Environment Monograph No. 45 (OCDE/GD (92) 32); and are in conformity with, and implement, the requirements of Directives 87/18/EEC and 88/320/EEC.

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


..... DATE: 14 FEB 1996
M.S. Wragg BSc (Sp Hons)
Study Director

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

T. Blagden M.I.A.T.
P.W. Thompson H.N.C.
N. Doleman H.N.C.

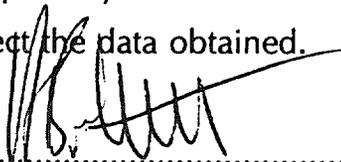
AUTHENTICATION

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


..... DATE: **13 FEB 1996**

P.N. Brooks B.Sc., M.I. Biol., C. Biol.
Study Pathologist

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


..... DATE: **13 FEB 1996**

A.J. Bartlett L.R.S.C.
Head of Analytical Chemistry

Approved for issue:


..... DATE: **14 FEB 1996**

M.P. Blackwell B.Sc. (Hons), F.I.A.T.
Head of Repeat Dose and Inhalation Toxicology

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P A R T I

**ALLYL SUCROSE:
TWENTY-EIGHT DAY SUB-ACUTE
ORAL (GAVAGE) TOXICITY STUDY
IN THE RAT**

SUMMARY

STUDY SPONSOR : BF GOODRICH COMPANY

STUDY TYPE : TWENTY-EIGHT DAY SUB-ROUTE
ORAL (GAVAGE) TOXICITY STUDY
IN THE RAT

TEST MATERIAL : ALLYL SUCROSE

1. The study was designed to investigate the systemic toxicity of the test material and complies with the testing method described in Annex V of Commission Directive 92/69/EEC (Method B7) and the recommendations of the OECD Guidelines for Testing of Chemicals No. 407.

The test material was administered by gavage to three groups, each of five male and five female Sprague-Dawley CD strain rats, for twenty-eight consecutive days, at dose levels of 15, 150 and 650 mg/kg/day. A control group of five males and five females was dosed with vehicle alone (Polyethylene glycol 400).

Clinical signs, bodyweight, food and water consumption were monitored during the study. Haematology and blood chemistry were evaluated for all animals at the end of the study.

All animals were subjected to a gross necropsy examination and a limited histopathological evaluation of tissues from high dose and control animals was performed.

The results are summarised as follows:

2. Mortality

There were no deaths during the study.

3. Clinical Observations

Females dosed at 650 mg/kg/day showed fur loss from the dorso-cervical region from Day 2 to Day 11 inclusive. One male dosed at 150 mg/kg/day also showed discrete areas of fur loss from Day 10 to Day 21. In addition, animals of either sex dosed at 650 or 150 mg/kg/day showed short-lived increased salivation before or immediately after dosing for most of the study, together with associated fur wetting and red/brown staining. Sporadic incidents of prolonged increased salivation were also observed amongst animals dosed at 650 mg/kg/day from Day 6.

Females dosed at 150 mg/kg/day and animals of either sex dosed at 15 mg/kg/day showed no clinical signs of toxicity during the study.

4. Bodyweight

Males dosed at 650 mg/kg/day showed an 18% lower bodyweight gain than controls during the second half of the treatment period.

There was no adverse effect on bodyweight development amongst females dosed at 650 mg/kg/day or amongst animals of either sex from the remaining dose groups.

5. Food Consumption

There was no adverse effect on food consumption during the study.

Males dosed at 650 mg/kg/day showed a slightly lower food efficiency than controls during the second half of the treatment period. Females dosed at 650 mg/kg/day and animals from the remaining dose group showed a similar food efficiency to controls during the study.

6. Water Consumption

Daily visual inspection of the water bottles showed a possible increase in consumption during the final week of treatment amongst animals dosed at 650 mg/kg/day.

There was no adverse effect on water consumption at the remaining dose levels.

7. Haematology

Males dosed at 650 or 150 mg/kg/day showed a slightly reduced haemoglobin compared with controls. In addition, males dosed at 650 mg/kg/day showed a lower haematocrit than controls whilst females from the same dose group showed a reduced mean corpuscular haemoglobin. Animals of either sex dosed at 650 mg/kg/day also showed a lower mean corpuscular volume than controls. In addition, males dosed at 650 mg/kg/day showed a slightly higher leucocyte count than controls, reflecting an increased lymphocyte count, and females dosed at 650 or 150 mg/kg/day showed a slightly reduced prothrombin time compared with controls.

Animals dosed at 15 mg/kg/day showed no toxicologically significant changes in the parameters measured.

8. Blood Chemistry

Animals of either sex dosed at 650 mg/kg/day showed a reduced albumin/globulin ratio compared with controls, reflecting an increased plasma globulin concentration amongst the males and a reduced plasma albumin concentration amongst the females. Males dosed at 650 mg/kg/day also showed an increased plasma cholesterol concentration compared with controls, with all individual values outside the normally expected range for rats of the strain and age used in the study, and a slightly increased total protein concentration.

Animals dosed at 150 or 15 mg/kg/day showed no toxicologically significant changes in the parameters measured.

9. Organ Weights

Animals of either sex dosed at 650 mg/kg/day showed a substantially higher liver weight, both absolute and relative to terminal bodyweight, than controls. The adverse effect was slightly more pronounced amongst the females (58% increase in relative liver weight compared with a 38% increase amongst the males) and for either sex most of the individual values were outside the normally expected range for rats of the strain and age used in the study. In addition, one male dosed at 650 mg/kg/day showed a substantially lower testes weight, both absolute and relative to terminal bodyweight, than either controls or the other four animals from the same dose group.

Animals dosed at 150 or 15 mg/kg/day showed no toxicologically significant organ weight changes.

10. Necropsy

Two males dosed at 650 mg/kg/day showed patchy pallor of the liver at terminal kill. Another male from this dose group showed small testes.

Females dosed at 650 mg/kg/day and animals from the remaining dose groups showed no toxicologically significant macroscopic abnormalities at necropsy.

11. Histopathology

Animals of either sex dosed at 650 mg/kg/day and males dosed at 150 mg/kg/day showed generalised hepatocyte enlargement and lipid-type vacuolation of periportal hepatocytes. One male dosed at 15 mg/kg/day also showed generalised hepatocyte enlargement. Hepatocyte enlargement is commonly observed in the rodent liver following the administration of xenobiotics and in the absence of any associated degeneration or inflammatory changes, is generally regarded as adaptive in nature.

Females dosed at 150 or 15 mg/kg/day showed no toxicologically significant microscopic lesions.

12. **Conclusion**

Oral administration of the test material, Allyl Sucrose, to rats, by gavage, for a period of twenty-eight consecutive days at dose levels of 15, 150 and 650 mg/kg/day resulted in treatment-related changes at all dose levels amongst the males and at 150 and 650 mg/kg/day amongst the females. No such changes were detected amongst females dosed at 15 mg/kg/day and the "No Observed Effect Level" (NOEL) for females was considered to be 15 mg/kg/day. A NOEL was not established for males because of adaptive liver changes in one animal dosed at 15 mg/kg/day.

The nature of the changes seen at 150 mg/kg/day amongst animals of either sex were considered not to be indicative of serious damage to the health of the animals, as defined by the criteria given in the labelling guide of Directive 93/21/EEC, and 150 mg/kg/day was therefore considered to represent the "No Observed Adverse Effect Level" (NOAEL).

**ALLYL SUCROSE:
TWENTY-EIGHT DAY SUB-ACUTE
ORAL (GAVAGE) TOXICITY STUDY IN THE RAT**

1. INTRODUCTION

The study was performed according to the protocol presented in Appendix VII and was designed to investigate the systemic toxicity of Allyl Sucrose, by repeated oral administration to the Sprague-Dawley strain CD rat for a period of twenty-eight consecutive days at dose levels of 15, 150 and 650 mg/kg/day.

The study was designed to comply with the testing method described in Annex V of Council Directive 92/69/EEC (Method B7) and follows the recommendations of the OECD Guidelines for Testing of Chemicals No. 407 "Repeated Dose Oral Toxicity - Rodent 28-day or 14-day study".

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

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

The study was performed between 19 May 1995 and 06 November 1995.

2. TEST MATERIAL AND EXPERIMENTAL PREPARATION

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	Allyl Sucrose
Description	:	pale straw-coloured viscous liquid
Chemical name	:	α -D-Glucopyranoside, β -D-fructofuranosyl, allyl ethers
Batch number	:	43254
Purity	:	99.7%
Date received	:	11 May 1995
Storage conditions	:	at approximately 4°C

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

A Certificate of purity is included in Appendix XIV.

2.2 Experimental Preparation

For the purpose of this study the test material was prepared at the appropriate concentrations as a solution in Polyethylene glycol 400. The stability of the test material formulations were determined by Safepharm Analytical Laboratory. Results are given in Appendix IX and show the formulations to be stable for at least ten days. Formulations were therefore prepared weekly and stored at 4°C in the dark.

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

3. METHODS

3.1 Animals and Animal Husbandry

A sufficient number of male and female Sprague-Dawley CD strain rats were obtained from Charles River (UK) Limited, Manston, Kent. On receipt the animals were examined for signs of ill-health or injury. The animals were acclimatised for eight days during which time their health status was assessed. A total of forty animals (twenty males and twenty females) were accepted into the study. At the start of treatment the males weighed 139 to 165g, and the females weighed 123 to 159g, and were approximately five to six weeks old.

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

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

The animals were randomly allocated to dose groups using random letter tables, and the group mean bodyweights were then determined to ensure similarity between the dose groups. The cage distribution within the holding rack was also randomised.

The animals were uniquely identified within the study by an ear punching system routinely used in these laboratories. Colour coded cage labels were used to assist recognition of dose groups according to the following schedule:

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	COLOUR CODE	ANIMAL NUMBERS	
			MALE	FEMALE
1	0 (Control)	Buff	1 - 5	6 - 10
2	15	Green	11 - 15	16 - 20
3	150	Blue	21 - 25	26 - 30
4	650	Pink	31 - 35	36 - 40

3.2 Procedure

Four groups, each of ten rats (five males and five females) were dosed as follows:

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	TREATMENT VOLUME (ml/kg)	CONCENTRATION (mg/ml)
1	0 (Control)	2	0
2	15	2	7.5
3	150	2	75
4	650	2	325

The test material was administered daily, for twenty-eight consecutive days, by gavage using a stainless steel cannula attached to a disposable plastic syringe. Control animals were treated in an identical manner with 2 mg/kg/day of Polyethylene glycol 400.

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

3.3 Observations

3.3.1 Clinical Observations

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

3.3.2 Bodyweight

Individual bodyweights were recorded on Day 0 (the day before the start of treatment) and on Days 7, 14, 21 and 28. Bodyweights were also recorded at necropsy.

3.3.3 Food Consumption

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

3.3.4 Water Consumption

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

3.3.5 Laboratory Investigations

Haematological and blood chemical investigations were performed on all animals from each test and control group at the end of the study (Day 28). Blood samples were obtained from the lateral tail vein. A number of repeat samples were obtained by cardiac puncture prior to necropsy on Day 29. Animals were not fasted prior to sampling.

The methods used for haematological and blood chemical investigations are given in Appendix X and, with the exception of plasma globulin, normal ranges are shown in Appendix XII.

3.3.5.1 Haematology

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

Haemoglobin (Hb)

Erythrocyte count (RBC)

Haematocrit (Hct)

Erythrocyte indices - mean corpuscular haemoglobin (MCH)

- mean corpuscular volume (MCV)

- mean corpuscular haemoglobin concentration (MCHC)

Total leucocyte count (WBC)

Differential leucocyte count - neutrophils (Neut)

- lymphocytes (Lymph)

- monocytes (Mono)

- eosinophils (Eos)

- basophils (Bas)

Platelet count (PLT)

Reticulocyte count (Retic)

Clotting (prothrombin) time (CT) and activated partial thromboplastin time (APTT) were assessed by 'Hepato Quick' using samples collected into sodium citrate solution (0.11 mol/l).

3.3.5.2 Blood Chemistry

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

Urea

Calcium (Ca + +)

Glucose

Inorganic phosphorus (P)

Total protein (Tot.Prot)

Aspartate aminotransferase (ASAT)

Globulin (by calculation)	Alanine aminotransferase (ALAT)
Albumin	Alkaline phosphatase (AP)
Albumin/Globulin (A/G) ratio (by calculation)	Creatinine (Creat)
Sodium (Na ⁺)	Total bilirubin (Bili)
Potassium (K ⁺)	Cholesterol (Chol)
Chloride (Cl ⁻)	Triglycerides (Tri)

3.3.6 Pathology

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

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

3.3.6.1 Organ Weights

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

Adrenals	Gonads	Kidneys	Pituitary	Thymus
Brain	Heart	Liver	Spleen	

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

3.3.6.2 Histopathology

The following organs, tissues or samples thereof were removed from all animals and preserved in buffered 10% formalin:

Adrenals	Mammary gland
Aorta (thoracic)	Muscle (skeletal, thigh)

Bone & bone marrow (femur including stifle joint and articular surface)	Pancreas
Bone & bone marrow (sternum)	Pituitary
Brain	Prostate
Caecum	Rectum
Colon	Salivary glands (submaxillary)
Duodenum	Sciatic nerve
Eyes with optic nerve	Seminal vesicles
Gross lesions	Skin (hind limb)
Heart	Spinal cord (cervical, midthoracic and lumber)
Ileum	Spleen
Jejunum	Stomach
Kidneys	Testes with epididymides
Liver	Thymus
Lungs including bronchi	Thyroid/parathyroid
Lymph nodes (cervical and mesenteric)	Tongue
Oesophagus	Trachea
Ovaries	Urinary bladder
	Uterus
	Vagina

All tissues were despatched to Finn International, One Eyed Lane, Weybread, Diss, Norfolk, UK for processing. The following preserved tissues from all control and high dose animals (Groups 1 and 4) were prepared as paraffin blocks, sectioned at nominal thickness of 5 μ m and stained with haematoxylin and eosin for subsequent microscopic examination:

Adrenals Heart Kidneys Liver Ovaries Spleen Testes

Macroscopically observed lesions were also processed.

Microscopic examination was conducted by the Study Pathologist. All findings were entered into the ROELEE84 pathology computerisation system for tabulation and report production.

Since there were indications of treatment-related hepatic changes, examination was subsequently extended to include similarly prepared sections of liver from all animals in the remaining dose groups.

3.4 Evaluation of Data

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

Absolute and relative organ weights, haematological and blood chemical data were analysed by one way analysis of variance incorporating 'F-max' test for homogeneity of variance. Data showing heterogeneous variances were analysed using Kruskal-Wallis non-parametric analysis of variance and Mann Whitney U-Test.

Probability values (p) are presented as follows:

$p < 0.001$ ***

$p < 0.01$ **

$p < 0.05$ *

$p \geq 0.05$ (not significant)

4. ARCHIVES

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

5. RESULTS

5.1 Mortality

There were no deaths during the study.

5.2 Clinical Observations

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

Females dosed at 650 mg/kg/day showed fur loss from the dorso-cervical/cranial region from Day 2 to Day 11 inclusive. One male dosed at 150 mg/kg/day also showed discrete areas of fur loss from Day 10 to Day 21. In addition, animals of either sex dosed at 650 or 150 mg/kg/day showed short-lived increased salivation before or immediately after dosing for most of the study, together with associated fur wetting and, less frequently, red/brown staining around the mouth and/or of the fur. Sporadic incidents of prolonged increased salivation were also observed amongst animals dosed at 650 mg/kg/day from Day 6.

Females dosed at 150 mg/kg/day and animals of either sex dosed at 15 mg/kg/day showed no clinical signs of toxicity during the study.

One control male showed an open wound in the dorso-cervical region from Day 19 onwards. Minor physical injuries occasionally arise when rats are housed in groups and this finding was clearly of no toxicological importance.

5.3 Bodyweight

Group mean weekly bodyweights and standard deviations are given in Tables 3 and 4 and are presented graphically in Figures I and II. Individual bodyweights are given in Appendix I.

Males dosed at 650 mg/kg/day showed an 18% lower bodyweight gain than controls during the second half of the treatment period.

There was no adverse effect on bodyweight development amongst females dosed at 650 mg/kg/day or amongst animals of either sex from the remaining dose groups.

5.4 Food Consumption

Group mean weekly food consumptions are given in Tables 5 and 6 and are presented graphically in Figures III and IV. Weekly food efficiencies are given in Tables 7 and 8.

There was no adverse effect on food consumption during the study.

Males dosed at 650 mg/kg/day showed a slightly lower food efficiency than controls during the second half of the treatment period. Females dosed at 650 mg/kg/day and animals from the remaining dose groups showed a similar food efficiency to controls during the study.

5.5 Water Consumption

Daily visual inspection of the water bottles showed a possible increase in water consumption during the final week of treatment amongst animals dosed at 650 mg/kg/day.

There was no visible adverse effect on water consumption at the remaining dose levels.

5.6 Laboratory Investigations

5.6.1 Haematology

Group mean values and standard deviations for test and control group animals are given in Tables 9 and 10 (statistically significant differences are indicated). Individual values are presented in Appendix II.

Males dosed at 650 or 150 mg/kg/day showed a slightly reduced haemoglobin compared with controls. In addition, males dosed at 650 mg/kg/day showed a

lower haematocrit than controls whilst females from the same dose group showed a reduced mean corpuscular haemoglobin. Animals of either sex dosed at 650 mg/kg/day also showed a lower mean corpuscular volume than controls. In addition, males dosed at 650 mg/kg/day showed a slightly higher leucocyte count than controls, reflecting an increased lymphocyte count, and females dosed at 650 or 150 mg/kg/day showed a slightly reduced prothrombin time compared with controls.

Animals dosed at 15 mg/kg/day showed no toxicologically significant changes in the parameters measured.

The remaining statistically significant intergroup differences involved a reduced neutrophil count, an increased reticulocyte count and an increased activated partial thromboplastin time. These changes were confined to females dosed at 150 and/or 15 mg/kg/day and, in the absence of any dose-response relationship, were considered not to be toxicologically important.

5.6.2 Blood Chemistry

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

Animals of either sex dosed at 650 mg/kg/day showed a reduced albumin/globulin ratio compared with controls, reflecting an increased plasma globulin concentration amongst the males and a reduced plasma albumin concentration amongst the females. Males dosed at 650 mg/kg/day also showed an increased plasma cholesterol concentration compared with controls, with all individual values outside the normally expected range for rats of the strain and age used in the study, and a slightly increased total protein concentration.

Animals dosed at 150 or 15 mg/kg/day showed no toxicologically significant changes in the parameters measured.

Statistically significant changes in plasma alkaline phosphatase concentration and inorganic phosphorus concentration at a dose level of 650 mg/kg/day were considered not to be toxicologically important. Animals of either sex showed a reduction in plasma alkaline phosphatase concentration compared with controls but none of the individual values were abnormally low for rats of the strain and age used in the study and, in any event, a reduction in alkaline phosphatase concentration is unlikely to be indicative of toxicity. Males also showed a reduction in plasma inorganic phosphorus concentration compared with controls but again none of the individual values were abnormally low for rats of the strain and age used and the intergroup difference probably arose because of higher than expected control values.

Females dosed at 15 mg/kg/day showed a statistically significant reduction in plasma sodium concentration but, in the absence of any dose-response relationship, this finding was considered not to be toxicologically significant.

5.7 Pathology

5.7.1 Organ Weights

Group mean absolute and relative organ weights and standard deviations for test and control group animals are presented in Tables 13 to 16 (statistically significant differences are indicated). Individual data are given in Appendix IV.

Animals of either sex dosed at 650 mg/kg/day showed a substantially higher liver weight, both absolute and relative to terminal bodyweight, than controls. The adverse effect was slightly more pronounced amongst the females (58% higher relative liver weight than controls compared with a 38% increase amongst the males) and, for animals of either sex, most of the individual values were outside the normally expected range for rats of the strain and age used in the study. In

addition, one male dosed at 650 mg/kg/day showed a substantially lower testes weight, both absolute and relative to terminal bodyweight, than either controls or the other four animals from the same dose group. There was no statistically significant difference between control and 650 mg/kg/day group mean testes weight however and this isolated change was, therefore, of equivocal toxicological importance.

Animals dosed at 150 or 15 mg/kg/day showed no toxicologically significant organ weight changes.

Males dosed at 650 mg/kg/day showed a statistically significant increase in relative heart weight compared with controls. None of the individual values were abnormally high for rats of the strain and age used and, in the absence of any toxicologically important changes in the myocardium, this finding was considered to be entirely attributable to the reduced bodyweight development seen at this dose level. Relative brain weight was increased amongst males dosed at 15 or 650 mg/kg/day compared with controls, but none of the individual values were outside the normally expected range for rats of the strain and age used and, in the absence of any dose-response relationship, this finding was considered also not to be toxicologically significant.

The remaining statistically significant intergroup differences involved a reduction in absolute and relative spleen weight and a reduction in relative adrenal weight amongst females dosed at 15 mg/kg/day. These changes showed no dose-response relationship and were, therefore, considered to be of no toxicological importance.

5.7.2 Necropsy

A summary incidence of necropsy findings is given in Tables 17 and 18. Individual post mortem examination findings are given in Appendix V.

