

P A R T I I

**ALLYL SUCROSE:
FOURTEEN DAY ORAL (GAVAGE)
RANGE-FINDING TOXICITY STUDY
IN THE RAT**

**ALLYL SUCROSE:
FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING
TOXICITY STUDY IN THE RAT**

1. INTRODUCTION

The study was performed to establish the maximum tolerated dose level (up to 1000 mg/kg/day) of the test material, Allyl Sucrose, following repeated oral administration to the Sprague-Dawley CD strain rat, and to establish a low dose level that did not produce evidence of toxicity. This information was used to determine dose levels for use in a twenty-eight day oral toxicity study.

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.

2.2 Experimental Preparation

For the purpose of the study the test material was prepared as a solution in Polyethylene glycol 400. A fresh formulation was made each day and the animals were dosed within three hours of preparation.

The concentration and stability of the test material formulations were not determined analytically.

3. METHODS

3.1 Animals and Animal Husbandry

Fifteen male and fifteen female Sprague-Dawley CD strain rats were obtained from Charles River (UK) Limited, Manston, Kent. After an acclimatisation period of at least five days, animals were selected at random and given a unique number within the study by ear punching.

At the start of treatment the males weighed 128 to 239g and the females weighed 122 to 169g. The animals were housed in groups of three by sex in polypropylene grid-floor cages suspended over trays containing absorbent paper. Free access to mains drinking water and food (Rat and Mouse SQC Expanded Diet No.1, Special Diets Services Limited, Witham, Essex, UK) was allowed throughout 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 the 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 the nominal values were considered not to have affected the purpose or integrity of the study.

3.2 Procedure

Five groups, each of six rats (three males and three 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
5	650	2	325
4	1000	2	500

The test material was administered daily, for up to fourteen 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 ml/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 Days 4, 7 (or 8) and 11, as applicable.

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 hour after dosing. An additional examination was performed on Days 1 and 2 for animals dosed at 1000 mg/kg/day, due to the severe signs of toxicity observed. All observations were recorded.

3.3.2 Bodyweight

Individual bodyweights were recorded on Days 1, 4, 7 (or 8), 11 and 14 of the study, as applicable.

3.3.3 Necropsy

On completion of the dosing period, all surviving animals were killed by cervical dislocation and immediately subjected to an internal and external macroscopic examination. All animals found dead or killed *in extremis* during the study were also necropsied. No tissues were retained.

3.4 Evaluation of Data

Necropsy data, bodyweights and clinical observations were examined for any adverse effects resulting from treatment.

The data obtained was summarised in tabular form and used to provide the basis for selection of dose levels for the main study.

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

On Day 2, one male dosed at 1000 mg/kg/day was found dead prior to dosing and one female from the same treatment group was found dead one hour after dosing. Another, moribund, female was killed at the same time and the three remaining animals from this treatment group were killed *in extremis* at the end of the working day, due to the severe signs of toxicity observed. There were no deaths at the other dose levels during the study.

5.2 Clinical Observations

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

Animals dosed at 1000 mg/kg/day showed short-lived increased salivation immediately after dosing on Days 1 and 2 and all animals from this dose group showed hunched posture and pilo-erection by the end of Day 1. One male was found dead before treatment was administered on Day 2 but the other two males appeared normal in comparison with controls until after treatment when both animals developed severe clinical abnormalities including hunched posture, pilo-erection, tiptoe gait, decreased respiratory rate and occasional body tremors. Both males were killed *in extremis* at the end of the working day. In contrast to the males, females showed no recovery between Day 1 and Day 2, with hunched posture, pilo-erection and diuresis observed before treatment on Day 2. The health of these animals further deteriorated following treatment, with one female found dead approximately one hour after dosing and another showing severe signs of toxicity including dehydration and body tremors. This moribund animal was killed *in extremis* immediately. The remaining female developed tiptoe gait after dosing on Day 2 and was also dehydrated at the end of the working day. This animal was killed *in extremis* without further treatment.

Animals dosed at 650 mg/kg/day showed short-lived increased salivation before or immediately after dosing from Day 2 onwards. More prolonged increased

salivation was also occasionally observed at this dose level during the study. In addition, one female from this treatment group showed hunched posture and diarrhoea on Days 3 and 4 respectively whilst another showed occasional body tremors on Day 3.

