



Great Lakes
Chemical Corporation

8EHQ0996-13677

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ATTN: Section 8(e) Coordinator

Re: TSCA Section 8(e) Follow-Up Submission (8EHQ-96-13677)
(When responding, please refer to PJB-96-350)

Great Lakes Chemical Corporation submitted a Section 8(e) substantial risk notification concerning an Acute Oral Toxicity study in rats with acetylfuran (CAS Registry Number 1192-62-7) on June 24, 1996 (EPA #8EHQ-96-13677). Attached is a copy of the actual study for your files.

If I can be of any further assistance, please do not hesitate to contact me at (317) 497-6391.

Sincerely,

Pamela J. Bricker
Regulatory Specialist



8EHQ-96-13677

PJB/
attachment

cc: 8(e) file-Acetylfuran (w.o.a.)

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ACETYL FURAN:

ACUTE ORAL TOXICITY

TEST IN THE RAT

SPL PROJECT NUMBER: 541/018

AUTHOR: R Driscoll

STUDY SPONSOR:

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Halebank
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WA8 8NS

ISSUED BY:

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QUALITY ASSURANCE REPORT

The routine inspection of short term studies at Safepharm Laboratories is carried out as a continuous process designed to encompass all major phases of each study type once per month. Dates of relevant monthly inspections are given below.

Date(s) of Inspection and Reporting:

11, 16, 30 April 1996

This report has been audited by Safepharm 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 May 1996

.....  DATE: -7 JUN 1996

J R Pateman CBiol MIBiol
For Safepharm Quality Assurance Unit

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 160, 40 CFR Part 792 and 21 CFR Part 58 (as amended).

..... *R Driscoll* DATE: **05 JUN 1996**

R Driscoll BTech (Hons)
Study Director
for Safepharm Laboratories

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SUMMARY

STUDY SPONSOR : GREAT LAKES FINE CHEMICALS
LIMITED

STUDY TITLE : ACUTE ORAL TOXICITY TEST IN THE
RAT

TEST MATERIAL : ACETYL FURAN

1. A study was performed to assess the acute oral toxicity of the test material in the Sprague-Dawley CD strain rat. The method used was based on the recommendations of the OECD Guidelines for Testing of Chemicals No. 401 "Acute Oral Toxicity" (adopted 24 February 1987) and Method B1 of Commission Directive 92/69/EEC (which constitutes Annex V of Council Directive 67/548/EEC).

The results may be used as a basis for classification and labelling under Annex VI of Council Directive 67/548/EEC (as adapted to technical progress by Commission Directive 93/21/EEC) relating to the classification, packaging and labelling of dangerous substances.

2. Following a range-finding study, three groups of five fasted male animals were given a single oral dose of test material, as a solution in arachis oil BP at dose levels of 10, 22 and 50 mg/kg bodyweight. A further group of five fasted females was similarly treated, at a dose level of 10 mg/kg bodyweight, to confirm that this sex was not markedly more sensitive to the test material. The surviving animals were observed for fourteen days after the day of dosing. All animals were subjected to gross pathological examination.
3. The males treated with 50 mg/kg were found dead one to three days after dosing. Common signs of systemic toxicity noted were ataxia, hunched posture, lethargy, decreased respiratory rate and laboured and noisy respiration with incidents of ptosis, gasping respiration and red/brown stains around the eyes and snout. Surviving animals appeared normal throughout the study or recovered one or two days after dosing.

4. Surviving animals showed expected gain in bodyweight during the study.
5. Abnormalities noted at necropsy of animals treated with 50 mg/kg that died during the study were haemorrhagic lungs, dark liver or patchy pallor of the liver, dark kidneys, gaseous distention of the stomach, haemorrhage of the gastric mucosa and sloughing of the non-glandular epithelium of the stomach. No abnormalities were noted at necropsy of animals that were killed at the end of the study.
6. The acute oral median lethal dose (LD₅₀) and 95% confidence limits of the test material were calculated by the method of Thompson W R to be:

Males only : 33 (22 - 50) mg/kg bodyweight

The test material was classified as TOXIC and the symbol "T" and risk phrase R 25 "TOXIC IF SWALLOWED" are therefore required according to EU labelling regulations.

Female animals were considered not to be markedly more sensitive to the test material than male animals.

**ACETYL FURAN:
ACUTE ORAL TOXICITY
TEST IN THE RAT**

1. INTRODUCTION

The study was performed to assess the acute oral toxicity of the test material in the Sprague-Dawley CD strain rat (Safepharm Standard Method Number OECD 39). The method was based on the recommendations of the OECD Guidelines for Testing of Chemicals No. 401 "Acute Oral Toxicity" (adopted 24 February 1987) and Method B1 of Commission Directive 92/69/EEC (which constitutes Annex V of Council Directive 67/548/EEC).