Two males dosed at 650 mg/kg/day showed patchy pallor of the liver at terminal kill. Another male from this dose group showed small testes.

Females dosed at 650 mg/kg/day and animals from the remaining dose groups showed no toxicologically significant macroscopic abnormalities at necropsy.

The remaining macroscopic lesions observed at necropsy represent normally expected, low incidence findings amongst laboratory maintained rats of the strain and age used and, as such, were considered not to be toxicologically significant.

5.7.3 Histopathology

A summary incidence of histopathological findings is given in Tables 19 and 20. Details of the grading system used, together with all individual animal histopathological findings, are given in Appendix VI.

Treatment-related changes were observed in the liver. Generalised hepatocyte enlargement and lipid-type vacuolation of periportal hepatocytes were observed for rats of either sex dosed at 650 mg/kg/day, and for male rats dosed at 150 mg/kg/day. One male rat receiving 15 mg/kg/day also demonstrated generalised hepatocyte enlargement. Hepatocyte enlargement is commonly observed in the rodent liver following the administration of xenobiotics and, in the absence of associated degenerative or inflammatory changes, is generally regarded as adaptive in nature.

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

6. DISCUSSION

Oral administration of Allyl Sucrose to rats for twenty-eight consecutive days, by gavage, at dose levels of 15, 150 and 650 mg/kg/day resulted in treatment-related changes at all dose levels amongst the males and at 150 and 650 mg/kg/day amongst the females.

An adverse effect on the liver was detected amongst animals of either sex dosed at 650 mg/kg/day. Two males showed patchy pallor of the liver at necropsy and animals of either sex showed a substantially increased liver weight, both absolute and relative to terminal bodyweight. In addition, histopathological examination revealed generalised hepatocyte enlargement and lipid-type vacuolation of periportal hepatocytes amongst these animals. In the absence of any degenerative or inflammatory changes, the generalised hepatocyte enlargement was considered to represent an adaptive response to the repeated administration of a xenobiotic substance whilst lipid-type vacuolation represents a commonly encountered hepatocyte lesion in toxicological studies of this type. These morphological changes are usually fully reversible upon cessation of treatment.

Blood chemical determinations showed a slightly increased plasma globulin and cholesterol concentration amongst males dosed at 650 mg/kg/day, with all individual cholesterol values outside the normally expected historical range for this parameter. Several blood constituents, including cholesterol and other lipids, bind to alpha- and beta-globulins and increased globulin levels often accompany an elevated plasma lipid concentration. It is possible, therefore, that these blood chemical findings were associated. In addition, the liver is involved in many phases of lipid metabolism including synthesis, esterification and excretion of cholesterol. With the exception of a marginal reduction in plasma albumin concentration amongst the females however, there was no convincing evidence of liver dysfunction at this dose level and determination of total cholesterol alone, as in this study, is of limited diagnostic value because a variety of conditions, other than those involving the liver, may result in an increased plasma cholesterol level.

Haematological determinations showed a mild microcytic, hypochromic anaemia amongst males and, to a lesser extent, amongst females dosed at 650 mg/kg/day. In short-term toxicological evaluations, this condition normally develops either due to a chronic disease state, of which there is no evidence in this study, or secondary to an adverse effect on iron metabolism. Given that the liver is an important site of iron storage, it is therefore plausible that the haematological abnormalities could be associated with an adverse effect on the liver. The precise aetiology and toxicological importance of the other haematological changes identified at this dose level is less certain from these data.

Other toxicologically important findings at 650 mg/kg/day could not easily be attributed to an effect on a specific organ, tissue or physiological process. Patchy fur loss was observed amongst females during the first half of the treatment period whilst males showed a reduced bodyweight gain during the second half of the study together with a reduced food efficiency (the ratio of bodyweight gain to food intake). In addition, one of the males dosed at 650 mg/kg/day showed small testes at necropsy together with a substantially reduced testes weight and histopathological examination showed a severe grade of atrophy in both gonads. These findings were considered to be of equivocal toxicological importance however, as similar testicular changes were not evident amongst the remainder of the dose group and testicular atrophy occasionally accompanies reduced bodyweight gain, which was evident at this dose level.

An increased water consumption was observed towards the end of the study amongst animals dosed at 650 mg/kg/day. This finding was most likely associated with the increased salivation seen at this dose level (and amongst animals dosed at 150 mg/kg/day), which was itself probably associated with the dosing procedure rather than being indicative of toxicity.

At 150 mg/kg/day, animals showed minimal treatment-related changes. Two males showed generalised hepatocyte enlargement and another male showed periportal hepatocyte vacuolation. Haematological determinations showed a slightly reduced haemoglobin concentration amongst males and a reduced prothrombin time amongst

females at this dose level (activated partial thromboplastin time was unaffected). One of the males showed transient fur loss during the study, although this latter finding was considered to be of dubious toxicological importance given the absence of a similar finding amongst males dosed at 650 mg/kg/day.

Treatment-related effects at 15 mg/kg/day were confined to one male rat which showed generalised hepatocyte enlargement. As described above, this morphological lesion was considered to represent a normally expected adaptive response of the liver to repeated oral administration of the test material.

The remaining four males and all of the females dosed at 15 mg/kg/day showed no treatment-related changes in the parameters measured. Furthermore, the nature of the treatment-related findings amongst animals of either sex dosed at 150 mg/kg/day were considered not to be indicative of serious damage to the health of the animals, in accordance with the labelling criteria given in Directive 93/21/EEC.

7. CONCLUSION

Oral administration of the test material, Allyl Sucrose, to rats, by gavage, for a period of twenty-eight consecutive days at dose levels of 15, 150 and 650 mg/kg/day resulted in treatment-related changes at all dose levels amongst the males and at 150 and 650 mg/kg/day amongst the females. No such changes were detected amongst females dosed at 15 mg/kg/day and the "No Observed Effect Level" (NOEL) for females was considered to be 15 mg/kg/day. A NOEL was not established for males because of adaptive liver changes in one animal dosed at 15 mg/kg/day.

The nature of the changes seen at 150 mg/kg/day amongst animals of either sex were considered not to be indicative of serious damage to the health of the animals, as defined by the criteria given in the labelling guide of Directive 93/21/EEC, and 150 mg/kg/day was therefore considered to represent the "No Observed Adverse Effect Level" (NOAEL).

T A B L E S

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 1 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 1 TO DAY 7 - MALES

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION															
			DAY: 1		DAY: 2		DAY: 3		DAY: 4		DAY: 5		DAY: 6		DAY: 7			
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	
1	0 (Control)	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
2	15	Increased salivation immediately after dosing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	150	Increased salivation immediately after dosing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	650	Increased salivation immediately after dosing	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Pre - immediately before dosing 1h - one hour after dosing 5h - five hours after dosing
 * - five hour observation not performed at weekend or on public holiday

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
 TABLE 1 (continued)
 SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 8 TO DAY 14 - MALES

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																				
			DAY: 8		DAY: 9		DAY: 10		DAY: 11		DAY: 12		DAY: 13		DAY: 14								
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h						
1	0 (Control)	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5					
2	15	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5					
3	150	Increased salivation immediately after dosing	0	0	0	0	0	0	4	0	0	4	0	0	5	0	0	4	0	0			
		Increased salivation	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0		
		Patchy fur loss	0	0	0	0	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1		
4	650	No abnormalities detected	5	5	5	5	5	5	4	4	0	4	4	4	4	4	4	4	4	4	4		
		Increased salivation immediately after dosing	5	0	0	5	0	0	4	0	0	4	0	0	4	0	0	4	0	0	5	0	0
		Increased salivation	0	0	0	0	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0
		No abnormalities detected	5	5	5	5	5	4	5	0	4	5	0	4	5	5	4	5	5	4	5	5	5

Pre - immediately before dosing

1h - one hour after dosing

5h - five hours after dosing

* - five hour observation not performed at weekend

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 1 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 22 TO DAY 28 - MALES

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION														
			DAY: 22		DAY: 23		DAY: 24		DAY: 25		DAY: 26		DAY: 27		DAY: 28		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
1	0 (Control)	Open wound in cervical region	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
		No abnormalities detected	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
2	15	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
3	150	Increased salivation immediately after dosing	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0
		No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
4	650	Increased salivation immediately after dosing	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0
		Increased salivation	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0
		Wet fur	0	3	0	0	1	0	0	1	0	0	3	0	1	0	0
		No abnormalities detected	5	2	5	5	4	5	5	4	5	5	2	5	4	5	5

Pre = immediately before dosing
 1h = one hour after dosing
 5h = five hours after dosing
 * = five hour observation not performed at weekend

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 1 TO DAY 7 - FEMALES

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																		
			DAY: 1		DAY: 2		DAY: 3		DAY: 4		DAY: 5		DAY: 6		DAY: 7						
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h				
1	0 (Control)	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5			
2	15	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5			
3	150	Increased salivation immediately after dosing	0	0	0	0	0	0	5	0	0	5	0	0	5	0	0	0	0		
		No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
4	650	Increased salivation immediately after dosing	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0	
		Increased salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Fur loss from cranial/cervical region	0	0	0	4	4	4	3	3	0	4	4	4	4	4	4	4	4	4	4
		Red/brown staining around mouth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		No abnormalities detected	5	5	5	1	1	1	2	2	0	1	1	0	1	1	0	1	1	1	

Pre - immediately before dosing 1h - one hour after dosing 5h - five hours after dosing
 * - five hour observation not performed at weekend or on public holiday

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 8 TO DAY 14 - FEMALES

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																					
			DAY: 8		DAY: 9		DAY: 10		DAY: 11		DAY: 12		DAY: 13		DAY: 14									
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h							
1	0 (Control)	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5					
2	15	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5					
3	150	Increased salivation immediately after dosing	0	0	0	0	0	3	0	0	2	0	0	3	0	0	5	0	0	4	0	0		
		No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
		Increased salivation immediately after dosing	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0	
		Increased salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	
		Fur loss	4	4	2	1	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
4	650	Red/brown staining of fur	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0	0	0	0	0	0	
		Red/brown staining around mouth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
		Wet fur	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
		No abnormalities detected	1	1	3	4	4	4	5	5	5	0	0	0	5	2	4	5	4	5	5	2	4	4

Pre - immediately before dosing 1h - one hour after dosing 5h - five hours after dosing
 * - five hour observation not performed at weekend

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 15 TO DAY 21 - FEMALES

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																				
			DAY: 15		DAY: 16		DAY: 17		DAY: 18		DAY: 19		DAY: 20		DAY: 21								
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h						
1	0 (Control)	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5						
			5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5					
2	15	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5						
			5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5					
3	150	Increased salivation immediately after dosing	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0	5					
		Red/brown staining of fur	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0				
		Wet fur	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0			
		No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	4	5	5	5			
4	650	Increased salivation immediately after dosing	4	0	0	4	0	0	5	0	0	5	0	0	4	0	0	5	0	0			
		Increased salivation	1	0	0	1	0	0	0	0	0	0	0	0	1	2	0	0	1	0	0		
		Wet fur	0	4	0	0	5	0	0	5	0	0	4	0	0	4	0	0	3	0	0	4	0
		No abnormalities detected	4	1	5	4	0	5	5	0	0	5	1	0	5	4	1	5	5	2	5	4	1

Pre - immediately before dosing
 1h - one hour after dosing
 5h - five hours after dosing
 * - five hour observation not performed at weekend

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS FROM DAY 22 TO DAY 28 - FEMALES

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	CLINICAL OBSERVATIONS	NUMBER SHOWING EFFECTS AT OBSERVATION																		
			DAY: 22		DAY: 23		DAY: 24		DAY: 25		DAY: 26		DAY: 27		DAY: 28						
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h				
1	0 (Control)	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5			
2	15	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5			
3	150	Increased salivation immediately after dosing	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0	
		No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
4	650	Increased salivation immediately after dosing	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0	
		Increased salivation	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
		Wet fur	0	5	0	0	5	0	0	5	0	0	5	0	0	2	0	0	1	0	0
		No abnormalities detected	5	0	5	5	0	5	5	0	5	5	0	5	3	5	5	4	5	4	4

Pre = immediately before dosing
 1h = one hour after dosing
 5h = five hours after dosing
 * = five hour observation not performed at weekend

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

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

DOSE LEVEL		Bodyweight (g) at Day				
		0	7	14	21	28
1 Control	mean	151	212	262	311	357
	sd	9	14	12	12	16
2 15	mean	144	202	252	299	342
	sd	2	3	6	15	24
3 150	mean	151	208	259	309	353
	sd	9	14	19	23	28
4 650	mean	152	208	253	293	331
	sd	9	10	16	19	22

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

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

DOSE LEVEL		Bodyweight (g) at Day				
		0	7	14	21	28
1 Control	mean	138	169	194	215	234
	sd	8	11	12	16	20
2 15	mean	142	177	196	219	231
	sd	7	8	9	13	15
3 150	mean	142	173	190	213	229
	sd	12	13	13	14	18
4 650	mean	133	164	183	200	218
	sd	8	10	16	15	17

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
 TABLE 5
 GROUP MEAN WEEKLY FOOD CONSUMPTION - MALES

GROUP NUMBER	DOSE LEVEL (mg/kg/day)		MEAN FOOD CONSUMPTION (g/rat/week)			
			1	2	3	4
1	0 (Control)		202	227	240	239
2	15	■	186 (-8)	206 (-9)	219 (-9)	222 (-7)
3	150	■	189 (-6)	208 (-8)	228 (-5)	232 (-3)
4	650	■	200 (-1)	223 (-2)	238 (-1)	242 (+1)

■ - % change compared to control group value

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 6
GROUP MEAN WEEKLY FOOD CONSUMPTION - FEMALES

GROUP NUMBER	DOSE LEVEL (mg/kg/day)		MEAN FOOD CONSUMPTION (g/rat/week)			
			1	2	3	4
1	0 (Control)		162	189	203	199
2	15	■	140 (-14)	146 (-23)	152 (-25)	155 (-22)
3	150	■	138 (-15)	146 (-23)	156 (-23)	158 (-21)
4	650	■	147 (-9)	153 (-19)	164 (-19)	181 (-9)

■ - % change compared to control group value

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 7
WEEKLY FOOD EFFICIENCY* - MALES

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	FOOD EFFICIENCY* DURING WEEK			
		1	2	3	4
1	0 (Control)	0.30	0.22	0.20	0.19
2	15	0.31	0.24	0.21	0.19
3	150	0.30	0.25	0.22	0.19
4	650	0.28	0.20	0.17	0.16

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

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 8
WEEKLY FOOD EFFICIENCY* - FEMALES

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	FOOD EFFICIENCY* DURING WEEK			
		1	2	3	4
1	0 (Control)	0.19	0.13	0.10	0.10
2	15	0.25	0.13	0.15	0.08
3	150	0.22	0.12	0.15	0.10
4	650	0.21	0.12	0.10	0.10

Mean bodyweight gain (g/rat/week)

Group mean food consumption (g/rat/week)

*Food efficiency =

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 9
GROUP MEAN HAEMATOLOGICAL VALUES AND
STANDARD DEVIATIONS (SD) - MALES

DOSE LEVEL mg/kg/day		Hb (g/dl)	RBC (10 ¹² /l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10 ⁹ /l)	RETIC (%)	DIFFERENTIAL (10 ⁹ /l)					CT (secs)	PLT (10 ⁹ /l)	APTT (secs)		
										Neut	Lymph	Mono	Eos	Bas					
1	0(Control)	mean	15.5	7.68	44.5	20.1	58.0	34.7	12.4	4									
		sd	0.6	0.29	1.8	0.5	1.3	0.4	2.3	1									
2	15	mean	15.3	7.48	44.3	20.4	59.3	34.5	13.2	5									
		sd	0.2	0.24	1.1	0.5	1.5	0.5	1.0	1									
3	150	mean	14.7*	7.28	42.2	20.3	58.0	35.0	12.7	5									
		sd	0.4	0.35	1.7	0.6	1.5	0.5	2.8	1									
4	650	mean	14.4**	7.42	41.3*	19.5	55.6	35.0	17.8**	5									
		sd	0.8	0.33	3.5	0.4	2.9	1.1	2.8	1									
1	0(Control)	mean									1.15	11.01	0.09	0.13	0.00	25	1206	16	
		sd									0.71	1.52	0.14	0.18	0.00	1	138	1	
2	15	mean									1.42	11.53	0.13	0.11	0.00	27	1076	17	
		sd									0.71	0.78	0.12	0.14	0.00	2	121	3	
3	150	mean									0.89	11.62	0.13	0.08	0.00	25	1177	15	
		sd									0.51	2.31	0.14	0.17	0.00	2	165	3	
4	650	mean									2.08	15.42**	0.04	0.25	0.00	24	1258	18	
		sd									1.01	2.56	0.09	0.22	0.00	1	161	4	

* = significantly different from control group value p < 0.05

** = significantly different from control group value p < 0.01

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 10
GROUP MEAN HAEMATOLOGICAL VALUES AND
STANDARD DEVIATIONS (SD) - FEMALES

DOSE LEVEL mg/kg/day			Hb	RBC	Hct	MCH	MCV	MCHC	WBC	RETIC
			(g/dl)	(10 ¹² /l)	(%)	(pg)	(fl)	(g/dl)	(10 ⁹ /l)	(%)
1 0(Control)	mean		14.5	7.20	41.2	20.1	57.2	35.3	9.5	3
	sd		0.5	0.25	1.4	0.3	1.7	0.7	2.6	1
2 15	mean		15.1	7.58*	42.7	19.9	56.3	35.3	10.0	4
	sd		0.8	0.28	2.7	0.4	1.8	0.8	3.6	1
3 150	mean		14.0	7.18	39.6	19.5	55.5	35.4	10.2	5**
	sd		0.5	0.17	1.8	1.1	1.3	2.6	3.0	1
4 650	mean		13.8	7.34	40.2	18.9*	54.8*	34.4	12.1	4
	sd		0.2	0.29	0.8	0.9	1.5	1.2	2.5	1

			DIFFERENTIAL (10 ⁹ /l)				Bas	CT (secs)	PLT (10 ⁹ /l)	APTT (secs)
			Neut	Lymph	Mono	Eos				
1 0(Control)	mean		1.30	7.92	0.04	0.21	0.00	26	1068	16
	sd		0.53	2.00	0.06	0.11	0.00	1	80	5
2 15	mean		0.57**	9.25	0.05	0.11	0.00	25	1126	22*
	sd		0.13	3.73	0.05	0.13	0.00	1	93	6
3 150	mean		0.70*	9.33	0.03	0.18	0.00	24*	1244	15
	sd		0.35	2.60	0.04	0.11	0.00	2	321	2
4 650	mean		1.01	10.76	0.13	0.20	0.00	23**	1061	18
	sd		0.39	2.61	0.13	0.25	0.00	1	138	3

* = significantly different from control group value p < 0.05

** = significantly different from control group value p < 0.01

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 11
GROUP MEAN BLOOD CHEMICAL VALUES AND
STANDARD DEVIATIONS (SD) - MALES

DOSE LEVEL mg/kg/day		UREA (mg/dl)	GLUCOSE (mg/dl)	TOT.PROT (g/dl)	ALBUMIN (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)	Ca++ (mmol/l)
1 0(Control)	mean	31	148	6.58	3.66	1.25	149	5.53	98	2.66
	sd	7	11	0.21	0.19	0.07	4	0.22	2	0.08
2 15	mean	27	138	6.40	3.62	1.30	151	5.27	99	2.62
	sd	5	13	0.36	0.18	0.07	3	0.26	1	0.18
3 150	mean	30	144	6.77	3.64	1.17	148	5.35	98	2.61
	sd	2	21	0.34	0.16	0.07	5	0.38	2	0.28
4 650	mean	29	143	7.13*	3.65	1.05***	152	5.15	97	2.62
	sd	5	6	0.40	0.16	0.03	3	0.32	1	0.18

		P (mmol/l)	GLOBULIN (g/dl)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	CREAT (mg/dl)	TRI (mg/dl)	Cho1 (mg/dl)	Bili (mg/dl)
1 0(Control)	mean	3.17	2.92	96	72	796	0.52	170	93	0.40
	sd	0.16	0.08	7	15	140	0.05	55	20	0.07
2 15	mean	3.16	2.78	96	66	664	0.48	139	87	0.38
	sd	0.20	0.20	13	17	92	0.03	57	19	0.03
3 150	mean	2.99	3.13	93	71	660	0.51	127	93	0.35
	sd	0.22	0.23	5	5	138	0.03	46	16	0.09
4 650	mean	2.67***	3.48***	105	71	443***	0.53	133	116*	0.43
	sd	0.16	0.24	4	9	62	0.07	36	10	0.04

* = significantly different from control group value $p < 0.05$

*** = significantly different from control group value $p < 0.01$

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

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

DOSE LEVEL mg/kg/day		UREA (mg/dl)	GLUCOSE (mg/dl)	TOT.PROT (g/dl)	ALBUMIN (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)	Ca++ (mmol/l)
1 0(Control)	mean	32	153	7.32	4.09	1.27	151	5.29	99	2.74
	sd	2	7	0.34	0.14	0.04	2	0.40	1	0.26
2 15	mean	34	149	7.52	4.28	1.32	144**	5.41	99	2.73
	sd	2	13	0.36	0.21	0.02	2	0.22	1	0.22
3 150	mean	32	161	7.25	4.03	1.25	148	5.11	98	2.72
	sd	5	22	0.20	0.19	0.12	4	0.28	2	0.15
4 650	mean	33	143	7.06	3.73**	1.12**	147	5.44	99	2.81
	sd	3	4	0.43	0.21	0.03	4	0.20	2	0.04