Animals dosed at 400 or 150 mg/kg/day showed short-lived increased salivation immediately after dosing from Day 1 onwards. One male dosed at 400 mg/kg/day also showed more prolonged increased salivation on Day 8.

5.3 Bodyweight

Individual bodyweights are given in Table 3.

Animals dosed at 650 mg/kg/day showed a lower bodyweight gain than controls during the study, with two females showing a slight bodyweight loss at Day 4.

Animals dosed at 400 or 150 mg/kg/day showed a similar bodyweight gain to controls during the study.

5.4 Necropsy

Individual necropsy findings are given in Table 4.

1000 mg/kg/day animals killed *in extremis* during the study and animals from the remaining dose groups killed at Day 15 showed no macroscopic abnormalities at necropsy. The two 1000 mg/kg/day animals found dead on Day 2 showed dark red lungs, a darkened liver, patchy pallor of the kidneys, haemorrhage of the glandular gastric epithelium and liquid contents in the small intestine.

6. CONCLUSION

The dose levels for the main twenty-eight day study were chosen, following consultation with the sponsor, as:

High dose : 650 mg/kg/day

Intermediate dose : 150 mg/kg/day

Low dose : 15 mg/kg/day

- plus a control group treated with vehicle only

T A B L E S

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
 TABLE 1
 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	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h
1	0 (Control)	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
2	150	Increased salivation immediately after dosing	2	0	3	0	2	0	3	0	3	0	3	0	3	0
		No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
3	400	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0	3	0
		No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
5	650	Increased salivation immediately after dosing	0	0	3	0	3	0	3	0	3	0	3	0	3	0
		Increased salivation	0	0	0	0	0	0	0	1	0	0	0	0	0	0
		Wet fur	0	0	0	0	0	0	0	1	0	0	0	0	0	0
		No abnormalities detected	3	3	3	3	3	3	2	3	3	3	3	3	3	3

Pre - immediately before dosing (within fifteen minutes) 1h - one hour after dosing

ALLYL SUCCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING 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	2h	Pre	1h	3½h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h
4	1000	Increased salivation immediately after dosing	3	0	0	2	0	0	-	-	-	-	-	-	-	-	-	-
		Increased salivation	0	1	0	0	0	0	-	-	-	-	-	-	-	-	-	-
		Hunched posture	0	0	3	0	2	2	-	-	-	-	-	-	-	-	-	-
		Pilo-erection	0	0	3	0	0	2	-	-	-	-	-	-	-	-	-	-
		Occasional body tremors	0	0	0	0	1	2	-	-	-	-	-	-	-	-	-	-
		Tiptoe gait	0	0	0	0	1	0	-	-	-	-	-	-	-	-	-	-
		Decreased respiratory rate	0	0	0	0	0	1	-	-	-	-	-	-	-	-	-	-
		Death	0	0	0	1*	0	2#	-	-	-	-	-	-	-	-	-	-
No abnormalities detected	3	2	0	2	0	0	-	-	-	-	-	-	-	-	-	-		

Pre - immediately before dosing (within fifteen minutes) 1h - one hour after dosing 2h - two hours after dosing 3½h - three hours, thirty minutes after dosing
 * - animal killed in extremis # - animal killed in extremis - - not applicable, all animals dead

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
T A B L E 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	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h
1	0 (Control)	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	
2	150	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0	3	
3	400	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	
5	650	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0	3	
5	650	Increased salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	650	Wet fur	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	650	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	

1h = one hour after dosing

Pre = immediately before dosing (within fifteen minutes)

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING 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	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h
1	0 (Control)	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	
2	150	Increased salivation immediately after dosing	2	0	3	0	3	0	3	0	3	0	3	0	3	
3	400	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3		
5	650	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0		
5	650	Hunched posture	0	0	0	1	0	0	0	0	0	0	0	0		
5	650	Occasional body tremors	0	0	0	0	0	0	0	0	0	0	0	0		
5	650	Diarrhoea	0	0	0	0	0	0	0	1	0	0	0	0		
5	650	No abnormalities detected	3	3	3	3	3	1	3	2	3	3	3			

Pre = immediately before dosing (within fifteen minutes) 1h = one hour after dosing