	P (mmol/l)	GLOBULIN (g/dl)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	CREAT (mg/dl)	TRI (mg/dl)	Chol (mg/dl)	Bili (mg/dl)	
1 0(Control)	mean	2.80	3.23	104	63	508	0.59	82	117	0.36
	sd	0.18	0.21	13	12	133	0.07	16	21	0.02
2 15	mean	2.77	3.24	88	58	465	0.62	96	107	0.36
	sd	0.09	0.15	5	4	154	0.03	25	15	0.03
3 150	mean	2.72	3.22	91	59	364	0.57	77	100	0.36
	sd	0.29	0.20	9	14	50	0.07	12	19	0.02
4 650	mean	3.02	3.33	114	77	355*	0.55	97	103	0.36
	sd	0.52	0.22	24	15	76	0.06	24	37	0.03

* = significantly different from control group value p < 0.05

** = significantly different from control group value p < 0.01

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 13
GROUP MEAN ORGAN WEIGHTS AND
STANDARD DEVIATIONS (SD) - MALES

DOSE LEVEL	mg/kg/day	Organ weight (g)									
		adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus	
1	0(Control)	mean	0.0576	1.8577	4.0994	1.2254	2.5507	14.5195	0.0119	0.7144	0.5370
		sd	0.0080	0.1299	0.2429	0.0560	0.2055	1.8993	0.0031	0.0608	0.0987
2	15	mean	0.0541	1.9601	4.1979	1.1455	2.4674	13.4412	0.0107	0.7246	0.5831
		sd	0.0063	0.0783	0.2670	0.1398	0.0412	1.6728	0.0027	0.0827	0.1059
3	150	mean	0.0490	1.9381	3.9702	1.2352	2.5167	15.1851	0.0102	0.7177	0.6595
		sd	0.0069	0.0594	0.4243	0.1385	0.2993	1.8936	0.0029	0.1263	0.1697
4	650	mean	0.0499	1.8997	3.5767	1.2605	2.4744	18.3488**	0.0090	0.6410	0.5408
		sd	0.0060	0.0311	1.2622	0.1279	0.3737	2.1691	0.0010	0.0759	0.0145

** = significantly different from control group value p < 0.01

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 14
GROUP MEAN ORGAN WEIGHTS AND
STANDARD DEVIATIONS (SD) - FEMALES

DOSE LEVEL mgg/kg/day		Organ weight (g)								
		adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
1 0(Control)	mean	0.0761	1.8066	0.1207	0.8598	1.7277	8.6840	0.0131	0.6070	0.5487
	sd	0.0092	0.0468	0.0186	0.0497	0.1779	0.7756	0.0024	0.0623	0.0647
2 15	mean	0.0652	1.7948	0.1201	0.7917	1.6013	7.9087	0.0146	0.4338*	0.5230
	sd	0.0139	0.0378	0.0199	0.0649	0.0816	0.7739	0.0036	0.0510	0.1372
3 150	mean	0.0780	1.7934	0.1297	0.8400	1.6914	9.4546	0.0121	0.5331	0.5540
	sd	0.0043	0.0920	0.0136	0.0640	0.1443	1.2192	0.0012	0.0305	0.1139
4 650	mean	0.0701	1.7425	0.1187	0.8294	1.7345	13.0821***	0.0109	0.5783	0.4772
	sd	0.0042	0.0894	0.0224	0.0666	0.1921	1.4630	0.0037	0.1706	0.0896

*** = significantly different from control group value p < 0.001

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 15

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

DOSE LEVEL mg/kg/day	Relative Organ weight (%)									
	adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus	
1 0(Control)	mean	0.0162	0.5230	1.1558	0.3455	0.7179	4.0855	0.0033	0.2015	0.1506
	sd	0.0019	0.0201	0.0690	0.0151	0.0342	0.4426	0.0008	0.0181	0.0216
2 15	mean	0.0160	0.5784*	1.2380	0.3361	0.7284	3.9444	0.0032	0.2129	0.1708
	sd	0.0023	0.0420	0.1008	0.0187	0.0510	0.2684	0.0008	0.0158	0.0211
3 150	mean	0.0139	0.5513	1.1279	0.3494	0.7108	4.2859	0.0029	0.2029	0.1874
	sd	0.0021	0.0456	0.1295	0.0240	0.0340	0.1940	0.0007	0.0278	0.0486
4 650	mean	0.0154	0.5864*	1.0935	0.3889*	0.7594	5.6379***	0.0028	0.1976	0.1671
	sd	0.0018	0.0365	0.3738	0.0448	0.0819	0.4570	0.0002	0.0232	0.0136

* = significantly different from control group value p < 0.05

*** = significantly different from control group value p < 0.001

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 16

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

DOSE LEVEL mg/kg/day		Relative Organ weight (%)								
		adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
1 0(Control)	mean	0.0333	0.7940	0.0529	0.3770	0.7558	3.7946	0.0057	0.2653	0.2400
	sd	0.0039	0.0773	0.0076	0.0282	0.0617	0.1492	0.0011	0.0183	0.0234
2 15	mean	0.0285*	0.7899	0.0527	0.3484	0.7039	3.4730	0.0064	0.1903**	0.2287
	sd	0.0051	0.0345	0.0074	0.0293	0.0198	0.2504	0.0015	0.0163	0.0537
3 150	mean	0.0344	0.7922	0.0571	0.3699	0.7479	4.1515	0.0053	0.2350	0.2439
	sd	0.0017	0.0630	0.0029	0.0135	0.0877	0.2673	0.0004	0.0108	0.0489
4 650	mean	0.0315	0.7999	0.0542	0.3800	0.7934	5.9902***	0.0050	0.2624	0.2192
	sd	0.0018	0.0439	0.0088	0.0152	0.0441	0.4402	0.0016	0.0603	0.0450

* = significantly different from control group value $p < 0.05$

** = significantly different from control group value $p < 0.01$

*** = significantly different from control group value $p < 0.001$

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 17

SUMMARY INCIDENCE OF NECROPSY FINDINGS - MALES

	GROUP 1 0 (Control)	GROUP 2 15 mg/kg/day	GROUP 3 150 mg/kg/day	GROUP 4 650 mg/kg/day
Number of animals	5	5	5	5
No abnormalities detected	5	5	5	1
Liver: patchy pallor	0	0	0	2
Non-glandular stomach: two small raised white nodules	0	0	0	1
Testes: small	0	0	0	1

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 18

SUMMARY INCIDENCE OF NECROPSY FINDINGS - FEMALES

	GROUP 1 0 (Control)	GROUP 2 15 mg/kg/day	GROUP 3 150 mg/kg/day	GROUP 4 650 mg/kg/day
Number of animals	5	5	5	5
No abnormalities detected	5	5	5	4
Kidneys: hydronephrosis	0	0	0	1

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TABLE 19

SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS - MALES

	Group 1 0 Control	Group 2 15 mg/kg/day	Group 3 150 mg/kg/day	Group 4 650 mg/kg/day
number of animals	5	5	5	5
	Heart			
Focal myocarditis				
no data	0	5	5	0
absent	1	0	0	2
(minimal)	4	0	0	3
	Kidneys			
Groups of basophilic tubules				
no data	0	5	5	0
absent	4	0	0	2
(minimal)	1	0	0	3
Globular accumulations of eosinophilic material				
no data	0	5	5	0
absent	3	0	0	1
(minimal)	1	0	0	3
(slight)	1	0	0	1
	Liver			
Mononuclear cell foci				
absent	1	0	0	0
(minimal)	4	4	5	3
(slight)	0	1	0	2
Focal hepatocyte necrosis				
absent	5	4	4	5
(minimal)	0	1	1	0
Generalised hepatocyte enlargement				
absent	5	4	3	0
(minimal)	0	1	1	2
(slight)	0	0	1	3
Periportal hepatocyte vacuolation				
absent	5	5	4	3
(minimal)	0	0	1	1
(slight)	0	0	0	1

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 19 (continued)

SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS - MALES

	Group 1 0 Control	Group 2 15 mg/kg/day	Group 3 150 mg/kg/day	Group 4 650 mg/kg/day
number of animals	5	5	5	5
Testes				
Atrophy gonad 1				
no data	0	5	5	0
absent	5	0	0	4
(severe)	0	0	0	1
Atrophy gonad 2				
no data	0	5	5	0
absent	5	0	0	4
(severe)	0	0	0	1
Non-Protocol Organs				
Forestomach				
Ectopic glandular tissue	0	0	0	1
Statistical Information				
Mode of death				
Terminal kill	5	5	5	5

ALLYL SUCROSE: TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
T A B L E 20
SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS - FEMALES

	Group 1 0 Control	Group 2 15 mg/kg/day	Group 3 150 mg/kg/day	Group 4 650 mg/kg/day
number of animals	5	5	5	5
Heart				
Focal myocarditis				
no data	0	5	5	0
absent	0	0	0	1
(minimal)	5	0	0	4
Kidneys				
Groups of basophilic tubules				
no data	0	5	5	0
absent	4	0	0	4
(minimal)	1	0	0	1
Hydronephrosis				
no data	0	5	5	0
absent	5	0	0	4
(slight)	0	0	0	1
Liver				
Mononuclear cell foci				
absent	0	0	0	1
(minimal)	5	5	4	4
(slight)	0	0	1	0
Generalised hepatocyte enlargement				
absent	5	5	5	1
(minimal)	0	0	0	4
Periportal hepatocyte vacuolation				
absent	5	5	5	2
(slight)	0	0	0	3
Single cell hepatocyte necrosis				
absent	5	5	5	4
present	0	0	0	1
Multifocal erythrophagocytosis				
absent	5	5	5	4
present	0	0	0	1

ALLYL SUCROSE: TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

T A B L E 20 (continued)

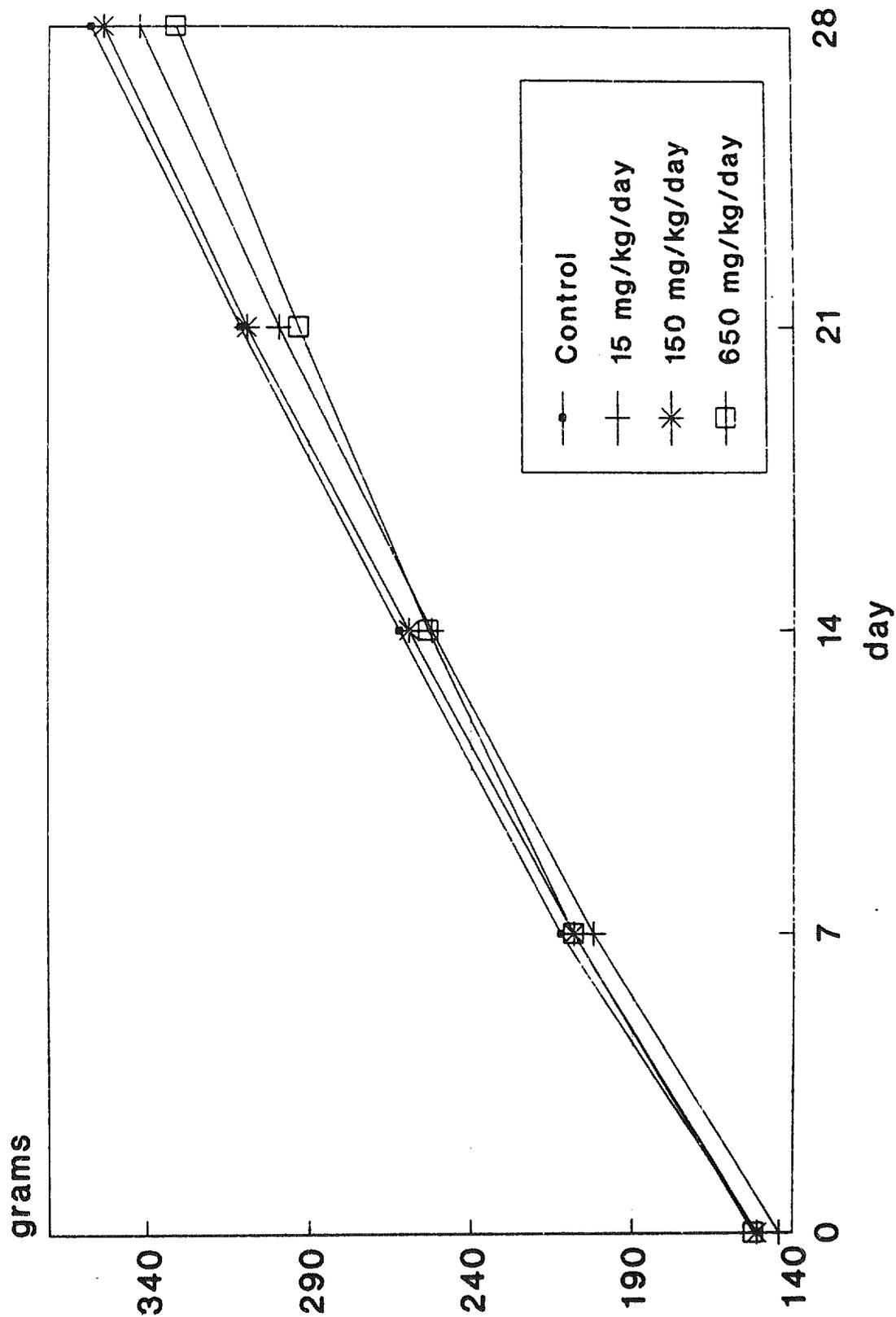
SUMMARY INCIDENCE OF HISTOPATHOLOGICAL FINDINGS - FEMALES

	Group 1 0 Control	Group 2 15 mg/kg/day	Group 3 150 mg/kg/day	Group 4 650 mg/kg/day
number of animals	5	5	5	5
Statistical Information				
Mode of death				
Terminal kill	5	5	5	5

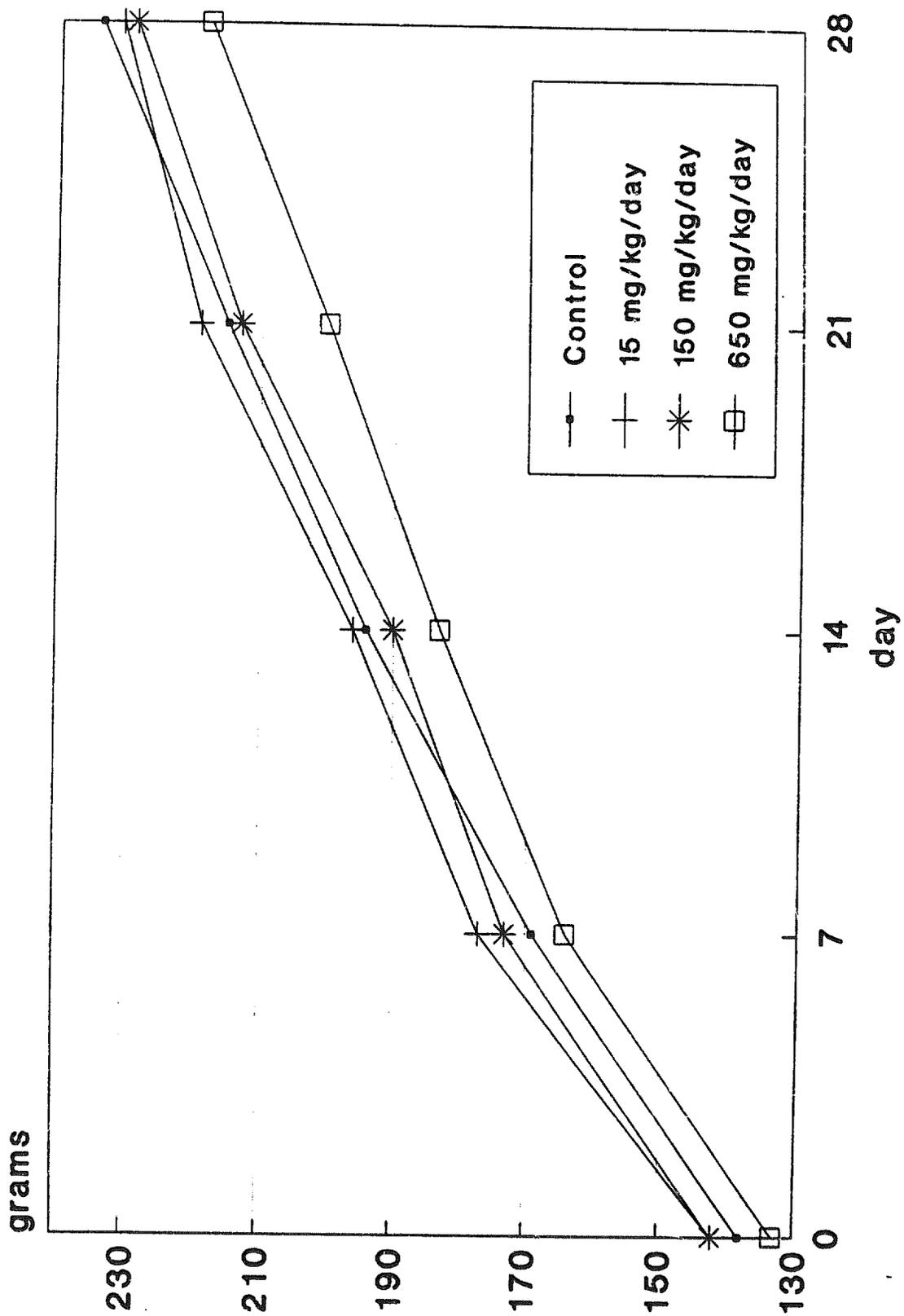
FIGURES

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

FIGURE I
MEAN WEEKLY BODYWEIGHT - MALES



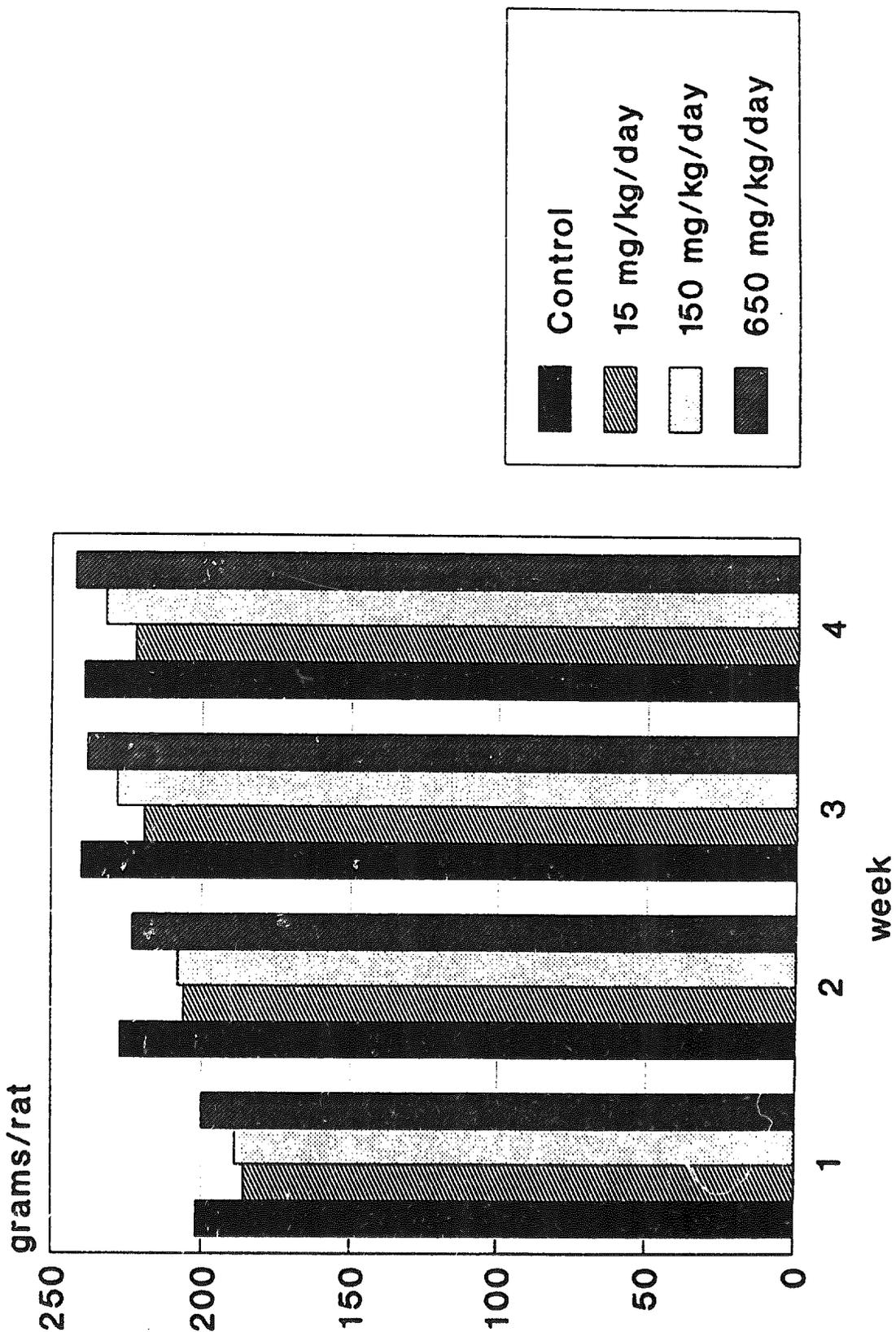
ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
FIGURE 11
MEAN WEEKLY BODYWEIGHT - FEMALES



ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

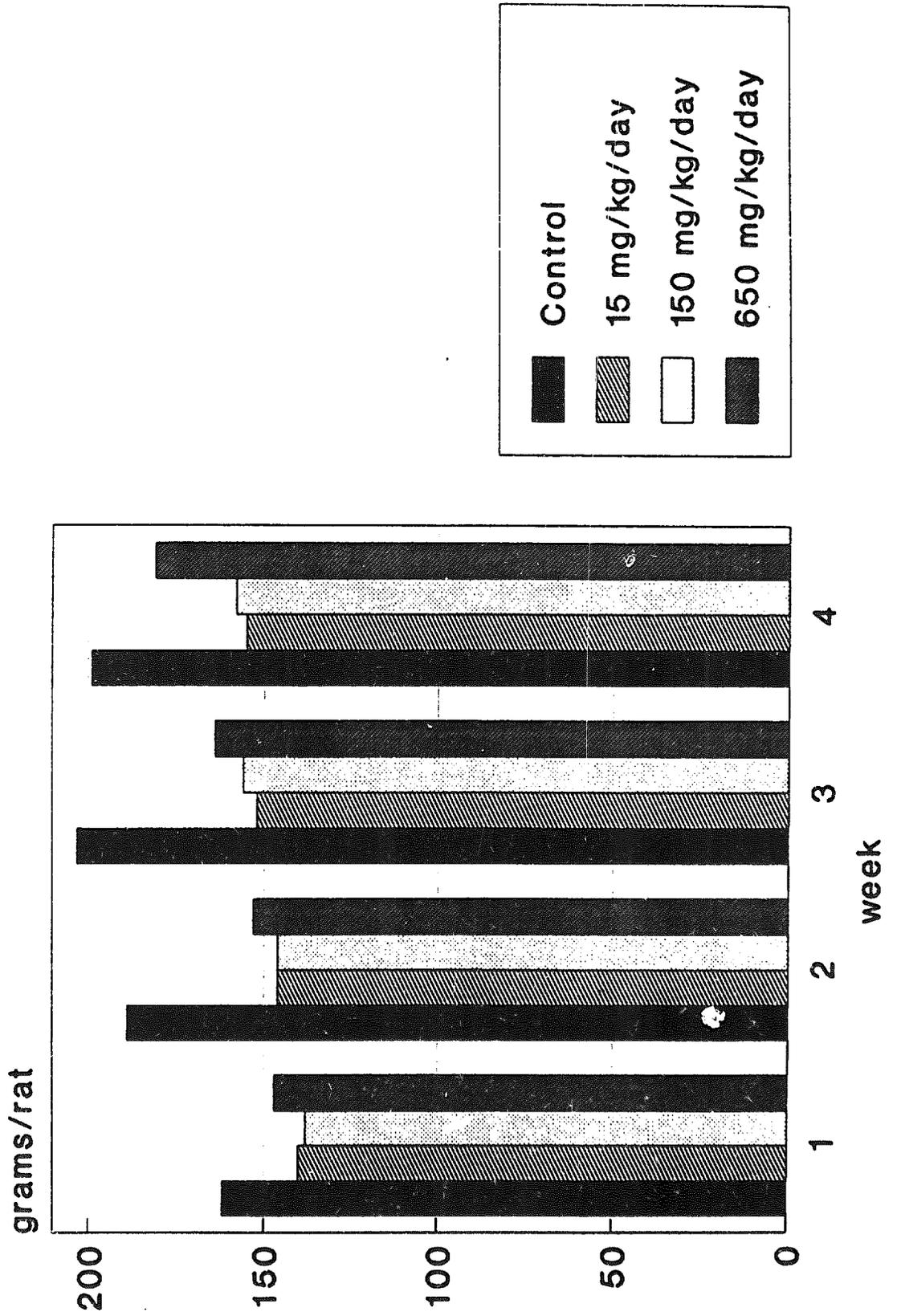
FIGURE III

WEEKLY FOOD CONSUMPTION - MALES



ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

FIGURE IV
WEEKLY FOOD CONSUMPTION - FEMALES



APPENDICES

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I

INDIVIDUAL AND GROUP MEAN BODYWEIGHTS AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 0 (Control)

SEX : Male

Animal number	Bodyweight (g) at Day				
	0	7	14	21	28
1	165	234	281	328	376
2	142	195	249	299	341
3	153	214	259	304	341
4	146	210	265	317	369
5	148	205	255	307	358
mean	151	212	262	311	357
sd	9	14	12	12	16
Incr/wk		61	50	49	46

SEX : Female

Animal number	Bodyweight (g) at Day				
	0	7	14	21	28
6	140	178	198	207	245
7	132	155	176	191	204
8	148	177	206	226	248
9	127	159	187	224	223
10	142	178	201	226	248
mean	138	169	194	215	234
sd	8	11	12	16	20
Incr/wk		31	25	21	19

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I (continued)

INDIVIDUAL AND GROUP MEAN BODYWEIGHTS AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 15 mg/kg/day

		SEX : Male				
		Bodyweight (g) at Day				
Animal number	0	7	14	21	28	
11	144	207	261	326	384	
12	142	202	249	294	334	
13	143	202	248	288	321	
14	142	198	248	293	339	
15	148	201	252	294	334	
mean	144	202	252	299	342	
sd	2	3	6	15	24	
Incr/wk		58	50	47	43	

		SEX : Female				
		Bodyweight (g) at Day				
Animal number	0	7	14	21	28	
16	151	185	199	230	242	
17	148	182	205	229	236	
18	139	175	199	222	243	
19	133	164	181	197	207	
20	138	178	198	218	227	
mean	142	177	196	219	231	
sd	7	8	9	13	15	
Incr/wk		35	19	23	12	

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I (continued)

INDIVIDUAL AND GROUP MEAN BODYWEIGHTS AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 150 mg/kg/day

SEX : Male

Animal number	Bodyweight (g) at Day				
	0	7	14	21	28
21	150	212	266	316	364
22	139	192	235	281	321
23	144	196	243	289	328
24	159	222	275	324	364
25	161	219	277	334	389
mean	151	208	259	309	353
sd	9	14	19	23	28
Incr/wk		57	51	50	44

SEX : Female

Animal number	Bodyweight (g) at Day				
	0	7	14	21	28
26	159	193	211	235	259
27	146	166	190	210	221
28	127	164	181	204	220
29	133	163	177	200	213
30	143	177	192	216	233
mean	142	173	190	213	229
sd	12	13	13	14	18
Incr/wk		31	17	23	16

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

APPENDIX I (continued)

INDIVIDUAL AND GROUP MEAN BODYWEIGHTS AND STANDARD DEVIATIONS (SD)

DOSE LEVEL: 650 mg/kg/day

SEX : Male

Animal number	Bodyweight (g) at Day				
	0	7	14	21	28
31	151	204	238	278	315
32	147	200	238	276	312
33	160	216	264	308	346
34	160	221	274	317	361
35	140	199	251	285	319
mean	152	208	253	293	331
sd	9	10	16	19	22
Incr/wk		56	45	40	38

SEX : Female

Animal number	Bodyweight (g) at Day				
	0	7	14	21	28
36	140	173	189	201	218
37	123	153	169	188	204
38	128	154	165	184	203
39	137	170	193	206	222
40	139	171	201	222	244
mean	133	164	183	200	218
sd	8	10	16	15	17
Incr/wk		31	19	17	18

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX II
INDIVIDUAL AND GROUP MEAN HAEMATOLOGICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 0 (Control)

SEX: MALE

Animal number	Hb (g/dl)	RBC ($10^{12}/l$)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC ($10^9/l$)	RETIC (%)
1	14.9	7.30	43.1	20.4	59.1	34.5	15.6	5
2	15.1	7.70	43.9	19.6	57.0	34.4	9.5	4
3	16.3	8.10	47.5	20.1	58.7	34.3	12.3	4
4	15.2	7.70	43.4	19.7	56.3	35.1	11.2	4
5	15.8	7.60	44.8	20.8	59.0	35.2	13.3	5
mean	15.5	7.68	44.5	20.1	58.0	34.7	12.4	4
sd	0.6	0.29	1.8	0.5	1.3	0.4	2.3	1

Animal number	DIFFERENTIAL ($10^9/l$)					CT (secs)	PLT ($10^9/l$)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
1	2.18	13.10	0.31	0.00	0.00	25	1360	16
2	0.57	8.93	0.00	0.00	0.00	25	1290	15
3	0.62	11.44	0.00	0.25	0.00	26	1050	18
4	0.78	10.42	0.00	0.00	0.00	24	1260	16
5	1.60	11.17	0.13	0.40	0.00	25	1070	16
mean	1.15	11.01	0.09	0.13	0.00	25	1206	16
sd	0.71	1.52	0.14	0.18	0.00	1	138	1

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

APPENDIX II (continued)

INDIVIDUAL AND GROUP MEAN HAEMATOLOGICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 0 (Control)
SEX: FEMALE

Animal number	Hb (g/dl)	RBC ($10^{12}/l$)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC ($10^9/l$)	RETIC (%)
6	15.2	7.40	43.4	20.5	58.6	35.1	13.2	2
7	14.7	7.50	41.1	19.6	54.8	35.8	6.5	4
8	13.9	6.90	40.8	20.1	59.1	34.1	10.4	3
9	14.2	7.00	39.5	20.3	56.5	35.9	9.8	2
10	14.5	7.20	41.0	20.1	56.9	35.4	7.5	3
mean	14.5	7.20	41.2	20.1	57.2	35.3	9.5	3
sd	0.5	0.25	1.4	0.3	1.7	0.7	2.6	1

Animal number	DIFFERENTIAL ($10^9/l$)					CT (secs)	PLT ($10^9/l$)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
6	2.11	10.56	0.13	0.40	0.00	27	990	21
7	0.78	5.59	0.00	0.13	0.00	26	1040	21
8	1.46	8.84	0.00	0.10	0.00	26	1030	18
9	1.27	8.33	0.00	0.20	0.00	26	1080	11
10	0.90	6.30	0.08	0.23	0.00	25	1200	11
mean	1.30	7.92	0.04	0.21	0.00	26	1068	16
sd	0.53	2.00	0.06	0.11	0.00	1	80	5

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I I (continued)

INDIVIDUAL AND GROUP MEAN HAEMATOLOGICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 15 mg/kg/day

SEX: MALE

Animal number	Hb (g/dl)	RBC (10 ¹² /l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10 ⁹ /l)	RETIC (%)
11	15.1	7.30	44.5	20.7	61.0	33.9	14.4	6
12	15.4	7.60	44.1	20.3	58.0	34.9	12.3	4
13	15.1	7.50	43.3	20.1	57.8	34.8	12.8	4
14	15.6	7.80	46.0	20.0	59.0	33.9	12.4	4
15	15.2	7.20	43.6	21.1	60.6	34.8	14.0	5
mean	15.3	7.48	44.3	20.4	59.3	34.5	13.2	5
sd	0.2	0.24	1.1	0.5	1.5	0.5	1.0	1

Animal number	DIFFERENTIAL (10 ⁹ /l)					CT (secs)	PLT (10 ⁹ /l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
11	2.02	12.24	0.14	0.00	0.00	24	1220	17
12	0.86	10.95	0.25	0.25	0.00	26	1150	18
13	0.51	12.29	0.00	0.00	0.00	30	1040	12
14	1.61	10.54	0.25	0.00	0.00	28	900	21
15	2.10	11.62	0.00	0.28	0.00	26	1070	18
mean	1.42	11.53	0.13	0.11	0.00	27	1076	17
sd	0.71	0.78	0.12	0.14	0.00	2	121	3

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I I (continued)

INDIVIDUAL AND GROUP MEAN HAEMATOLOGICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 15 mg/kg/day

SEX: FEMALE

Animal number	Hb (g/dl)	RBC (10 ¹² /l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10 ⁹ /l)	RETIC (%)
16	15.0	7.50	41.1	20.0	54.8	36.5	5.8	3
17	15.8	7.80	46.3	20.3	59.3	34.2	11.9	4
18	13.9	7.20	39.5	19.3	54.9	35.2	6.6	5
19	15.7	7.90	44.3	19.9	56.1	35.4	11.8	3
20	15.0	7.50	42.4	20.0	56.5	35.4	13.8	3
mean	15.1	7.58	42.7	19.9	56.3	35.3	10.0	4
sd	0.8	0.28	2.7	0.4	1.8	0.8	3.6	1

Animal number	DIFFERENTIAL (10 ⁹ /l)					CT (secs)	PLT (10 ⁹ /l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
16	0.75	4.93	0.06	0.06	0.00	25	990	22
17	0.60	11.31	0.00	0.00	0.00	26	1130	24
18	0.59	5.68	0.07	0.26	0.00	27	1190	12
19	0.47	10.97	0.12	0.24	0.00	25	1091	27
20	0.41	13.39	0.00	0.00	0.00	24	1230	23
mean	0.57	9.25	0.05	0.11	0.00	25	1126	22
sd	0.13	3.73	0.05	0.13	0.00	1	93	6

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

APPENDIX II (continued)

INDIVIDUAL AND GROUP MEAN HAEMATOLOGICAL VALUES AND STANDARD DEVIATIONS (SD)

DOSE LEVEL: 150 mg/kg/day

SEX: MALE

Animal number	Hb (g/dl)	RBC (10 ¹² /l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10 ⁹ /l)	RETIC (%)
21	14.1	6.80	39.4	20.7	58.0	35.8	14.4	6
22	15.2	7.70	43.7	19.7	56.8	34.8	8.0	5
23	14.7	7.50	42.2	19.6	56.2	34.9	13.1	5
24	15.1	7.30	43.4	20.7	59.5	34.8	13.0	4
25	14.6	7.10	42.2	20.6	59.5	34.6	15.1	7
mean	14.7	7.28	42.2	20.3	58.0	35.0	12.7	5
sd	0.4	0.35	1.7	0.6	1.5	0.5	2.8	1

Animal number	DIFFERENTIAL (10 ⁹ /l)					CT (secs)	PLT (10 ⁹ /l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
21	1.30	13.10	0.00	0.00	0.00	26	1170	16
22	0.08	7.68	0.24	0.00	0.00	26	954	19
23	0.92	12.05	0.13	0.00	0.00	23	1400	15
24	0.78	11.83	0.00	0.39	0.00	25	1110	12
25	1.36	13.44	0.30	0.00	0.00	23	1250	14
mean	0.89	11.62	0.13	0.08	0.00	25	1177	15
sd	0.51	2.31	0.14	0.17	0.00	2	165	3

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I I (continued)

INDIVIDUAL AND GROUP MEAN HAEMATOLOGICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 150 mg/kg/day

SEX: FEMALE

Animal number	Hb (g/dl)	RBC (10 ¹² /l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10 ⁹ /l)	RETIC (%)
26	13.8	7.20	39.2	19.2	54.5	35.2	7.9	6
27	13.5	7.40	42.2	18.2	57.0	32.0	9.4	4
28	14.8	7.10	38.8	20.8	54.7	38.1	13.4	4
29	13.8	7.00	38.2	19.7	54.5	36.2	7.1	5
30	13.9	10.30*	58.7*	13.5*	57.0	23.7*	13.4	6
mean	14.0	7.18	39.6	19.5	55.5	35.4	10.2	5
sd	0.5	0.17	1.8	1.1	1.3	2.6	3.0	1

Animal number	DIFFERENTIAL (10 ⁹ /l)					CT (secs)	PLT (10 ⁹ /l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
26	0.32	7.35	0.08	0.16	0.00	23	1230	16
27	0.56	8.65	0.00	0.19	0.00	23	1197	12
28	1.07	12.06	0.00	0.27	0.00	28	1050	12
29	0.50	6.53	0.07	0.00	0.00	23	960	17
30	1.07	12.06	0.00	0.27	0.00	24	1713	16
mean	0.70	9.33	0.03	0.18	0.00	24	1244	15
sd	0.35	2.60	0.04	0.11	0.00	2	321	2

* spurious value omitted from mean & sd

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I I (continued)

INDIVIDUAL AND GROUP MEAN HAEMATOLOGICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 650 mg/kg/day

SEX: MALE

Animal number	Hb (g/dl)	RBC (10 ¹² /l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10 ⁹ /l)	RETIC (%)
31	14.1	7.50	38.5	18.8	51.3	36.6	19.2	5
32	13.5	7.00	38.2	19.3	54.6	35.3	20.1	5
33	14.6	7.40	41.6	19.7	56.2	35.1	17.2	3
34	14.3	7.30	41.4	19.6	56.7	34.5	19.3	6
35	15.7	7.90	46.8	19.9	59.2	33.6	13.1	7
mean	14.4	7.42	41.3	19.5	55.6	35.0	17.8	5
sd	0.8	0.33	3.5	0.4	2.9	1.1	2.8	1

Animal number	DIFFERENTIAL (10 ⁹ /l)					CT (secs)	PLT (10 ⁹ /l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
31	3.26	15.36	0.00	0.58	0.00	23	1440	13
32	1.21	18.69	0.20	0.00	0.00	26	1130	21
33	1.38	15.48	0.00	0.34	0.00	24	1420	18
34	3.09	16.02	0.00	0.19	0.00	24	1200	24
35	1.44	11.53	0.00	0.13	0.00	24	1100	15
mean	2.08	15.42	0.04	0.25	0.00	24	1258	18
sd	1.01	2.56	0.09	0.22	0.00	1	161	4

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

APPENDIX II (continued)

INDIVIDUAL AND GROUP MEAN HAEMATOLOGICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 650 mg/kg/day

SEX: FEMALE

Animal number	Hb (g/dl)	RBC (10 ¹² /l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10 ⁹ /l)	RETIC (%)
36	14.0	7.50	40.5	18.7	54.0	34.6	14.2	3
37	13.7	7.50	40.1	18.3	53.5	34.1	14.6	5
38	13.5	7.60	41.3	17.8	54.4	32.7	12.3	6
39	14.1	7.20	39.3	19.6	54.6	35.9	8.7	5
40	13.7	6.90	39.6	19.9	57.4	34.6	10.7	3
mean	13.8	7.34	40.2	18.9	54.8	34.4	12.1	4
sd	0.2	0.29	0.8	0.9	1.5	1.2	2.5	1

Animal number	DIFFERENTIAL (10 ⁹ /l)					CT (secs)	PLT (10 ⁹ /l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
36	0.57	12.78	0.28	0.57	0.00	22	954	18
37	0.88	13.72	0.00	0.00	0.00	23	990	21
38	1.11	10.95	0.25	0.00	0.00	23	1290	14
39	0.87	7.48	0.00	0.35	0.00	22	980	17
40	1.61	8.88	0.11	0.11	0.00	23	1090	19
mean	1.01	10.76	0.13	0.20	0.00	23	1061	18
sd	0.39	2.61	0.13	0.25	0.00	1	138	3

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I I I

INDIVIDUAL AND GROUP MEAN BLOOD CHEMICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 0 (Control)

SEX: MALE

Animal number	UREA (mg/dl)	GLUCOSE (mg/dl)	TOT.PROT (g/dl)	ALBUMIN (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)	Ca++ (mmol/l)
1	25	138	6.27	3.33	1.13	145	5.63	97	2.69
2	31	155	6.47	3.67	1.31	146	5.51	101	2.54
3	43	145	6.79	3.82	1.29	152	5.47	96	2.62
4	28	140	6.62	3.72	1.28	154	5.23	97	2.68
5	29	164	6.75	3.76	1.26	146	5.82	99	2.76
mean	31	148	6.58	3.66	1.25	149	5.53	98	2.66
sd	7	11	0.21	0.19	0.07	4	0.22	2	0.08

Animal number	P (mmol/l)	GLOBULIN (g/dl)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	CREAT (mg/dl)	TRI (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
1	3.35	2.94	99	69	623	0.54	139	100	0.40
2	2.96	2.80	97	72	913	0.45	124	64	0.39
3	3.06	2.97	89	58	869	0.56	187	84	0.29
4	3.26	2.90	89	66	667	0.48	142	118	0.43
5	3.24	2.99	104	97	907	0.56	259	98	0.47
mean	3.17	2.92	96	72	796	0.52	170	93	0.40
sd	0.16	0.08	7	15	140	0.05	55	20	0.07

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

APPENDIX III (continued)

INDIVIDUAL AND GROUP MEAN BLOOD CHEMICAL VALUES AND STANDARD DEVIATIONS (SD)

DOSE LEVEL: 0 (Control)

SEX: FEMALE

Animal number	UREA (mg/dl)	GLUCOSE (mg/dl)	TOT. PROT (g/dl)	ALBUMIN (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)	Ca++ (mmol/l)
6	31	145	7.12	4.04	1.31	148	5.62	97	2.41
7	31	157	7.13	4.02	1.29	151	4.65	100	2.52
8	33	162	7.05	3.95	1.27	150	5.14	99	2.86
9	29	151	7.45	4.17	1.27	152	5.59	98	2.92
10	34	149	7.86	4.29	1.20	152	5.43	99	3.01
mean	32	153	7.32	4.09	1.27	151	5.29	99	2.74
sd	2	7	0.34	0.14	0.04	2	0.40	1	0.26