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
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	2h	Pre	1h	3½h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	
4	1000	Increased salivation immediately after dosing	3	0	0	3	0	0	-	-	-	-	-	-	-	-	-	-	
		Hunched posture	0	0	3	3	2	1	-	-	-	-	-	-	-	-	-	-	-
		Pilo-erection	0	0	3	3	2	1	-	-	-	-	-	-	-	-	-	-	-
		Body tremors	0	0	0	0	1	0	-	-	-	-	-	-	-	-	-	-	-
		Diuresis	0	0	0	2	0	0	-	-	-	-	-	-	-	-	-	-	-
		Tiptoe gait	0	0	0	0	1	1	-	-	-	-	-	-	-	-	-	-	-
		Dehydration	0	0	0	0	1	1	-	-	-	-	-	-	-	-	-	-	-
		Red/brown staining around mouth	0	0	0	1	1	0	-	-	-	-	-	-	-	-	-	-	-
		Red/brown staining around ano-genital region	0	0	0	0	1	1	-	-	-	-	-	-	-	-	-	-	-
		Death	0	0	0	0	2*	1#	-	-	-	-	-	-	-	-	-	-	-
No abnormalities detected	3	3	0	0	0	0	-	-	-	-	-	-	-	-	-	-	-		

Pre = immediately before dosing (within fifteen minutes) 1h = one hour after dosing 2h = two hours after dosing 3½h = three hours, thirty minutes after dosing
 * = one animal found dead and one moribund animal killed in extremis # = animal killed in extremis
 - = not applicable, all animals dead

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
 TABLE 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	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h
1	0 (Control)	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	
2	150	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0	3	
3	400	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	
5	650	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0	3	
		Increased salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	
		No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	

Pre - immediately before dosing (within fifteen minutes)

1h - one hour after dosing

3. METHODS

3.1 Animals and Animal Husbandry

Fifteen male and fifteen female Sprague-Dawley CD strain rats were obtained from Charles River (UK) Limited, Manston, Kent. After an acclimatisation period of at least five days, animals were selected at random and given a unique number within the study by ear punching.

At the start of treatment the males weighed 128 to 239g and the females weighed 122 to 169g. The animals were housed in groups of three by sex in polypropylene grid-floor cages suspended over trays containing absorbent paper. Free access to mains drinking water and food (Rat and Mouse SQC Expanded Diet No.1, Special Diets Services Limited, Witham, Essex, UK) was allowed throughout 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 the 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 the nominal values were considered not to have affected the purpose or integrity of the study.

3.2 Procedure

Five groups, each of six rats (three males and three 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
5	650	2	325
4	1000	2	500

The test material was administered daily, for up to fourteen 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 ml/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 Days 4, 7 (or 8) and 11, as applicable.

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 hour after dosing. An additional examination was performed on Days 1 and 2 for animals dosed at 1000 mg/kg/day, due to the severe signs of toxicity observed. All observations were recorded.

3.3.2 Bodyweight

Individual bodyweights were recorded on Days 1, 4, 7 (or 8), 11 and 14 of the study, as applicable.

3.3.3 Necropsy

On completion of the dosing period, all surviving animals were killed by cervical dislocation and immediately subjected to an internal and external macroscopic examination. All animals found dead or killed *in extremis* during the study were also necropsied. No tissues were retained.

3.4 Evaluation of Data

Necropsy data, bodyweights and clinical observations were examined for any adverse effects resulting from treatment.

The data obtained was summarised in tabular form and used to provide the basis for selection of dose levels for the main study.

4. ARCHIVES

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

5. RESULTS

5.1 Mortality

On Day 2, one male dosed at 1000 mg/kg/day was found dead prior to dosing and one female from the same treatment group was found dead one hour after dosing. Another, moribund, female was killed at the same time and the three remaining animals from this treatment group were killed *in extremis* at the end of the working day, due to the severe signs of toxicity observed. There were no deaths at the other dose levels during the study.

5.2 Clinical Observations

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

Animals dosed at 1000 mg/kg/day showed short-lived increased salivation immediately after dosing on Days 1 and 2 and all animals from this dose group showed hunched posture and pilo-erection by the end of Day 1. One male was found dead before treatment was administered on Day 2 but the other two males appeared normal in comparison with controls until after treatment when both animals developed severe clinical abnormalities including hunched posture, pilo-erection, tiptoe gait, decreased respiratory rate and occasional body tremors. Both males were killed *in extremis* at the end of the working day. In contrast to the males, females showed no recovery between Day 1 and Day 2, with hunched posture, pilo-erection and diuresis observed before treatment on Day 2. The health of these animals further deteriorated following treatment, with one female found dead approximately one hour after dosing and another showing severe signs of toxicity including dehydration and body tremors. This moribund animal was killed *in extremis* immediately. The remaining female developed tiptoe gait after dosing on Day 2 and was also dehydrated at the end of the working day. This animal was killed *in extremis* without further treatment.