Animal number	P (mmol/l)	GLOBULIN (g/dl)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	CREAT (mg/dl)	TRI (mg/dl)	Chol (mg/dl)	Billi (mg/dl)
6	2.90	3.08	113	71	648	0.47	71	96	0.33
7	2.50	3.11	89	56	336	0.59	69	98	0.36
8	2.94	3.10	116	70	620	0.62	73	119	0.35
9	2.77	3.28	90	46	519	0.58	93	123	0.38
10	2.87	3.57	111	73	416	0.67	104	147	0.36
mean	2.80	3.23	104	63	508	0.59	82	117	0.36
sd	0.18	0.21	13	12	133	0.07	16	21	0.02

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I I I (continued)

INDIVIDUAL AND GROUP MEAN BLOOD CHEMICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 15 mg/kg/day

SEX: MALE

Animal number	UREA (mg/dl)	GLUCOSE (mg/dl)	TOT. PROT (g/dl)	ALBUMIN (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)	Ca++ (mmol/l)
11	36	157	6.87	3.90	1.31	148	5.15	100	2.87
12	24	138	6.29	3.49	1.25	156	5.71	99	2.40
13	26	135	6.10	3.45	1.30	152	5.12	100	2.52
14	24	121	6.07	3.56	1.42	149	5.08	100	2.57
15	27	138	6.69	3.71	1.24	151	5.27	98	2.73
mean	27	138	6.40	3.62	1.30	151	5.27	99	2.62
sd	5	13	0.36	0.18	0.07	3	0.26	1	0.18

Animal number	P (mmol/l)	GLOBULIN (g/dl)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	CREAT (mg/dl)	TRI (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
11	3.16	2.97	117	93	792	0.53	129	100	0.39
12	2.96	2.80	88	54	541	0.45	240	96	0.42
13	2.98	2.65	82	48	641	0.46	101	60	0.36
14	3.38	2.51	99	70	700	0.48	120	75	0.36
15	3.34	2.98	93	63	645	0.46	106	106	0.35
mean	3.16	2.78	96	66	664	0.48	139	87	0.38
sd	0.20	0.20	13	17	92	0.03	57	19	0.03

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

APPENDIX III (continued)

INDIVIDUAL AND GROUP MEAN BLOOD CHEMICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 15 mg/kg/day

SEX: FEMALE

Animal number	UREA (mg/dl)	GLUCOSE (mg/dl)	TOT. PROT (g/dl)	ALBUMIN (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)	Ca++ (mmol/l)
16	35	166	7.79	4.42	1.31	145	5.55	98	2.45
17	32	131	6.90	3.91	1.31	144	5.25	99	2.55
18	35	149	7.60	4.36	1.35	145	5.73	97	2.87
19	32	143	7.59	4.36	1.35	141	5.23	100	2.91
20	35	154	7.72	4.37	1.30	145	5.30	100	2.89
mean	34	149	7.52	4.28	1.32	144	5.41	99	2.73
sd	2	13	0.36	0.21	0.02	2	0.22	1	0.22

Animal number	P (mmol/l)	GLOBULIN (g/dl)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	CREAT (mg/dl)	TRI (mg/dl)	Chol (mg/dl)	BiLi (mg/dl)
16	2.80	3.37	92	59	437	0.59	90	105	0.32
17	2.89	2.99	94	62	406	0.59	68	87	0.38
18	2.80	3.24	85	54	391	0.67	114	100	0.40
19	2.72	3.23	81	52	356	0.62	81	120	0.34
20	2.64	3.35	86	61	736	0.62	129	123	0.36
mean	2.77	3.24	88	58	465	0.62	96	107	0.36
sd	0.09	0.15	5	4	154	0.03	25	15	0.03

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I I I (continued)

INDIVIDUAL AND GROUP MEAN BLOOD CHEMICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 150 mg/kg/day

SEX: MALE

Animal number	UREA (mg/dl)	GLUCOSE (mg/dl)	TOT.PROT (g/dl)	ALBUMIN (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)	Ca++ (mmol/l)
21	26	123	6.30	3.48	1.23	153	5.37	95	2.69
22	32	128	6.54	3.49	1.14	151	5.80	99	2.42
23	31	140	6.99	3.66	1.10	141	5.51	98	2.22
24	30	177	6.92	3.86	1.26	151	4.77	97	2.77
25	31	150	7.10	3.73	1.11	145	5.32	99	2.93
mean	30	144	6.77	3.64	1.17	148	5.35	98	2.61
sd	2	21	0.34	0.16	0.07	5	0.38	2	0.28

Animal number	P (mmol/l)	GLOBULIN (g/dl)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	CREAT (mg/dl)	TRI (mg/dl)	Chol (mg/dl)	Billi (mg/dl)
21	2.96	2.82	100	75	685	0.53	95	95	0.35
22	2.74	3.05	96	69	871	0.49	80	66	0.38
23	2.95	3.33	88	64	504	0.50	160	100	0.20
24	2.98	3.06	88	75	658	0.48	190	110	0.42
25	3.34	3.37	91	70	580	0.56	111	93	0.39
mean	2.99	3.13	93	71	660	0.51	127	93	0.35
sd	0.22	0.23	5	5	138	0.03	46	16	0.09

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I I I (continued)

INDIVIDUAL AND GROUP MEAN BLOOD CHEMICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 150 mg/kg/day

SEX: FEMALE

Animal number	UREA (mg/dl)	GLUCOSE (mg/dl)	TOT. PROT (g/dl)	ALBUMIN (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)	Ca++ (mmol/l)
26	33	197	7.12	4.03	1.30	154	5.30	95	2.81
27	37	163	7.25	3.76	1.08	146	5.15	100	2.83
28	25	141	7.01	3.95	1.29	145	5.27	99	2.45
29	35	148	7.51	4.11	1.21	148	5.21	98	2.76
30	29	156	7.36	4.28	1.39	147	4.62	98	2.73
mean	32	161	7.25	4.03	1.25	148	5.11	98	2.72
sd	5	22	0.20	0.19	0.12	4	0.28	2	0.15

Animal number	P (mmol/l)	GLOBULIN (g/dl)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	CREAT (mg/dl)	TRI (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
26	3.16	3.09	76	48	299	0.65	68	127	0.33
27	2.81	3.49	95	52	355	0.58	73	73	0.38
28	2.52	3.06	89	82	366	0.46	64	98	0.36
29	2.71	3.40	99	49	440	0.59	92	103	0.38
30	2.41	3.08	96	63	360	0.59	87	99	0.35
mean	2.72	3.22	91	59	364	0.57	77	100	0.36
sd	0.29	0.20	9	14	50	0.07	12	19	0.02

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I I I (continued)

INDIVIDUAL AND GROUP MEAN BLOOD CHEMICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 650 mg/kg/day

SEX: MALE

Animal number	UREA (mg/dl)	GLUCOSE (mg/dl)	TOT. PROT (g/dl)	ALBUMIN (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)	Ca++ (mmol/l)
31	22	151	7.01	3.64	1.08	154	4.75	99	2.78
32	32	142	6.52	3.40	1.09	151	5.26	97	2.60
33	27	141	7.28	3.72	1.04	149	4.89	97	2.56
34	28	136	7.60	3.84	1.02	155	5.37	96	2.80
35	35	147	7.24	3.67	1.03	150	5.49	98	2.35
mean	29	143	7.13	3.65	1.05	152	5.15	97	2.62
sd	5	6	0.40	0.16	0.03	3	0.32	1	0.18

Animal number	P (mmol/l)	GLOBULIN (g/dl)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	CREAT (mg/dl)	TRI (mg/dl)	Chol (mg/dl)	Billi (mg/dl)
31	2.60	3.37	98	63	405	0.47	154	106	0.44
32	2.62	3.12	110	66	400	0.61	128	111	0.38
33	2.61	3.56	105	82	535	0.46	179	123	0.41
34	2.96	3.76	107	79	481	0.58	123	130	0.45
35	2.56	3.57	105	64	396	0.52	83	110	0.49
mean	2.67	3.48	105	71	443	0.53	133	116	0.43
sd	0.16	0.24	4	9	62	0.07	36	10	0.04

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I I I (continued)

INDIVIDUAL AND GROUP MEAN BLOOD CHEMICAL VALUES AND
STANDARD DEVIATIONS (SD)

DOSE LEVEL: 650 mg/kg/day

SEX: FEMALE

Animal number	UREA (mg/dl)	GLUCOSE (mg/dl)	TOT.PROT (g/dl)	ALBUMIN (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)	Ca++ (mmol/l)
36	31	144	7.39	3.94	1.14	150	5.23	99	2.79
37	36	143	6.41	3.44	1.16	141	5.71	95	2.84
38	32	139	6.95	3.63	1.09	151	5.40	101	2.75
39	35	140	7.50	3.93	1.10	143	5.30	100	2.85
40	30	149	7.03	3.70	1.11	148	5.57	99	2.81
mean	33	143	7.06	3.73	1.12	147	5.44	99	2.81
sd	3	4	0.43	0.21	0.03	4	0.20	2	0.04

Animal number	P (mmol/l)	GLOBULIN (g/dl)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	CREAT (mg/dl)	TRI (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
36	2.66	3.45	100	59	371	0.56	96	133	0.39
37	3.94	2.97	156	98	300	0.47	69	59	0.35
38	2.87	3.32	105	87	317	0.54	129	66	0.40
39	2.87	3.57	109	69	481	0.63	112	126	0.35
40	2.77	3.33	102	72	307	0.57	80	132	0.33
mean	3.02	3.33	114	77	355	0.55	97	103	0.36
sd	0.52	0.22	24	15	76	0.06	24	37	0.03

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
A P P E N D I X I V
 INDIVIDUAL AND GROUP MEAN ORGAN WEIGHTS WITH CORRESPONDING
 RELATIVE ORGAN WEIGHTS (% OF BODYWEIGHT) AND STANDARD
 DEVIATIONS (SD)

DOSE LEVEL: 0 (Control)
 SEX: MALE

Animal number	bodywt(g) at necropsy	ORGAN WEIGHT (g)								
		adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
1	375	0.0707	1.9403	4.1460	1.2941	2.6078	13.8644	0.0162	0.6660	0.6101
2	345	0.0491	1.8730	4.3898	1.1494	2.4546	12.9696	0.0102	0.6790	0.4251
3	333	0.0582	1.6726	3.8010	1.2108	2.2592	12.9323	-	0.6747	0.4532
4	368	0.0543	2.0071	4.2528	1.2080	2.8078	17.3875	0.0092	0.7445	0.6556
5	354	0.0556	1.7954	3.9074	1.2645	2.6242	15.4435	0.0122	0.8076	0.5410
mean	355	0.0576	1.8577	4.0994	1.2254	2.5507	14.5195	0.0119	0.7144	0.5370
sd	17	0.0080	0.1299	0.2429	0.0560	0.2055	1.8993	0.0031	0.0608	0.0987

	RELATIVE ORGAN WEIGHT (%)									
	adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus	
1	0.0189	0.5174	1.1056	0.3451	0.6954	3.6972	0.0043	0.1776	0.1627	
2	0.0142	0.5429	1.2724	0.3332	0.7115	3.7593	0.0030	0.1968	0.1232	
3	0.0175	0.5023	1.1414	0.3636	0.6784	3.8836	-	0.2026	0.1361	
4	0.0148	0.5454	1.1557	0.3283	0.7630	4.7249	0.0025	0.2023	0.1782	
5	0.0157	0.5072	1.1038	0.3572	0.7413	4.3626	0.0034	0.2281	0.1528	
mean	0.0162	0.5230	1.1558	0.3455	0.7179	4.0855	0.0033	0.2015	0.1506	
sd	0.0019	0.0201	0.0690	0.0151	0.0342	0.4426	0.0008	0.0181	0.0216	

- organ not weighed due to technician's error

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I V (continued)

INDIVIDUAL AND GROUP MEAN ORGAN WEIGHTS WITH CORRESPONDING
RELATIVE ORGAN WEIGHTS (% OF BODYWEIGHT) AND STANDARD
DEVIATIONS (SD)

DOSE LEVEL: 0 (Control)

SEX: FEMALE

Animal number	bodywt(g) at necropsy	ORGAN WEIGHT (g)								
		adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
6	241	0.0836	1.8129	0.1146	0.9425	2.0233	8.9671	0.0101	0.6507	0.5119
7	202	0.0757	1.8751	0.1108	0.8438	1.5636	7.7747	0.0115	0.5540	0.4927
8	236	0.0839	1.7655	0.1011	0.8640	1.6182	8.6992	0.0138	0.6780	0.6522
9	222	0.0613	1.7599	0.1281	0.8131	1.7205	8.1794	0.0163	0.5321	0.5161
10	243	0.0759	1.8197	0.1491	0.8358	1.7130	9.7994	0.0136	0.6203	0.5706
mean	229	0.0761	1.8066	0.1207	0.8598	1.7277	8.6840	0.0131	0.6070	0.5487
sd	17	0.0092	0.0468	0.0186	0.0497	0.1779	0.7756	0.0024	0.0623	0.0647

	RELATIVE ORGAN WEIGHT (%)									
	adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus	
6	0.0347	0.7522	0.0476	0.3911	0.8395	3.7208	0.0042	0.2700	0.2124	
7	0.0375	0.9283	0.0549	0.4177	0.7741	3.8489	0.0057	0.2743	0.2439	
8	0.0356	0.7481	0.0428	0.3661	0.6857	3.6861	0.0058	0.2873	0.2764	
9	0.0276	0.7927	0.0577	0.3663	0.7750	3.6844	0.0073	0.2397	0.2325	
10	0.0312	0.7488	0.0614	0.3440	0.7049	4.0327	0.0056	0.2553	0.2348	
mean	0.0333	0.7940	0.0529	0.3770	0.7558	3.7946	0.0057	0.2653	0.2400	
sd	0.0039	0.0773	0.0076	0.0282	0.0617	0.1492	0.0011	0.0183	0.0234	

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

APPENDIX IV (continued)

INDIVIDUAL AND GROUP MEAN ORGAN WEIGHTS WITH CORRESPONDING RELATIVE ORGAN WEIGHTS (% OF BODYWEIGHT) AND STANDARD DEVIATIONS (SD)

DOSE LEVEL: 15 mg/kg/day

SEX: MALE

Animal number	bodywt(g) at necropsy	ORGAN WEIGHT (g)								
		adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
11	380	0.0535	1.9562	4.3598	1.3893	2.4359	16.1893	0.0119	0.8216	0.7545
12	327	0.0489	1.9299	3.8546	1.0759	2.4190	11.9490	0.0145	0.6312	0.5637
13	324	0.0633	1.8831	4.5505	1.0943	2.4843	12.7536	0.0102	0.6534	0.5725
14	338	0.0569	1.9398	4.0792	1.1268	2.4742	12.5324	0.0096	0.7888	0.5624
15	331	0.0479	2.0914	4.1452	1.0411	2.5234	13.7817	0.0074	0.7282	0.4624
mean	340	0.0541	1.9601	4.1979	1.1455	2.4674	13.4412	0.0107	0.7246	0.5831
sd	23	0.0063	0.0783	0.2670	0.1398	0.0412	1.6728	0.0027	0.0827	0.1059

	RELATIVE ORGAN WEIGHT (%)									
	adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus	
11	0.0141	0.5148	1.1473	0.3656	0.6410	4.2603	0.0031	0.2162	0.1986	
12	0.0150	0.5902	1.1788	0.3290	0.7398	3.6541	0.0044	0.1930	0.1724	
13	0.0195	0.5812	1.4045	0.3377	0.7668	3.9363	0.0031	0.2017	0.1767	
14	0.0168	0.5739	1.2069	0.3334	0.7320	3.7078	0.0028	0.2334	0.1664	
15	0.0145	0.6318	1.2523	0.3145	0.7624	4.1637	0.0022	0.2200	0.1397	
mean	0.0160	0.5784	1.2380	0.3361	0.7284	3.9444	0.0032	0.2129	0.1708	
sd	0.0023	0.0420	0.1008	0.0187	0.0510	0.2684	0.0008	0.0158	0.0211	

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

APPENDIX IV (continued)

INDIVIDUAL AND GROUP MEAN ORGAN WEIGHTS WITH CORRESPONDING RELATIVE ORGAN WEIGHTS (% OF BODYWEIGHT) AND STANDARD DEVIATIONS (SD)

DOSE LEVEL: 15 mg/kg/day

SEX: FEMALE

Animal number	bodywt(g) at necropsy	ORGAN WEIGHT (g)								
		adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
16	236	0.0709	1.7877	0.1223	0.8014	1.6869	8.0274	0.0153	0.4724	0.4146
17	233	0.0569	1.7785	0.1061	0.7090	1.5765	7.9482	0.0116	0.4302	0.5690
18	235	0.0814	1.8469	0.1531	0.8885	1.6813	9.1131	0.0146	0.4975	0.7096
19	207	0.0459	1.7466	0.1037	0.7686	1.4966	7.2040	0.0115	0.3855	0.3637
20	227	0.0711	1.8142	0.1155	0.7912	1.5651	7.2506	0.0202	0.3836	0.5583
mean	228	0.0652	1.7948	0.1201	0.7917	1.6013	7.9087	0.0146	0.4338	0.5230
sd	12	0.0139	0.0378	0.0199	0.0649	0.0816	0.7739	0.0036	0.0510	0.1372

	RELATIVE ORGAN WEIGHT (%)									
	adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus	
16	0.0300	0.7575	0.0518	0.3396	0.7148	3.4014	0.0065	0.2002	0.1757	
17	0.0244	0.7633	0.0455	0.3043	0.6766	3.4112	0.0050	0.1846	0.2442	
18	0.0346	0.7859	0.0651	0.3781	0.7154	3.8779	0.0062	0.2117	0.3020	
19	0.0222	0.8438	0.0501	0.3713	0.7230	3.4802	0.0056	0.1862	0.1757	
20	0.0313	0.7992	0.0509	0.3485	0.6895	3.1941	0.0089	0.1690	0.2459	
mean	0.0285	0.7899	0.0527	0.3484	0.7039	3.4730	0.0064	0.1903	0.2287	
sd	0.0051	0.0345	0.0074	0.0293	0.0198	0.2504	0.0015	0.0163	0.0537	

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I V (continued)

INDIVIDUAL AND GROUP MEAN ORGAN WEIGHTS WITH CORRESPONDING
RELATIVE ORGAN WEIGHTS (% OF BODYWEIGHT) AND STANDARD
DEVIATIONS (SD)

DOSE LEVEL: 150 mg/kg/day

SEX: MALE

Animal number	bodywt(g)		ORGAN WEIGHT (g)							
	at necropsy	adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
21	365	0.0513	2.0328	4.7040	1.2969	2.5860	15.4676	0.0086	0.7511	0.4824
22	318	0.0547	1.9375	3.6779	1.0307	2.2888	12.8052	0.0094	0.7071	0.5806
23	327	0.0385	1.8920	3.9309	1.1806	2.1372	13.9965	0.0098	0.6048	0.8146
24	368	0.0459	1.8836	3.6860	1.3996	2.7063	15.8828	0.0081	0.6116	0.5544
25	389	0.0547	1.9447	3.8521	1.2684	2.8653	17.7734	0.0153	0.9141	0.8657
mean	353	0.0490	1.9381	3.9702	1.2352	2.5167	15.1851	0.0102	0.7177	0.6595
sd	30	0.0069	0.0594	0.4243	0.1385	0.2993	1.8936	0.0029	0.1263	0.1697

	RELATIVE ORGAN WEIGHT (%)									
	adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus	
21	0.0141	0.5569	1.2888	0.3553	0.7085	4.2377	0.0024	0.2058	0.1322	
22	0.0172	0.6093	1.1566	0.3241	0.7197	4.0268	0.0030	0.2224	0.1826	
23	0.0118	0.5786	1.2021	0.3610	0.6536	4.2803	0.0030	0.1850	0.2491	
24	0.0125	0.5118	1.0016	0.3803	0.7354	4.3160	0.0022	0.1662	0.1507	
25	0.0141	0.4999	0.9903	0.3261	0.7366	4.5690	0.0039	0.2350	0.2225	
mean	0.0139	0.5513	1.1279	0.3494	0.7108	4.2859	0.0029	0.2029	0.1874	
sd	0.0021	0.0456	0.1295	0.0240	0.0340	0.1940	0.0007	0.0278	0.0486	

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I V (continued)

INDIVIDUAL AND GROUP MEAN ORGAN WEIGHTS WITH CORRESPONDING
RELATIVE ORGAN WEIGHTS (% OF BODYWEIGHT) AND STANDARD
DEVIATIONS (SD)

DOSE LEVEL: 150 mg/kg/day

SEX: FEMALE

Animal number	bodywt(g) at necropsy	ORGAN WEIGHT (g)								
		adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
26	256	0.0848	1.8754	0.1533	0.9267	1.6694	11.5374	0.0132	0.5643	0.5944
27	221	0.0732	1.7894	0.1266	0.7805	1.7069	9.1363	0.0120	0.5456	0.7205
28	218	0.0773	1.8467	0.1189	0.8172	1.9268	9.4005	0.0101	0.4977	0.4347
29	213	0.0786	1.8160	0.1275	0.7887	1.5549	8.4565	0.0120	0.5035	0.4631
30	228	0.0761	1.6393	0.1224	0.8869	1.5989	8.7422	0.0131	0.5545	0.5571
mean	227	0.0780	1.7934	0.1297	0.8400	1.6914	9.4546	0.0121	0.5331	0.5540
sd	17	0.0043	0.0920	0.0136	0.0640	0.1443	1.2192	0.0012	0.0305	0.1139

	RELATIVE ORGAN WEIGHT (%)								
	adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
26	0.0331	0.7326	0.0599	0.3620	0.6521	4.5068	0.0052	0.2204	0.2322
27	0.0331	0.8097	0.0573	0.3532	0.7724	4.1341	0.0054	0.2469	0.3260
28	0.0355	0.8471	0.0545	0.3749	0.8839	4.3122	0.0046	0.2283	0.1994
29	0.0369	0.8526	0.0599	0.3703	0.7300	3.9702	0.0056	0.2364	0.2174
30	0.0334	0.7190	0.0537	0.3890	0.7013	3.8343	0.0057	0.2432	0.2443
mean	0.0344	0.7922	0.0571	0.3699	0.7479	4.1515	0.0053	0.2350	0.2439
sd	0.0017	0.0630	0.0029	0.0135	0.0877	0.2673	0.0004	0.0108	0.0489

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I V (continued)

INDIVIDUAL AND GROUP MEAN ORGAN WEIGHTS WITH CORRESPONDING
RELATIVE ORGAN WEIGHTS (% OF BODYWEIGHT) AND STANDARD
DEVIATIONS (SD)

DOSE LEVEL: 650 mg/kg/day

SEX: MALE

Animal number	bodywt(g) at necropsy	ORGAN WEIGHT (g)								
		adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
31	308	0.0424	1.9097	3.8638	1.4251	2.1153	17.4566	0.0083	0.5550	0.5271
32	305	0.0464	1.8490	1.3630	1.1521	2.1803	15.0003	0.0078	0.6613	0.5594
33	340	0.0560	1.9272	4.4656	1.3457	3.0454	20.4122	0.0105	0.5681	0.5276
34	356	0.0484	1.8929	3.9207	1.2582	2.5987	19.7404	0.0090	0.7236	0.5379
35	316	0.0561	1.9195	4.2703	1.1216	2.4324	19.1344	0.0093	0.6968	0.5522
mean	325	0.0499	1.8997	3.5767	1.2605	2.4744	18.3488	0.0090	0.6410	0.5408
sd	22	0.0060	0.0311	1.2622	0.1279	0.3737	2.1691	0.0010	0.0759	0.0145

	RELATIVE ORGAN WEIGHT (%)								
	adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
31	0.0138	0.6200	1.2545	0.4627	0.6868	5.6677	0.0027	0.1802	0.1711
32	0.0152	0.6062	0.4469	0.3777	0.7149	4.9181	0.0026	0.2168	0.1834
33	0.0165	0.5668	1.3134	0.3958	0.8957	6.0036	0.0031	0.1671	0.1552
34	0.0136	0.5317	1.1013	0.3534	0.7300	5.5451	0.0025	0.2033	0.1511
35	0.0178	0.6074	1.3514	0.3549	0.7697	6.0552	0.0029	0.2205	0.1747
mean	0.0154	0.5864	1.0935	0.3889	0.7594	5.6379	0.0028	0.1976	0.1671
sd	0.0018	0.0365	0.3738	0.0448	0.0819	0.4570	0.0002	0.0232	0.0136

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I V (continued)

INDIVIDUAL AND GROUP MEAN ORGAN WEIGHTS WITH CORRESPONDING
RELATIVE ORGAN WEIGHTS (% OF BODYWEIGHT) AND STANDARD
DEVIATIONS (SD)

DOSE LEVEL: 650 mg/kg/day

SEX: FEMALE

Animal number	bodywt(g) at necropsy	ORGAN WEIGHT (g)								
		adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus
36	217	0.0738	1.7978	0.1271	0.7957	1.6163	12.5646	0.0047	0.6228	0.4681
37	205	0.0643	1.6050	0.0800	0.8072	1.5509	12.9237	0.0107	0.5530	0.6070
38	201	-	1.7004	0.1193	0.7855	1.6864	12.3219	0.0121	0.4120	0.3589
39	225	0.0700	1.8198	0.1348	0.8115	1.7746	11.9755	0.0127	0.4578	0.4517
40	244	0.0723	1.7897	0.1323	0.9472	2.0444	15.6250	0.0145	0.8458	0.5001
mean	218	0.0701	1.7425	0.1187	0.8294	1.7345	13.0821	0.0109	0.5783	0.4772
sd	17	0.0042	0.0894	0.0224	0.0666	0.1921	1.4630	0.0037	0.1706	0.0896

	RELATIVE ORGAN WEIGHT (%)									
	adrenals	brain	gonads	heart	kidneys	liver	pituitary	spleen	thymus	
36	0.0340	0.8285	0.0586	0.3667	0.7448	5.7901	0.0022	0.2870	0.2157	
37	0.0314	0.7829	0.0390	0.3938	0.7565	6.3042	0.0052	0.2698	0.2961	
38	-	0.8460	0.0594	0.3908	0.8390	6.1303	0.0060	0.2050	0.1786	
39	0.0311	0.8088	0.0599	0.3607	0.7887	5.3224	0.0056	0.2035	0.2008	
40	0.0296	0.7335	0.0542	0.3882	0.8379	6.4037	0.0059	0.3466	0.2050	
mean	0.0315	0.7999	0.0542	0.3800	0.7934	5.9902	0.0050	0.2624	0.2192	
sd	0.0018	0.0439	0.0088	0.0152	0.0441	0.4402	0.0016	0.0603	0.0450	

- organ not weighed due to technician's error

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY
IN THE RAT

A P P E N D I X V
INDIVIDUAL POST MORTEM EXAMINATION FINDINGS

GROUP NUMBER AND SEX	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER	DAY OF NECROPSY	MACROSCOPIC OBSERVATIONS
1 M	0 (Control)	1	29	No abnormalities detected
		2	29	No abnormalities detected
		3	29	No abnormalities detected
		4	29	No abnormalities detected
		5	29	No abnormalities detected
1 F	0 (Control)	6	29	No abnormalities detected
		7	29	No abnormalities detected
		8	29	No abnormalities detected
		9	29	No abnormalities detected
		10	29	No abnormalities detected

M = male

F = female

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY
IN THE RAT

A P P E N D I X V (continued)

INDIVIDUAL POST MORTEM EXAMINATION FINDINGS

GROUP NUMBER AND SEX	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER	DAY OF NECROPSY	MACROSCOPIC OBSERVATIONS
2 M	15	11	29	No abnormalities detected
		12	29	No abnormalities detected
		13	29	No abnormalities detected
		14	29	No abnormalities detected
		15	29	No abnormalities detected
2 F	15	16	29	No abnormalities detected
		17	29	No abnormalities detected
		18	29	No abnormalities detected
		19	29	No abnormalities detected
		20	29	No abnormalities detected

M - male F - female

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY
IN THE RAT

A P P E N D I X V (continued)
INDIVIDUAL POST MORTEM EXAMINATION FINDINGS

GROUP NUMBER AND SEX	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER	DAY OF NECROPSY	MACROSCOPIC OBSERVATIONS
3 M	150	21	29	No abnormalities detected
		22	29	No abnormalities detected
		23	29	No abnormalities detected
		24	29	No abnormalities detected
		25	29	No abnormalities detected
3 F	150	26	29	No abnormalities detected
		27	29	No abnormalities detected
		28	29	No abnormalities detected
		29	29	No abnormalities detected
		30	29	No abnormalities detected

M = male

F = female

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY
IN THE RAT

A P P E N D I X V (continued)
INDIVIDUAL POST MORTEM EXAMINATION FINDINGS

GROUP NUMBER AND SEX	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER	DAY OF NECROPSY	MACROSCOPIC OBSERVATIONS
4 M	650	31	29	No abnormalities detected
		32	29	Testes: small
		33	29	Liver: patchy pallor
		34	29	Liver: patchy pallor
		35	29	Non-glandular stomach: two small, raised white nodules
4 F	650	36	29	No abnormalities detected
		37	29	No abnormalities detected
		38	29	No abnormalities detected
		39	29	Kidneys: hydronephrosis
		40	29	No abnormalities detected

M - male F - female

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X V I

INDIVIDUAL HISTOPATHOLOGICAL FINDINGS

The histopathology report following concerns these routinely processed organs

Adrenals	Ovaries
Heart	Spleen
Kidneys	Testes
Liver	

The following specified conditions have been routinely evaluated:

Heart	Focal myocarditis	graded 1
Kidneys	Groups of basophilic tubules	graded 1
	Globular accumulations of eosinophilic material	graded 1
	Hydronephrosis	graded 1
Liver	Mononuclear cell foci	graded 1
	Focal hepatocyte necrosis	graded 1
	Generalised hepatocyte enlargement	graded 1
	Periportal hepatocyte vacuolation	graded 1
	Single cell hepatocyte necrosis	graded 6
	Multifocal erythrophagocytosis	graded 6
Testes	Atrophy gonad 1	graded 1
	Atrophy gonad 2	graded 1

The grading systems used are as follows:

Grading Level
System

1	1	(minimal)
	2	(slight)
	3	(moderate)
	4	(marked)
	5	(severe)
6	1	[present]

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X V I (continued)

INDIVIDUAL HISTOPATHOLOGICAL FINDINGS

0(Control) Male

Animal	Tissue	Observation
1		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Liver	Mononuclear cell foci (minimal)
2		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Liver	Mononuclear cell foci (minimal)
3		Mode of death : Terminal kill
	Liver	Mononuclear cell foci (minimal)
4		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Kidneys	Globular accumulations of eosinophilic material (slight)
	Liver	Mononuclear cell foci (minimal)
5		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Kidneys	Groups of basophilic tubules (minimal)
		Globular accumulations of eosinophilic material (minimal)

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X V I (continued)

INDIVIDUAL HISTOPATHOLOGICAL FINDINGS

0(Control) Female

Animal	Tissue	Observation
6		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Kidneys	Groups of basophilic tubules (minimal)
	Liver	Mononuclear cell foci (minimal)
7		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Liver	Mononuclear cell foci (minimal)
8		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Liver	Mononuclear cell foci (minimal)
9		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Liver	Mononuclear cell foci (minimal)
10		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Liver	Mononuclear cell foci (minimal)

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X V I (continued)

INDIVIDUAL HISTOPATHOLOGICAL FINDINGS

15mg/kg/day Male

Animal	Tissue	Observation
11	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)
12	Liver	Mode of death : Terminal kill Mononuclear cell foci (slight) Focal hepatocyte necrosis (minimal) Generalised hepatocyte enlargement (minimal)
13	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)
14	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)
15	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X VI (continued)

INDIVIDUAL HISTOPATHOLOGICAL FINDINGS

15mg/kg/day Female

Animal	Tissue	Observation
16	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)
17	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)
18	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)
19	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)
20	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X VI (continued)

INDIVIDUAL HISTOPATHOLOGICAL FINDINGS

150mg/kg/day Male

Animal	Tissue	Observation
21	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)
22	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal) Generalised hepatocyte enlargement (minimal)
23	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal) Generalised hepatocyte enlargement (slight)
24	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal) Focal hepatocyte necrosis (minimal) Periportal hepatocyte vacuolation (minimal)
25	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X V I (continued)

INDIVIDUAL HISTOPATHOLOGICAL FINDINGS

150mg/kg/day Female

Animal	Tissue	Observation
26	Liver	Mode of death : Terminal kill Mononuclear cell foci (slight)
27	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)
28	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)
29	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)
30	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal)

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X V i (continued)

INDIVIDUAL HISTOPATHOLOGICAL FINDINGS

650mg/kg/day Male

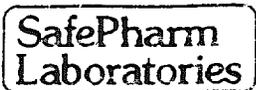
Animal	Tissue	Observation
31		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Kidneys	Groups of basophilic tubules (minimal)
		Globular accumulations of eosinophilic material (minimal)
	Liver	Mononuclear cell foci (minimal)
		Generalised hepatocyte enlargement (minimal)
32		Mode of death : Terminal kill
	Adrenals	one section examined
	Kidneys	Groups of basophilic tubules (minimal)
	Liver	Mononuclear cell foci (minimal)
		Generalised hepatocyte enlargement (minimal)
	Testes	Atrophy gonad 1 (severe)
		Atrophy gonad 2 (severe)
33		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Kidneys	Groups of basophilic tubules (minimal)
		Globular accumulations of eosinophilic material (minimal)
	Liver	Mononuclear cell foci (slight)
		Generalised hepatocyte enlargement (slight)
		Periportal hepatocyte vacuolation (slight)
34		Mode of death : Terminal kill
	Heart	Focal myocarditis (minimal)
	Kidneys	Globular accumulations of eosinophilic material (minimal)
	Liver	Mononuclear cell foci (slight)
		Generalised hepatocyte enlargement (slight)
35		Mode of death : Terminal kill
	Kidneys	Globular accumulations of eosinophilic material (slight)
	Liver	Mononuclear cell foci (minimal)
		Generalised hepatocyte enlargement (slight)
		Periportal hepatocyte vacuolation (minimal)
	Forestomach	Ectopic glandular tissue

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VI (continued)
INDIVIDUAL HISTOPATHOLOGICAL FINDINGS

650mg/kg/day Female

Animal	Tissue	Observation
36	Heart Liver	Mode of death : Terminal kill Focal myocarditis (minimal) Mononuclear cell foci (minimal) Generalised hepatocyte enlargement (minimal)
37	Liver	Mode of death : Terminal kill Mononuclear cell foci (minimal) Generalised hepatocyte enlargement (minimal) Periportal hepatocyte vacuolation (slight)
38	Heart Liver	Mode of death : Terminal kill Focal myocarditis (minimal) Mononuclear cell foci (minimal) Generalised hepatocyte enlargement (minimal)
39	Heart Kidneys Liver	Mode of death : Terminal kill Focal myocarditis (minimal) Hydronephrosis (slight) One kidney Mononuclear cell foci (minimal) Generalised hepatocyte enlargement (minimal) Periportal hepatocyte vacuolation (slight)
40	Heart Kidneys Liver	Mode of death : Terminal kill Focal myocarditis (minimal) Groups of basophilic tubules (minimal) Periportal hepatocyte vacuolation (slight) Single cell hepatocyte necrosis Multifocal erythrophagocytosis

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII

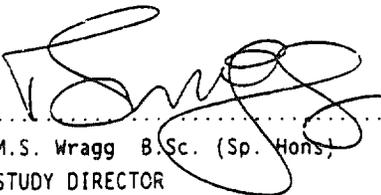


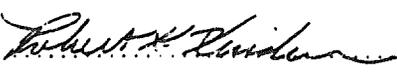
PROTOCOL

PROJECT NO: 826/009

P.O. Box 45 Derby DE1 2BT, England
Tel: (01332) 792896 Fax: (01332) 799018

TEST MATERIAL	:	Allyl Sucrose
STUDY TYPE	:	Twenty-Eight Day Sub-Acute Oral (Gavage) Toxicity Study in the Rat
PROPOSED START DATE	:	May 1995
PROPOSED COMPLETION DATE	:	June 1995
TARGET (DRAFT) REPORT DATE	:	September 1995
SPONSOR	:	BF Goodrich Company Specialty Polymers & Chemicals Division 9911 Brecksville Road Cleveland OHIO 44141-3247 UNITED STATES OF AMERICA

AUTHORISED BY:  DATE : 27/03/95
M.S. Wragg B.Sc. (Sp. Hons)
STUDY DIRECTOR

AUTHORISED FOR SPONSOR BY:  DATE : April 14, 1995

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

TWENTY EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

1. INTRODUCTION AND OBJECTIVES

This protocol details a study designed to comply with the requirements for notification of a new chemical substance in the E.C. and follows the testing method described in Annex V of Council Directive 67/548/EEC (Method B7) and the OECD guidelines for Testing of Chemicals No. 407 "Repeated Dose Oral Toxicity - Rodent 28 day or 14 day study".

The purpose of this study is to establish the effects of repeated oral exposure of rats to the test material over a period of up to twenty-eight days. The results of the study are believed to be of value in predicting the toxicity of the test material to man and can identify the organs and tissues which may be injured by exposure, can enable detection of possible cumulative toxicity and the estimation of the "No Observed Effect Level" (NOEL).

This study will be conducted in accordance with internationally accepted principles of Good Laboratory Practice and Safepharm Standard Operating Procedures.

2. ANIMALS

Specification: Sprague Dawley CD rats obtained from Charles River (U.K.) Limited, Manston, Kent. At the start of the main study animals will be aged five to eight weeks. The weight variation will not exceed $\pm 20\%$ of the mean weight for either sex.

Justification: Preferred species of choice as historically used for safety evaluation studies and specified by appropriate regulatory authorities.

3. ANIMAL HUSBANDRY

Environment: Temperature: 19 - 25°C
 Humidity : 40 - 75%

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

5. TEST MATERIAL AND EXPERIMENTAL PREPARATION

- Identification: Supplied by the study sponsor with details of purity stability and hazardous properties if known.
- Storage: Room temperature unless otherwise specified by the sponsor.
- Preparation: The test material will be dissolved or suspended in a suitable vehicle weekly (subject to confirmation of stability). Wherever possible, an aqueous formulation will be used, followed by consideration of formulation in vegetable oil (e.g. Arachis oil), then other specified vehicles. The method of preparation will be documented in the study records.
- Analysis: Details of identification of the test material will be supplied by the study sponsor. The test material formulations will be analysed for concentration, stability and, if applicable, homogeneity by Safepharm Analytical Laboratory. Analysis will be charged at extra cost to the sponsor.

6. STUDY DESIGN

- Administration: Once daily, by gavage, using a stainless steel dosing cannula attached to a graduated syringe for up to twenty-eight consecutive days. Dosing will be performed at a similar time each day wherever possible.
- Dose Groups: Four dose groups (control, low, intermediate and high) each comprising ten animals (five male and five female) will be used. Dose levels will be based on available toxicity data following a range-finding study (Appendix I), up to a maximum

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

6. STUDY DESIGN (contd)

Dose Groups: dose of 1000 mg/kg/day. The dose levels to be used
(contd) in the study will be documented as a protocol
addendum together with the treatment volume.

The control group will be handled in an identical
manner to the test animals and will be dosed with
the vehicle alone.

7. OBSERVATIONS

Morbidity/Mortality Inspection: Twice daily, early and late during the working
period.

Clinical Observations: Immediately before dosing and one hour after
dosing. An additional observation made five hours
after dosing during the normal working week (not at
weekends or on public holidays). All observations
will be recorded.

Bodyweights: Individual bodyweights recorded on Day 0 (the day
before the start of dosing) and at weekly intervals
thereafter.

Food Consumption: Dietary intake recorded weekly for each cage group.
Weekly food efficiency (bodyweight gain/food
intake) will be calculated.

Water Consumption: Monitored daily by visual inspection of water
bottles. Measurement will be initiated if a
treatment-related effect is suspected, at the
discretion of the Study Director.

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

7. OBSERVATIONS (contd)

Post Mortem Studies: Carried out on animals dying or killed in extremis and on all animals killed by intravenous sodium pentobarbitone followed by exsanguination at termination.

i) Gross Examination: Full external and internal examination of all animals.

ii) Organ Weights: Adrenals Brain Gonads Heart
 Kidneys Liver Pituitary Spleen

Carried out on all survivors at termination.

iii) Histopathology: Samples of the following tissues will be preserved from all animals in buffered 10% formalin.

Adrenals	Muscle (skeletal)
Aorta (thoracic)	Oesophagus
Bone & bone marrow (femur including stifle joint)	Ovaries
Bone & bone marrow (sternum)	Pancreas
Brain	Pituitary
Caecum	Prostate
Colon	Rectum
Duodenum	Salivary glands
Eyes	Sciatic nerve
Gross lesions	Seminal vesicles
Heart	Skin (hind limb)
Ileum	Spleen
Jejunum	Stomach
Kidneys	Testes
Liver	Thymus
Lungs	Thyroid/parathyroid
Lymph nodes (cervical and mesenteric)	Trachea
	Urinary bladder
	Uterus

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

7. OBSERVATIONS (contd)

iii) Histopathology: Initially the following tissues from:
(contd)

- a) all animals that die or are killed in extremis during the study.
- b) all animals in the control and high dose groups (Groups 1 and 4).

will be routinely processed to paraffin wax, sectioned, stained with haematoxylin and eosin and examined microscopically.

Adrenals	Liver
Gross lesions	Spleen
Heart	Target organs
Kidneys	Testes

Where treatment-related lesions are seen in the high dose group, these examinations will be extended to intermediate and low dose animals following consultation with, and at extra cost to, the sponsor.

8. EVALUATION OF DATA

All data will be summarised in tabular form and analysed statistically, where appropriate, to assess the significance of intergroup differences.