Animals dosed at 650 mg/kg/day showed short-lived increased salivation before or immediately after dosing from Day 2 onwards. More prolonged increased

salivation was also occasionally observed at this dose level during the study. In addition, one female from this treatment group showed hunched posture and diarrhoea on Days 3 and 4 respectively whilst another showed occasional body tremors on Day 3.

Animals dosed at 400 or 150 mg/kg/day showed short-lived increased salivation immediately after dosing from Day 1 onwards. One male dosed at 400 mg/kg/day also showed more prolonged increased salivation on Day 8.

5.3 Bodyweight

Individual bodyweights are given in Table 3.

Animals dosed at 650 mg/kg/day showed a lower bodyweight gain than controls during the study, with two females showing a slight bodyweight loss at Day 4.

Animals dosed at 400 or 150 mg/kg/day showed a similar bodyweight gain to controls during the study.

5.4 Necropsy

Individual necropsy findings are given in Table 4.

1000 mg/kg/day animals killed *in extremis* during the study and animals from the remaining dose groups killed at Day 15 showed no macroscopic abnormalities at necropsy. The two 1000 mg/kg/day animals found dead on Day 2 showed dark red lungs, a darkened liver, patchy pallor of the kidneys, haemorrhage of the glandular gastric epithelium and liquid contents in the small intestine.

6. CONCLUSION

The dose levels for the main twenty-eight day study were chosen, following consultation with the sponsor, as:

High dose	:	650 mg/kg/day
Intermediate dose	:	150 mg/kg/day
Low dose	:	15 mg/kg/day

- plus a control group treated with vehicle only

T A B L E S

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
T A B L E 1
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	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h		
1	0 (Control)	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
2	150	Increased salivation immediately after dosing	2	0	3	0	2	0	3	0	3	0	3	0	3	0	3	0
		No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
3	400	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0
		No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
		Increased salivation immediately after dosing	0	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0
5	650	Increased salivation	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
		Wet fur	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
		No abnormalities detected	3	3	3	3	3	3	3	2	3	3	3	3	3	3	3	3

Pre - immediately before dosing (within fifteen minutes) 1h - one hour after dosing

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING 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	2h	Pre	1h	3½h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	
4	1000	Increased salivation immediately after dosing	3	0	0	2	0	0	-	-	-	-	-	-	-	-	-
		Increased salivation	0	1	0	0	0	0	-	-	-	-	-	-	-	-	-
		Hunched posture	0	0	3	0	2	2	-	-	-	-	-	-	-	-	-
		Pilo-erection	0	0	3	0	0	2	-	-	-	-	-	-	-	-	-
		Occasional body tremors	0	0	0	0	1	2	-	-	-	-	-	-	-	-	-
		Tiptoe gait	0	0	0	0	1	0	-	-	-	-	-	-	-	-	-
		Decreased respiratory rate	0	0	0	0	0	1	-	-	-	-	-	-	-	-	-
		Death	0	0	0	1*	0	2#	-	-	-	-	-	-	-	-	-
No abnormalities detected	3	2	0	2	0	0	-	-	-	-	-	-	-	-	-		

Pre - immediately before dosing (within fifteen minutes) 1h - one hour after dosing 2h - two hours after dosing 3½h - three hours, thirty minutes after dosing
 * - animal killed in extremis # - animal killed in extremis - - not applicable, all animals dead

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING 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	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h
1	0 (Control)	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
			3	0	3	0	3	0	3	0	3	0	3	0	3	0
			3	3	3	3	3	3	3	3	3	3	3	3	3	3
2	150	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0	3	0
			3	3	3	3	3	3	3	3	3	3	3	3	3	3
			3	0	3	0	3	0	3	0	3	0	3	0	3	0
3	400	Increased salivation immediately after dosing	0	1	0	0	0	0	0	0	0	0	0	0	0	0
			3	2	3	3	3	3	3	3	3	3	3	3	3	3
			3	0	3	0	3	0	3	0	3	0	3	0	3	0
5	650	Increased salivation immediately after dosing	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	0
			3	3	3	3	3	3	3	3	3	3	3	3	3	3
		Wet fur	3	3	3	3	3	3	3	3	3	3	3	3	3	3
			3	3	3	3	3	3	3	3	3	3	3	3	3	3
			3	3	3	3	3	3	3	3	3	3	3	3	3	3
		No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
			3	3	3	3	3	3	3	3	3	3	3	3	3	3
			3	3	3	3	3	3	3	3	3	3	3	3	3	3