Haematological, blood chemical and organ weight data will be assessed using one way analysis of variance incorporating "F- max" test for homogeneity of variance. Organ weights will be expressed as a percentage of final bodyweight. Log or square root transformations may be used to stabilise the variances or a non-parametric test such as Kruskal-Wallis one way analysis of variance and Mann-Whitney "U" test may be used in preference.

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

9. QUALITY ASSURANCE

Study procedures will be inspected and the final report will be audited by Safepharm Laboratories Quality Assurance Unit, in accordance with QAU Standard Operating Procedures.

10. PROTOCOL CHANGES

Amendments to this protocol will be made only by completion of an amendment to protocol form issued by Safepharm Laboratories Limited and authorised by the study sponsor.

Minor deviations will be documented as a file note and detailed in the final report.

11. REPORT

The sponsor will be informed immediately of all relevant findings.

A full report containing a description of the test material, detailed description of the experimental procedures, summary of the observations together with tabulated group mean and individual animal data, discussion and interpretation of the results will be presented. A draft report will be sent to the sponsor for review and comments before issue of the final report.

12. ARCHIVE

A copy of the final report together with all laboratory raw data, computer print-outs, tissue blocks, slides, wet tissues and a sample of the test material will be kept in Safepharm Central Archives, London Road, Shardlow, Derbyshire for a period of ten years. At the end of this period the sponsor will be contacted and a decision made either to dispose of the data or to despatch the data direct to the sponsor.

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
A P P E N D I X V I I (continued)

A P P E N D I X I

FOURTEEN-DAY ORAL RANGE-FINDING STUDY IN THE RAT

1. INTRODUCTION

The purpose of this study is to provide information as the basis for selection of dose levels for a twenty-eight day oral toxicity study in rats.

Animals will be observed with attention to clinical observations, bodyweight and gross pathology, for any adverse effects resulting from toxicity of the test material.

This study will be conducted in accordance with internationally accepted principles of Good Laboratory Practice and Safepharm Standard Operating Procedures.

2. ANIMALS

As described for main study.

3. ANIMAL HUSBANDRY

Environment: As described for main study.

Housing: Groups of three by sex in polypropylene cages with stainless steel lids and grid bases, suspended over trays containing absorbent paper.

Diet and Water: As described for main study.

4. PRE-TEST PROCEDURES

As described for main study, except that the animals will not be allocated to dose groups using total randomisation procedure.

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

APPENDIX I (contd)

5. TEST MATERIAL AND EXPERIMENTAL PREPARATION

- Identification: Supplied by study sponsor, with details of purity, stability and hazardous properties if known.
- Storage: Room temperature unless otherwise specified by sponsor.
- Preparation: The test material will be dissolved or suspended in a suitable vehicle. Wherever possible an aqueous formulation will be used, followed by consideration of formulation in vegetable oil (eg. Arachis oil), then other specified vehicles. Fresh formulations will be prepared each day and dosed within three hours of preparation. The method of preparation will be documented in the study records.
- Analysis: Details of identification of the test material will be supplied by the study sponsor. No analysis of the formulations will be performed during the study but preliminary analytical work may be carried out to prepare for the main study.

6. STUDY DESIGN

- Administration: Once daily, by gavage, for up to fourteen consecutive days.
- Dose Groups: A number of dose groups will be used sufficient for the purpose of the study, each comprising six animals (three male and three female). Dose levels will be selected on the basis of available toxicity data and may be adjusted during the course of the study so that distinct evidence of toxicity is observed in at least one dose level, up to a maximum dose of 1000 mg/kg/day. Control animals will receive vehicle only.

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
A P P E N D I X V I I (continued)

A P P E N D I X I (contd)

7. OBSERVATIONS

- Morbidity/Mortality Inspection: Twice daily, early and late during the working period.
- Clinical Observations: Immediately before dosing and one hour after dosing. All observations will be recorded.
- Bodyweights: Individual bodyweights recorded at twice-weekly intervals.
- Post Mortem Studies: Carried out on animals dying or killed in extremis during the study and on all animals killed by cervical dislocation at termination.
- i) Gross Examination: Full external and internal examination of all animals.
- ii) Histopathology: At the discretion of the Study Director, samples of tissues showing macroscopic abnormalities may be preserved in buffered 10% formalin for possible future histopathological examination.

8. EVALUATION OF DATA

All data will be summarised in tabular form and used to provide the basis for a selection of dose levels for the main study.

9. QUALITY ASSURANCE

The routine inspection of short term toxicity studies is carried out as a continuous process designed to encompass all major phases of each study type once per month.

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
A P P E N D I X V I I (continued)

A P P E N D I X I (contd)

10. PROTOCOL CHANGES

Amendments to this protocol will be made only by completion of an amendment to protocol form issued by Safepharm Laboratories Limited and authorised by the study sponsor.

Minor deviations will be documented as a file note and detailed in the final report.

11. REPORT

Soon after completion of the study a brief summary of the results together with the recommended dose levels for use in the main sub-acute study will be sent to the sponsor. A detailed report containing a summary of the observations together with tabulated group mean and individual will be presented as an appendix to the main study report. Separate reports for range-finding studies will only be issued at the request of the sponsor.

12. ARCHIVE

A copy of the final report together with all laboratory raw data, computer print-outs, slides, wet tissues and a sample of the test material will be kept in Safepharm Central Archives, London Road, Shardlow, Derbyshire, U.K., for a period of ten years. At the end of this period the sponsor will be contacted and a decision made either to dispose of the data or to despatch the data direct to the sponsor.

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

RESPONSIBLE PERSONNEL

PROJECT NUMBER 826/009

ISSUE NUMBER 1

TITLE	NAME	REPLACEMENT DATE
STUDY DIRECTOR	M.S. WRAGG	
DEPUTY STUDY DIRECTOR	L.J. COLES	
STUDY PATHOLOGIST	P.N. BROOKS	

STUDY SUPERVISION

STUDY SUPERVISOR	O. THOMAS
ANIMAL HUSBANDRY	K. FORD
ANIMAL HEALTH	P.W. HIGHTON
CLINICAL PATHOLOGY	P. THOMPSON
HISTOLOGY	EXPERIMENTAL PATHOLOGY SERVICES U.K. LTD
FORMULATION	L. COLES
CHEMICAL ANALYSIS	A. BARTLETT
DATA PROCESSING	M. COOK

QUALITY ASSURANCE

QUALITY ASSURANCE MANAGER	J.R. PATEMAN
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PROPOSED DATES

ANIMALS ON SITE 23/05/95	STUDY TERMINATION 28/06/95
FIRST TREATMENT 31/05/95	DRAFT REPORT SEPTEMBER 1995

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

SAFEPHARM LABORATORIES LIMITED
PROTOCOL ADDENDUM

ADDENDUM NUMBER: ONE

PROTOCOL TITLE: TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

TEST MATERIAL: ALLYL SUCROSE

PROJECT NUMBER: 826/009

SPONSOR: BF GOODRICH COMPANY
SPECIALTY POLYMERS & CHEMICALS DIVISION
9911 BRECKSVILLE ROAD
CLEVELAND
OHIO 44141-3247
UNITED STATES OF AMERICA

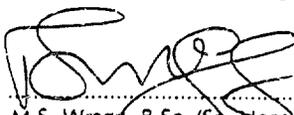
Page 4:

6. Study Design: On the basis of a range-finding study the dose levels have been selected as follows:

GROUP	DOSE LEVEL	TREATMENT	DURATION OF	NECROPSY
	mg/kg/day	VOLUME (ml/kg)	TREATMENT	DAY
1. Control	0*	2	28 Days	29
2. Low	15	2	28 Days	29
3. Intermediate	150	2	28 Days	29
4. High	650	2	28 Days	29

* Control animals treated with vehicle only (Polyethylene glycol 400)

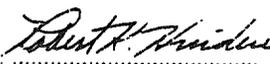
PREPARED FOR SAFEPHARM
LABORATORIES LIMITED BY:



M.S. Wragg, B.Sc. (Sp. Honor)
STUDY DIRECTOR

DATE: 12/08/95

AUTHORISED FOR SPONSOR BY:



DATE: 8-25-95

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

SAFEPHARM LABORATORIES LIMITED

AMENDMENT TO PROTOCOL

AMENDMENT NUMBER: ONE

PROTOCOL TITLE: TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY
IN THE RAT

TEST MATERIAL: ALLYL SUCROSE

PROJECT NUMBER: 826/009

SPONSOR: BF GOODRICH COMPANY
SPECIALTY POLYMERS AND CHEMICALS DIVISION
9911 BRECKSVILLE ROAD
CLEVELAND
OHIO 44141-3247
UNITED STATES OF AMERICA

AMENDMENT

The following amendments were requested by the study sponsor:

Page 6, Section 7, OBSERVATIONS, Laboratory Investigations

- i) Haematology - The following will be added to the list of parameters:
Activated partial thromboplastin time
Reticulocyte count
- ii) Blood Chemistry - The following will be added to the list of parameters:
Cholesterol
Triglycerides
Globin (calculated)

Page 7, Section 7, OBSERVATIONS, Post Mortem Studies

- i) Organ weights - Thymus will be added to the list of organs to be weighed at termination.
- ii) Histopathology - Delete this section and replace with the following:
The following organs, tissues or samples thereof will be preserved from all animals in buffered 10% formalin:

Adrenals	Ovaries
Aorta (thoracic)	Pancreas
Bone & bone marrow (femur including stifle joint and articular surface)	Pituitary
	Prostate

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

-2-

Bone & bone marrow (sternum)	Rectum
Brain	Salivary glands (submaxillary)
Caecum	Sciatic nerve
Colon	Seminal vesicles
Duodenum	Skin (hind limb)
Eyes with optic nerve	Spinal cord (cervical, midthoracic and lumbar)
Cross sections	Spleen
Heart	Stomach
Intestine	Testes with epididymides
Jejunum	Thymus
Kidneys	Thyroid/parathyroid
Liver	Tongue
Lungs (including bronchi)*	Trachea
Lymph nodes (cervical and mesenteric)	Urinary bladder
Mammary gland	Uterus
Muscle (skeletal, thigh)	Vagina
Oesophagus	

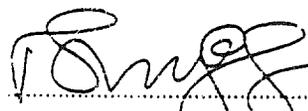
* Lungs will be perfused to normal inspiratory volume with buffered 10% formalin prior to fixation

Page 8, Section 7, OBSERVATIONS, Post Mortem Studies, Histopathology

Ovaries will be added to the list of tissues to be processed to paraffin wax, stained with haematoxylin and eosin and examined microscopically.

The cost of this additional work will be £1600.

PREPARED FOR SAFEPHARM
LABORATORIES LIMITED BY:


M.S. Wragg B.Sc. (So. Hons)
STUDY DIRECTOR

DATE: 04/05/95

AUTHORISED FOR SPONSOR BY:

 DATE: 10/5/95
10 May 1995

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VII (continued)

SAFEPHARM LABORATORIES LIMITED

AMENDMENT TO PROTOCOL

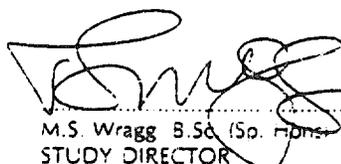
ADDENDUM NUMBER: TWO
PROTOCOL TITLE: TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
TEST MATERIAL: ALLYL SUCROSE
PROJECT NUMBER: 826/009
SPONSOR: 3F GOODRICH COMPANY
SPECIALTY POLYMERS & CHEMICALS DIVISION
9911 BRECKSVILLE ROAD
CLEVELAND
OHIO 44141-3247
UNITED STATES OF AMERICA

AMENDMENT

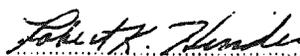
Due to a delay in the Data Sharing Enquiry, the study was rescheduled. Revised study dates are as follows:

Animals on site	15/08/95
First treatment	24/08/95
Study termination	21/09/95
Draft report	December 1995

PREPARED FOR SAFEPHARM
LABORATORIES LIMITED BY:


M.S. Wragg B.Sc. (Sp. Hon.)
STUDY DIRECTOR

DATE: 17/08/95

AUTHORISED FOR SPONSOR BY:  DATE: 8-25-95

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VIII



SPECIAL QUALITY CONTROL OF
SMALL ANIMAL DIETS

CERTIFICATE OF ANALYSIS

PRODUCT: R/M 1(B) SQC

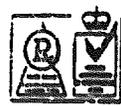
BATCH NO: 1901

PREMIX BATCH NO: 380/901

DATE OF MANUFACTURE: 30-MAY-95

Nutrient	Found Analysis	Contaminant	Found Analysis	Unit of Detection
Moisture	9.7 %	Fluoride	21 mg/kg	1.0 mg/kg
Crude Fat	2.3 %	Nitrate as NaNO ₃	27 mg/kg	1.0 mg/kg
Crude Protein	14.6 %	Nitrite as NaNO ₂	1.0 mg/kg	1.0 mg/kg
Crude Fibre	4.2 %	Lead	0.85 mg/kg	0.25 mg/kg
Ash	4.9 %	Arsenic	Non Detected	0.2 mg/kg
Calcium	0.71 %	Cadmium	0.12 mg/kg	0.05 mg/kg
Phosphorus	0.57 %	Mercury	Non Detected	0.01 mg/kg
Sodium	0.20 %	Selenium	0.08 mg/kg	0.05 mg/kg
Chloride	0.33 %			
Potassium	0.74 %			
Magnesium	0.15 %	Total Aflatoxins	Non Detected	1 mcg/kg each of B1, B2, G1, G2
Iron	113 mg/kg	Total P.C.B	Non Detected	10.0 mcg/kg
Copper	8 mg/kg	Total D.D.T	Non Detected	1.0 mcg/kg
Manganese	58 mg/kg	Dieldrin	Non Detected	1.0 mcg/kg
Zinc	39 mg/kg	Lindane	Non Detected	1.0 mcg/kg
		Heptachlor	Non Detected	1.0 mcg/kg
		Malathion	174 mcg/kg	20.0 mcg/kg
Vitamin A	4.0 IU/g	Total Viable Organisms x 1000	Non Detected	per gram 1000/g
Vitamin E	49 mg/kg			
Vitamin C	mg/kg	Mesophilic Spores x 100	Non Detected	per gram 100/g
		Salmonellae Species	Non Detected	Absent in 20 gram
		Presumptive E.coli	Non Detected	Absent in 20 gram
		E.coli Type 1	Non Detected	Absent in 20 gram
		Fungal Units	Non Detected	Absent in 20 gram
		Antibiotic Activity	Non Detected	

Signed R S F. Gould
Dated 22/6/95



ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX VIII (continued)



Special Quality Control
Certificate of Analysis

PRODUCT: RMI (E) SQC

BATCH NO: 1716

PREMIX BATCH NO: 902/945/946

DATE OF MANUFACTURE: 04-JUL-95

Nutrient	Found Analysis	Contaminant	Found Analysis	Limit of Detection
Moisture	8.1	Fluoride	20 mg/kg	1.0 mg/kg
Crude Fat	3.1	Nitrate as NaNO3	25 mg/kg	1.0 mg/kg
Crude Protein	16.1	Nitrite as NaNO2	Non Detected	1.0 mg/kg
Crude Fibre	4.3	Lead	0.45 mg/kg	0.25 mg/kg
Ash	5.6	Arsenic	Non Detected	0.2 mg/kg
Calcium	1.02	Cadmium	0.10 mg/kg	0.05 mg/kg
Phosphorus	0.62	Mercury	Non Detected	0.01 mg/kg
Sodium	0.23	Selenium	0.15 mg/kg	0.05 mg/kg
Chloride	0.37			
Potassium	0.76			
Magnesium	0.18	Total Aflatoxins	Non Detected mcg/kg	1 mcg/kg each of B1, B2, G1, G2
Iron	134 mg/kg			
Copper	10 mg/kg	Total P.C.B	Non Detected mcg/kg	10.0 mcg/kg
Manganese	74 mg/kg	Total D.D.T	Non Detected mcg/kg	1.0 mcg/kg
Zinc	57 mg/kg	Dieldrin	Non Detected mcg/kg	1.0 mcg/kg
		Lindane	9 mcg/kg	1.0 mcg/kg
		Heptachlor	Non Detected mcg/kg	1.0 mcg/kg
		Malathion	97 mcg/kg	20.0 mcg/kg
Vitamin A	6.3 IU/g	Total Viable Organisms x 1000	Non Detected per gram	1000/g
Vitamin E	49 mg/kg			
Vitamin C	mg/kg	Mesophilic Spores x 100	Non Detected per gram	100/g
		Salmonellae Species	Non Detected per gram	Absent in 20 gram
		Presumptive E. coli	Non Detected per gram	Absent in 20 gram
		E. coli Type 1	Non Detected per gram	Absent in 20 gram
		Fungal Units	250 per gram	Absent in 20 gram
		Antibiotic Activity	Non Detected	

Signed RSF/ed
Dated 27/7/95



ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX IX
CHEMICAL ANALYSIS OF TEST MATERIAL FORMULATIONS,
METHODS AND RESULTS

1. METHOD OF ANALYSIS

1.1 Introduction

The Allyl Sucrose concentration in the test samples was determined by high performance liquid chromatography (HPLC) using an external standard technique.

1.2 Samples

The test material formulations were diluted with acetonitrile to give a final theoretical test material concentration of approximately 1 mg/ml.

1.3 Standards

Standard solutions were prepared in acetonitrile at a nominal concentration of 1 mg/ml.

1.4 Procedure

The standard and sample solutions were analysed by HPLC using the following conditions:

Column : C₁₈ Hypersil (150 x 4.6 mm i.d.)
Mobile phase gradient elution : Eluent A - acetonitrile:distilled water (70:30)
Eluant B - acetonitrile

<u>Time</u> (mins)	<u>% B</u>
0	0
4	0
7	20
15	20
25	100

Wavelength : 200 nm
Flow rate : 2 ml/min
Injection volume : 25 μ l

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X I X (continued)

CHEMICAL ANALYSIS OF TEST MATERIAL FORMULATIONS,
METHODS AND RESULTS

1.5 Homogeneity Determinations

It was apparent by visual inspection that the test material formulations were homogeneous.

1.6 Stability Determinations

The test material formulations were sampled and analysed initially and then after storage at approximately 4°C in the dark for ten days.

1.7 Verification of Test Material Formulation Concentrations

The test material formulations were sampled and analysed within three days of preparation.