1h = one hour after dosing

Pre = immediately before dosing (within fifteen minutes)

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING 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	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h
1	0 (Control)	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	
2	150	Increased salivation immediately after dosing	2	0	3	0	3	0	3	0	3	0	3	0	3	
3	400	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3		
5	650	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0		
5	650	Wet fur	0	0	0	1	0	0	0	0	0	0	0	0		
5	650	No abnormalities detected	3	3	3	2	3	3	3	3	3	3	3	3		
5	650	Increased salivation immediately after dosing	0	0	3	0	3	0	3	0	3	0	3	0		
5	650	Hunched posture	0	0	0	0	0	1	0	0	0	0	0	0		
5	650	Occasional body tremors	0	0	0	0	0	0	0	0	0	0	0	0		
5	650	Diarrhoea	0	0	0	0	0	0	0	0	0	0	0	0		
5	650	No abnormalities detected	3	3	3	3	3	1	3	2	3	3	3			

Pre = immediately before dosing (within fifteen minutes) 1h = one hour after dosing

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
T A B L E 2 (continued)
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	2h	Pre	1h	3 1/2h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	
4	1000	Increased salivation immediately after dosing	3	0	0	3	0	0	-	-	-	-	-	-	-	-	-	-	
		Hunched posture	0	0	3	3	2	1	-	-	-	-	-	-	-	-	-	-	-
		Pilo-erection	0	0	3	3	2	1	-	-	-	-	-	-	-	-	-	-	-
		Body tremors	0	0	0	0	1	0	-	-	-	-	-	-	-	-	-	-	-
		Diuresis	0	0	0	2	0	0	-	-	-	-	-	-	-	-	-	-	-
		Tiptoe gait	0	0	0	0	1	1	-	-	-	-	-	-	-	-	-	-	-
		Dehydration	0	0	0	0	1	1	-	-	-	-	-	-	-	-	-	-	-
		Red/brown staining around mouth	0	0	0	1	1	0	-	-	-	-	-	-	-	-	-	-	-
		Red/brown staining around ano-genital region	0	0	0	0	1	1	-	-	-	-	-	-	-	-	-	-	-
		Death	0	0	0	0	2*	1#	-	-	-	-	-	-	-	-	-	-	-
No abnormalities detected	3	3	0	0	0	0	-	-	-	-	-	-	-	-	-	-	-		

Pre = immediately before dosing (within fifteen minutes) 1h = one hour after dosing 2h = two hours after dosing 3 1/2h = three hours, thirty minutes after dosing
 * = one animal found dead and one moribund animal killed in extremis # = animal killed in extremis
 - = not applicable, all animals dead

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
 TABLE 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	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h		
1	0 (Control)	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
2	150	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0
		No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
3	400	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0
		No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
5	650	Increased salivation immediately after dosing	3	0	3	0	3	0	3	0	3	0	3	0	3	0	2	0
		Increased salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
		No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	3

Pre - immediately before dosing (within fifteen minutes)

1h - one hour after dosing

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
T A B L E 3
INDIVIDUAL AND GROUP MEAN TWICE WEEKLY BODYWEIGHTS

GROUP NUMBER AND SEX	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER	BODYWEIGHT (g) AT DAY						
			1	4	7	11	14		
1 M	0 (Control)	1	161	182	210	241	266		
		2	159	189	217	255	276		
		3	135	155	180	207	230		
		Mean	152	175	202	234	257		
1 F	0 (Control)	4	128	149	167	182	193		
		5	122	137	150	158	171		
		6	151	168	185	200	213		
		Mean	134	151	167	180	192		

M = male F = female

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
 TABLE 3 (continued)
 INDIVIDUAL AND GROUP MEAN TWICE WEEKLY BODYWEIGHTS

GROUP NUMBER AND SEX	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER	BODYWEIGHT (g) AT DAY						
			1	4	7	11	14		
2 M	150	7	160	182	211	251	278		
		8	156	180	212	255	281		
		9	135	161	187	221	242		
		Mean	150	174	203	242	267		
2 F	150	10	133	152	167	191	201		
		11	135	150	166	179	182		
		12	141	161	178	195	206		
		Mean	136	154	170	188	196		