2. RESULTS

2.1 Stability of Test Material Formulations

NOMINAL CONCENTRATION (mg/ml)	CONCENTRATION FOUND INITIALLY (mg/ml)	CONCENTRATION FOUND AFTER STORAGE FOR 10 DAYS	
		(mg/ml)	(expressed as % of initial)
7.5	7.12	7.27	102
75	71.4	75.1	105
325	354	358	101

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY
IN THE RAT

APPENDIX IX (continued)
CHEMICAL ANALYSIS OF TEST MATERIAL FORMULATIONS,
METHODS AND RESULTS

2.2 Verification of Concentration of Weekly Test Material Formulations

WEEK NUMBER	NOMINAL CONCENTRATION (mg/ml)	CONCENTRATION FOUND (mg/ml)	CONCENTRATION EXPRESSED AS % OF NOMINAL
1	0	N.D.	-
	7.5	7.55	101
	75	80.3	107
	325	354	109
2	0	N.D.	-
	7.5	7.34	98
	75	76.1	101
	325	333	103
3	0	N.D.	-
	7.5	7.48	100
	75	80.9	108
	325	358	110
4	0	N.D.	-
	7.5	7.92	106
	75	82.4	110
	325	338	104

N.D. = none detected

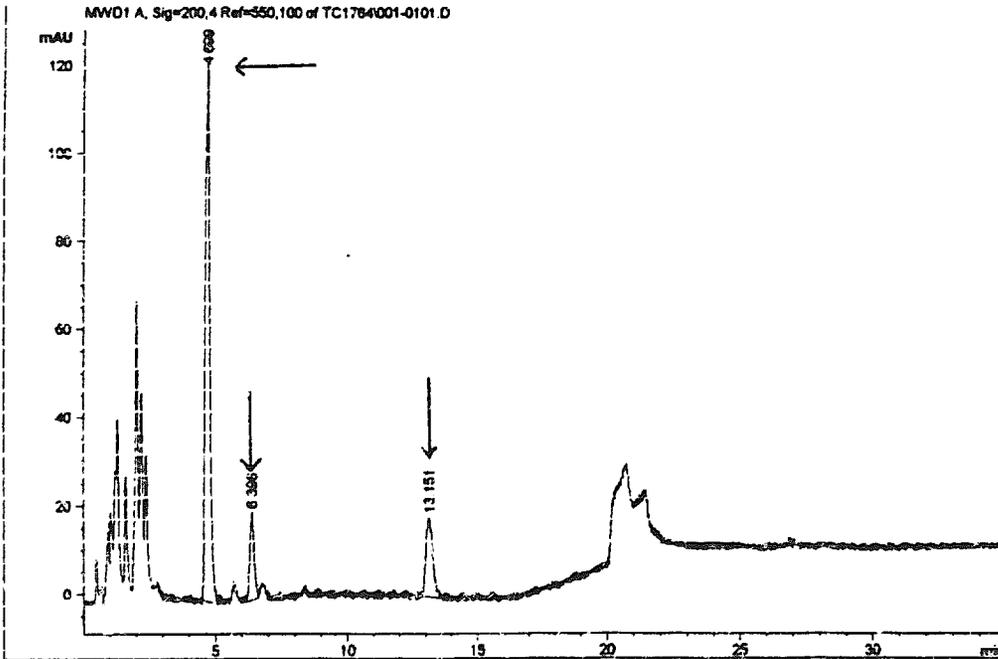
- = not applicable

2.3 Test Material Formulation Concentrations Over the Dosing Period

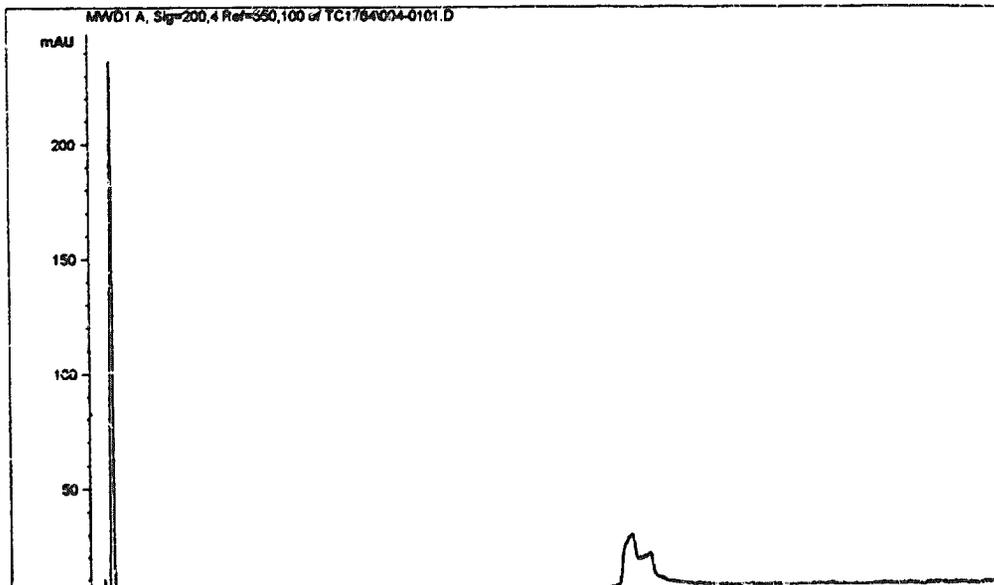
NOMINAL CONCENTRATION (mg/ml)	MEAN CONCENTRATION FOUND (mg/ml)	MEAN CONCENTRATION EXPRESSED AS % OF NOMINAL	RANGE (mg/ml)	RANGE EXPRESSED AS % OF NOMINAL
7.5	7.57	101	7.34 - 7.92	98 - 106
75	79.9	107	76.1 - 82.4	101 - 110
325	346	106	333 - 358	103 - 110

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX IX (continued)
CHEMICAL ANALYSIS OF TEST MATERIAL FORMULATIONS,
METHODS AND RESULTS

Examples of the typical chromatography generated during this study are given below:
Standard Solution



Control Formulation



0145

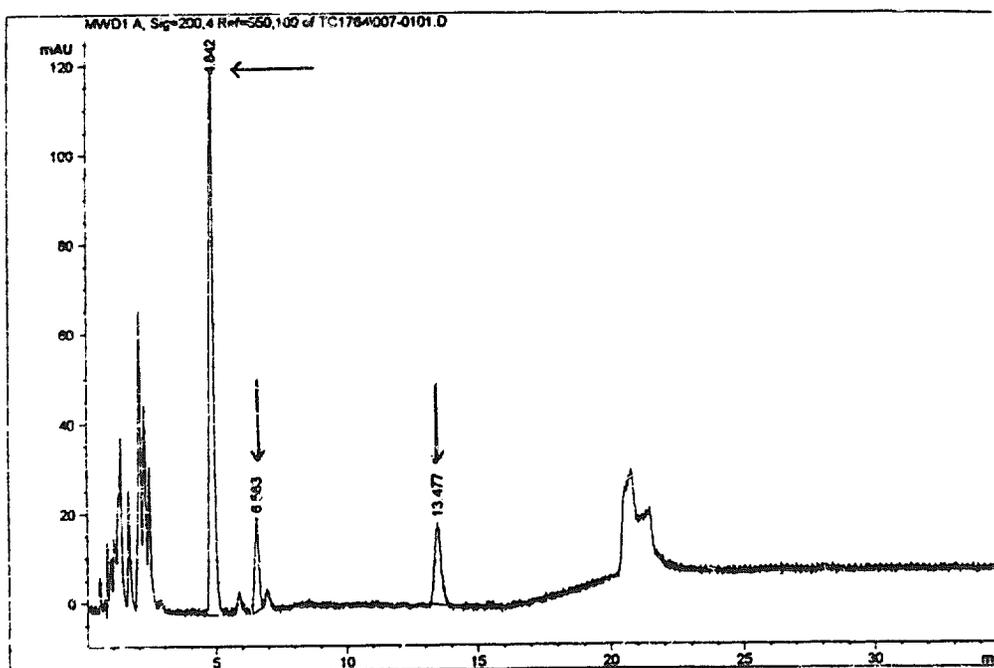
ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X (continued)

CHEMICAL ANALYSIS OF TEST MATERIAL FORMULATIONS,
METHODS AND RESULTS

Examples of the typical chromatography generated during this study are given below:

Test Material Formulation



ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X X
LABORATORY METHODS

HAEMATOLOGY	UNITS
Parameters measured on potassium EDTA - treated blood:	
Haemoglobin (Hb) - estimated by measurement of cyanmethaemoglobin using the Coulter S-plus IV system	g/dl
Total erythrocyte count (RBC) - estimated by the Coulter S-plus IV system	$10^{12}/l$
Haematocrit (Hct) - derived from MCV and RBC by the Coulter S-plus IV system	%
Mean Corpuscular Haemoglobin (MCH) - derived from the Hb concentration and RBC by the Coulter S-plus IV system	pg
Mean Corpuscular Volume (MCV) - estimated by the Coulter S-plus IV system	fl
Mean Corpuscular Haemoglobin Concentration (MCHC) - derived from Hb concentration, RBC and MCV by the Coulter S-plus IV system	g/dl
Total leucocyte count (WBC) - estimated by the Coulter S-plus IV system	$10^9/l$
Differential leucocyte count - determined by visual assessment of May-Gruenwald/Giemsa stained blood film:	
Neutrophils (Neut)	
Lymphocytes (Lymph)	
Monocytes (Mono)	
Eosinophils (Eos)	
Basophils (Bas)	
	$10^9/l$

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X X (continued)

LABORATORY METHODS

	UNITS
Platelet count (PLT) - estimated by the Coulter S-plus IV system	$10^9/l$

Reticulocyte count - determined by visual assessment of Brilliant Cresyl Blue stained blood film	%
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Parameters measured on citrate-treated blood:

Clotting (prothrombin) time (CT) - estimated by 'Hepato Quick' Boehringer Mannheim reagent kit no. 126535 and Bio Mérieux Option 4 coagulometer	secs
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Activated partial thromboplastin time (APTT) - estimated by Boehringer Mannheim kit no. 126551 and Bio Mérieux Option 4 coagulometer	secs
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BLOOD CHEMISTRY

Parameters measured on lithium heparin treated blood:

Urea - estimated by Boehringer Mannheim reagent kit no. 816361 and Hitachi 705 auto-analyser	mg/dl
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Glucose - estimated by Boehringer Mannheim reagent kit no. 704067 and Hitachi 705 auto-analyser	mg/dl
---	-------

Total protein (Tot. Prot) - estimated by Boehringer Mannheim reagent kit no. 1553828 and Hitachi 705 auto-analyser	g/dl
--	------

Albumin - estimated by Boehringer Mannheim reagent kit no. 704008 and Hitachi 705 auto-analyser	g/dl
---	------

Globulin - calculated from measured total protein and albumin	g/dl
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Albumin/Globulin (A/G) ratio = $\frac{\text{albumin}}{\text{globulin}}$

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X X (continued)

LABORATORY METHODS

	UNITS
Sodium (Na ⁺) - estimated by Technicon Chromolyte Sodium reagent product No. T01-3248 and Hitachi 705 auto-analyser	mmol/l
Potassium (K ⁺) - estimated by Technicon Chromolyte Potassium reagent product No. T01-2820-04 and Hitachi 705 auto-analyser	mmol/l
Chloride (Cl ⁻) - estimated using a Mercury thiocyanate/Ferric nitrate reagent and Hitachi 705 auto-analyser	mmol/l
Calcium (Ca ⁺⁺) - estimated by Boehringer Mannheim reagent kit No. 1125605 and Hitachi 705 auto-analyser	mmol/l
Inorganic phosphorus (P) - estimated by Boehringer Mannheim reagent kit No. 836281 and Hitachi 705 auto-analyser	mmol/l
Aspartate aminotransferase (ASAT) - estimated by Boehringer Mannheim reagent kit No. 620068 and Hitachi 705 auto-analyser	IU/l
Alanine aminotransferase (ALAT) - estimated by Boehringer Mannheim reagent kit No. 620076 and Hitachi 705 auto-analyser	IU/l
Alkaline phosphatase (AP) - estimated by Boehringer Mannheim reagent kit No. 798312 and Hitachi 705 auto-analyser	IU/l
Creatinine (Creat) - estimated by Boehringer Mannheim reagent kit No. 704130 and Hitachi 705 auto-analyser	mg/dl
Total bilirubin (Bili) - estimated by Boehringer Mannheim reagent kit No. 977179 and Hitachi 705 auto-analyser	mg/dl

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X X (continued)

LABORATORY METHODS

	UNITS
Total cholesterol (Chol) - estimated by Boehringer Mannheim reagent kit No. 704121 and Hitachi 705 auto-analyser	mg/dl
Triglycerides (Tri) - estimated by Boehringer Mannheim reagent kit No. 704113 and Hitachi 705 auto-analyser	mg/dl

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

APPENDIX XI



THE DEPARTMENT OF HEALTH OF THE GOVERNMENT
OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE
IN ACCORDANCE WITH DIRECTIVE 88/320 EEC

LABORATORY

*SafePharm Laboratories Limited
P O Box No 45
Derby
DE1 2BT*

DATE OF INSPECTION

31 January 1994

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of the UK GLP Compliance Programme.

At the time of the inspection no deviations were found of sufficient magnitude to affect the validity of studies performed at these facilities.

A handwritten signature in black ink, appearing to read 'D. F. Moore'.

16/3/94.

D. F. Moore
Director
UK GLP Monitoring Unit

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

APPENDIX XII

NORMAL RANGES FOR HAEMATOLOGICAL AND BLOOD CHEMICAL VALUES
IN THE SPRAGUE-DAWLEY CD RAT

SUPPLIER: Charles River (UK) Limited

APPROXIMATE AGE: Ten to twelve weeks

(Values in brackets indicate group
mean and standard deviation
respectively)

UPDATED: December 1994

HAEMATOLOGY	MALE		FEMALE	
	RANGE *	NO. OF ANIMALS	RANGE *	NO. OF ANIMALS
Hb (g/dl)	13.6 - 16.3 (15.0) (0.7)	274	13.2 - 15.9 (14.5) (0.7)	275
RBC (10 ¹² /l)	6.8 - 8.4 (7.6) (0.4)	274	6.7 - 8.2 (7.5) (0.4)	275
Hct (%)	39.5 - 47.0 (43.3) (1.9)	274	37.3 - 45.6 (41.5) (2.1)	275
MCH (pg)	18.2 - 21.2 (19.7) (0.8)	274	18.0 - 21.0 (19.5) (0.7)	275
MCV (fl)	53.2 - 60.6 (56.9) (1.9)	274	52.0 - 59.4 (55.7) (1.8)	275
MCHC (g/dl)	32.7 - 36.5 (34.6) (0.9)	274	32.9 - 37.2 (35.0) (1.1)	275
WBC (10 ⁹ /l)	8.5 - 20.4 (14.4) (3.0)	274	4.5 - 15.9 (10.2) (2.8)	275
Neut (10 ⁹ /l)	0.00 - 5.39 (2.55) (1.42)	274	0.00 - 4.47 (1.74) (1.37)	275

* Range = mean \pm 2 standard deviations

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

A P P E N D I X X I I (continued)

NORMAL RANGES FOR HAEMATOLOGICAL AND BLOOD CHEMICAL VALUES
IN THE SPRAGUE-DAWLEY CD RAT

SUPPLIER: Charles River (UK) Limited

APPROXIMATE AGE: Ten to twelve weeks

(Values in brackets indicate group mean and standard deviation respectively)

UPDATED: December 1994

HAEMATOLOGY	MALE		FEMALE	
	RANGE *	NO. OF ANIMALS	RANGE *	NO. OF ANIMALS
Lymph ($10^9/l$)	6.25 - 17.14 (11.70) (2.72)	274	3.63 - 12.90 (8.27) (2.32)	275
Mono ($10^9/l$)	0.00 - 0.34 (0.09) (0.13)	274	0.00 - 0.23 (0.05) (0.09)	275
Eos ($10^9/l$)	0.00 - 0.34 (0.08) (0.13)	274	0.00 - 0.31 (0.10) (0.11)	275
Bas ($10^9/l$)	0.00 (0.00) (0.00)	274	0.00 (0.00) (0.00)	275
CT (secs)	23 - 32 (27) (2)	274	23 - 32 (27) (2)	275
PLT ($10^9/l$)	816 - 1399 (1107) (146)	274	816 - 1394 (1105) (145)	275
Retic (%)	0 - 7 (3) (2)	81	0 - 5 (3) (1)	80

* Range = mean \pm 2 standard deviations

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

APPENDIX XII (continued)

NORMAL RANGES FOR HAEMATOLOGICAL AND BLOOD CHEMICAL VALUES
IN THE SPRAGUE-DAWLEY CD RAT

SUPPLIER: Charles River (UK) Limited

APPROXIMATE AGE: Ten to twelve weeks

(Values in brackets indicate group
mean and standard deviation
respectively)

UPDATED: December 1994

BLOOD CHEMISTRY	MALE		FEMALE	
	RANGE *	NO. OF ANIMALS	RANGE *	NO. OF ANIMALS
Urea (mg/dl)	14 - 43 (29) (7)	274	19 - 51 (35) (8)	275
Glucose (mg/dl)	126 - 183 (155) (14)	274	121 - 185 (153) (16)	275
Tot. Protein (g/dl)	5.92 - 7.33 (6.63) (0.35)	274	6.06 - 7.70 (6.88) (0.41)	275
Albumin (g/dl)	3.43 - 4.35 (3.89) (0.23)	274	3.53 - 4.64 (4.08) (0.28)	275
A/G Ratio	1.04 - 1.85 (1.44) (0.20)	274	1.06 - 1.90 (1.48) (0.21)	275
Na+ (mmol/l)	129 - 153 (141) (6)	274	127 - 153 (140) (7)	275
K+ (mmol/l)	3.78 - 5.87 (4.82) (0.52)	274	3.52 - 6.03 (4.77) (0.63)	275
Cl- (mmol/l)	92 - 107 (100) (4)	274	93 - 110 (102) (4)	275
Ca++ (mmol/l)	2.36 - 2.96 (2.66) (0.15)	274	2.33 - 2.96 (2.64) (0.16)	275

* Range = mean \pm 2 standard deviations

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX XII (continued)
**NORMAL RANGES FOR HAEMATOLOGICAL AND BLOOD CHEMICAL VALUES
 IN THE SPRAGUE-DAWLEY CD RAT**

SUPPLIER: Charles River (UK) Limited
 (Values in brackets indicate group mean and standard deviation respectively)

APPROXIMATE AGE: Ten to twelve weeks
UPDATED: December 1994

BLOOD CHEMISTRY	MALE		FEMALE	
	RANGE *	NO. OF ANIMALS	RANGE *	NO. OF ANIMALS
P (mmol/l)	1.67 - 3.08 (2.37) (0.35)	274	1.14 - 2.54 (1.84) (0.35)	275
ASAT (IU/l)	66 - 122 (94) (14)	274	63 - 121 (92) (14)	275
ALAT (IU/l)	40 - 98 (69) (15)	274	33 - 80 (56) (12)	275
AP (IU/l)	364 - 995 (680) (158)	274	226 - 702 (464) (119)	275
Creat (mg/dl)	0.46 - 0.71 (0.58) (0.06)	274	0.49 - 0.82 (0.65) (0.08)	275
Bili (mg/dl)	0.09 - 0.68 (0.38) (0.15)	274	0.08 - 0.62 (0.35) (0.14)	275
CHOL (mg/dl)	38 - 105 (72) (17)	139	41 - 98 (70) (14)	140
TRI (mg/dl)	36 - 171 (103) (34)	139	12 - 90 (51) (19)	140

* Range = mean ± 2 standard deviations

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX XIII
 NORMAL RANGES FOR ABSOLUTE AND RELATIVE ORGAN WEIGHT VALUES
 IN THE SPRAGUE-DAWLEY CD RAT

SUPPLIER: Charles River (UK) Limited
 (Values in brackets indicate group
 mean and standard deviation
 respectively)

APPROXIMATE AGE: Ten to twelve weeks
UPDATED: December 1994

ABSOLUTE ORGAN WEIGHTS	MALE		FEMALE	
	RANGE (g) *	NO. OF ANIMALS	RANGE (g) *	NO. OF ANIMALS
Adrenals	0.0311 - 0.0678 (0.0494) (0.0092)	274	0.0435 - 0.0842 (0.0638) (0.0102)	275
Brain	1.7944 - 2.1953 (1.9949) (0.1002)	274	1.7225 - 2.0348 (1.8786) (0.0781)	275
Gonads	3.3516 - 5.1841 (4.2678) (0.4581)	274	0.0907 - 0.1728 (0.1317) (0.0205)	275
Heart	0.9434 - 1.7796 (1.3615) (0.2090)	274	0.7559 - 1.1370 (0.9465) (0.0953)	275
Kidneys	1.9470 - 2.9367 (2.4419) (0.2474)	274	1.4162 - 2.0165 (1.7164) (0.1501)	275
Liver	10.1516 - 17.6640 (13.9078) (1.8781)	274	6.6267 - 10.5761 (8.6014) (0.9873)	275
Pituitary	0.0050 - 0.0139 (0.0095) (0.0022)	264	0.0057 - 0.0161 (0.0109) (0.0026)	264
Spleen	0.5196 - 1.2116 (0.8656) (0.1730)	274	0.3860 - 0.8862 (0.6361) (0.1250)	275
Thymus	0.3594 - 0.9612 (0.6603) (0.1505)	20	0.4721 - 0.7640 (0.6180) (0.0730)	20

* Range = mean ± 2 standard deviations

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX XIII (continued)
**NORMAL RANGES FOR ABSOLUTE AND RELATIVE ORGAN WEIGHT VALUES
 IN THE SPRAGUE-DAWLEY CD RAT**

SUPPLIER: Charles River (UK) Limited
 (Values in brackets indicate group mean and standard deviation respectively)

APPROXIMATE AGE: Ten to twelve weeks
UPDATED: December 1994

RELATIVE ORGAN WEIGHTS	MALE		FEMALE	
	RANGE (%) *	NO. OF ANIMALS	RANGE (%) *	NO. OF ANIMALS
Adrenals	0.0086 - 0.0191 (0.0139) (0.0026)	274	0.0186 - 0.0354 (0.0270) (0.0042)	275
Brain	0.4581 - 0.6620 (0.5600) (0.0510)	274	0.6784 - 0.9164 (0.7974) (0.0595)	275
Gonads	0.9325 - 1.4719 (1.2022) (0.1348)	274	0.0408 - 0.0710 (0.0559) (0.0075)	275
Heart	0.2690 - 0.4924 (0.3807) (0.0559)	274	0.3271 - 0.4741 (0.4006) (0.0367)	275
Kidneys	0.5877 - 0.7760 (0.6818) (0.0471)	274	0.6248 - 0.8275 (0.7262) (0.0507)	275
Liver	3.2816 - 4.4571 (3.8693) (0.2939)	274	2.9851 - 4.2370 (3.6110) (0.3130)	275
Pituitary	0.0014 - 0.0039 (0.0027) (0.0006)	264	0.0025 - 0.0068 (0.0046) (0.0011)	264
Spleen	0.1696 - 0.3140 (0.2418) (0.0361)	274	0.1793 - 0.3570 (0.2682) (0.0444)	275
Thymus	0.1120 - 0.2644 (0.1882) (0.0381)	20	0.1707 - 0.3369 (0.2538) (0.0416)	20

* Range = mean ± 2 standard deviations

ALLYL SUCROSE : TWENTY-EIGHT DAY SUB-ACUTE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT
APPENDIX XIV



ALLYL SUCROSE

RAW MATERIAL CT-35

LOT NUMBER 43254

	SPECIFICATION	ACTUAL VALUE	METHOD
HEAT LOSS	2.0% MAX	0.30	SA-028
FUNCTIONALITY			SA-029
	F(5) =	18.6	
	F(6) =	29.0	
	F(7) =	43.0	
	F(8) = 7.0-11.0	9.4	

Billy J. Pyle

BILLY J. PYLE
CHIEF CHEMIST
CALVERT CITY, KY



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