M -- male F -- female

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
 TABLE 3 (continued)
 INDIVIDUAL AND GROUP MEAN TWICE WEEKLY BODYWEIGHTS

GROUP NUMBER AND SEX	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER	BODYWEIGHT (g) AT DAY				
			1	4	7	11	
3 M	400	13	151	170	198	230	256
		14	131	152	177	206	222
		15	154	174	202	242	266
		Mean	145	165	192	226	248
3 F	400	16	123	137	155	171	184
		17	127	144	157	173	187
		18	124	141	159	179	193
		Mean	125	141	157	174	188

M - male F - female

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
 TABLE 3 (continued)
 INDIVIDUAL AND GROUP MEAN TWICE WEEKLY BODYWEIGHTS

GROUP NUMBER AND SEX	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER	BODYWEIGHT (g) AT DAY				
			1	4	8	11	14
5 M	650	25	190	199	224	244	263
		26	217	225	245	268	278
		27	239	244	287	309	327
		Mean	215	223	252	274	289
5 F	650	28	144	137	156	165	181
		29	169	163	188	205	213
		30	163	177	187	200	209
		Mean	159	159	177	190	201

M = male F = female

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY IN THE RAT
 TABLE 3 (continued)
 INDIVIDUAL AND GROUP MEAN TWICE WEEKLY BODYWEIGHTS

GROUP NUMBER AND SEX	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER	BODYWEIGHT (g) AT DAY					
			1	4	8	11	14	
4 M	1000	19	154	-	-	-	-	-
		20	149	-	-	-	-	-
		21	128	-	-	-	-	-
		Mean	144	-	-	-	-	-
4 F	1000	22	136	-	-	-	-	-
		23	137	-	-	-	-	-
		24	148	-	-	-	-	-
		Mean	140	-	-	-	-	-

M -- male F -- female - - not applicable, animal dead

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY
IN THE RAT

T A B L E 4
INDIVIDUAL NECROPSY FINDINGS

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER AND SEX	DAY OF NECROPSY	MACROSCOPIC OBSERVATIONS
1	0 (Control)	1 M	15	No abnormalities detected
		2 M	15	No abnormalities detected
		3 M	15	No abnormalities detected
		4 F	15	No abnormalities detected
		5 F	15	No abnormalities detected
		6 F	15	No abnormalities detected
2	150	7 M	15	No abnormalities detected
		8 M	15	No abnormalities detected
		9 M	15	No abnormalities detected
		10 F	15	No abnormalities detected
		11 F	15	No abnormalities detected
		12 F	15	No abnormalities detected

M - male

F - female

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY
IN THE RAT

T A B L E 4 (continued)
INDIVIDUAL NECROPSY FINDINGS

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER AND SEX	DAY OF NECROPSY	MACROSCOPIC OBSERVATIONS
3	400	13 M	15	No abnormalities detected
		14 M	15	No abnormalities detected
		15 M	15	No abnormalities detected
		16 F	15	No abnormalities detected
		17 F	15	No abnormalities detected
		18 F	15	No abnormalities detected
5	650	25 M	15	No abnormalities detected
		26 M	15	No abnormalities detected
		27 M	15	No abnormalities detected
		28 F	15	No abnormalities detected
		29 F	15	No abnormalities detected
		30 F	15	No abnormalities detected

M - male F - female

ALLYL SUCROSE : FOURTEEN DAY ORAL (GAVAGE) RANGE-FINDING TOXICITY STUDY
IN THE RAT

T A B L E 4 (continued)
INDIVIDUAL NECROPSY FINDINGS

GROUP NUMBER	DOSE LEVEL (mg/kg/day)	ANIMAL NUMBER AND SEX	DAY OF NECROPSY	MACROSCOPIC OBSERVATIONS
4	1000	19 M	2	No abnormalities detected
		20 M	2	No abnormalities detected
		21 M	2	Lungs - all lobes: dark red Liver: darkened Left kidney: patchy pallor Glandular stomach: haemorrhagic Small intestine: red liquid contents Gonads: cannibalised
		22 F	2	No abnormalities detected
		23 F	2	Lungs - all lobes: dark red Liver: darkened
		24 F	2	No abnormalities detected

M = male F = female

Best Available Copy