The results may be used as a basis for classification and labelling under Annex VI of Council Directive 67/548/EEC (as adapted to technical progress by Commission Directive 93/21/EEC) relating to the classification, packaging and labelling of dangerous substances.

The test system was chosen because the rat has been shown to be a suitable model for this type of study and is recommended in the test method. 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 March 1996 and 24 April 1996.

2. TEST MATERIAL AND EXPERIMENTAL PREPARATION

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	ACETYL FURAN
Batch number	:	9-5F13
Date received	:	12 March 1996
Description	:	dark yellow crystalline solid
Storage conditions	:	room temperature

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 freshly prepared, as required, as a solution at the appropriate concentration in arachis oil BP.

Determination by analysis of the concentration, homogeneity and stability of the test material preparations was not appropriate because it was not specified in the Study Plan and is not a requirement of the Test Guideline.

3. METHODS

3.1 Animals and Animal Husbandry

Male and female Sprague-Dawley CD strain rats supplied by Charles River (UK) Ltd, Margate, Kent were used. At the start of the main study the males weighed 132 to 159g, and the females 135 to 150g, and were five to eight weeks old. After a minimum acclimatisation period of five days the animals were selected at random and given a number unique within the study by indelible ink-marking on the tail and a number written on a cage card.

The animals were housed in groups of up to five by sex in solid-floor polypropylene cages furnished with woodflakes. With the exception of an overnight fast immediately before dosing and for approximately two hours after dosing, free access to mains drinking water and food (Rat and Mouse Expanded Diet No. 1, Special Diets Services Limited, Witham, Essex, UK) was allowed throughout the study.

The animal room was maintained at a temperature of 19 to 26 °C and relative humidity of 39 to 60%. On one occasion the temperature was above the limit specified in the protocol (25 °C). This deviation was considered not to affect the purpose or integrity of the study. The rate of air exchange was approximately fifteen changes per hour and the lighting was controlled by a time switch to give twelve hours continuous light and twelve hours darkness.

3.2 Procedure

All animals were dosed once only by gavage using a metal cannula attached to a graduated syringe. The volume administered to each animal was calculated according to its fasted bodyweight at the time of dosing.

3.2.1 Range-finding Study

A range-finding study was performed to establish a dosing regime as follows:

DOSE LEVEL (mg/kg)	CONCENTRATION (mg/ml)	DOSE VOLUME (ml/kg)	NUMBER OF RATS	
			MALE	FEMALE
500	50	10	1	1
200	20	10	1	1
100	10	10	1	1

The animals were observed for deaths or overt signs of toxicity ½, 1, 2 and 4 hours after dosing and subsequently once daily for five days.

Individual bodyweights were recorded on the day of dosing to allow calculation of individual dose volumes. No necropsies were performed.

3.2.2 Main Study

Based on the results of the range-finding study three groups of animals of the same sex were dosed at logarithmically spaced dose levels as follows:

DOSE LEVEL (mg/kg)	CONCENTRATION (mg/ml)	DOSE VOLUME (ml/kg)	NUMBER OF RATS
			MALE
10	1	10	5
22	2.2	10	5
50	5	10	5

The animals were observed for deaths or overt signs of toxicity ½, 1, 2 and 4 hours after dosing and subsequently once daily for fourteen days.

In order to establish that the untreated sex were not markedly more sensitive to the test material, an additional group of five female animals was treated as follows:

DOSE LEVEL (mg/kg)	CONCENTRATION (mg/ml)	DOSE VOLUME (ml/kg)	NUMBER OF RATS FEMALE
10	1	10	5

These animals were treated as previously described.

Individual bodyweights were recorded prior to dosing on Day 0 and on Days 7 and 14 or at death.

At the end of the study the surviving animals were killed by cervical dislocation. All animals, including those that died during the study, were subjected to gross pathological examination. This consisted of an external examination and examination of the major organs of the abdominal and thoracic cavities. The appearance of any macroscopic abnormalities was recorded. No tissues were retained.

3.3 Evaluation of Data

Data evaluations included the relationship, if any, between the animals' exposure to the test material and the incidence and severity of all abnormalities including behavioural and clinical observations, gross lesions, bodyweight changes, mortality and any other toxicological effects.

Using the mortality data obtained, the acute oral median lethal dose (LD₅₀) and 95% confidence limits of the test material were calculated using the method of Thompson W R, Bact. Reviews, 11, 115-145 (1947). The LD₅₀ and 95% confidence limits were calculated for males only.

3.3.1 Interpretation According to Annex VI Section 3.2

The results were interpreted according to the Commission Directive 93/21/EEC which adapts Council Directive 67/548/EEC on the regulations relating to the classification, packaging and labelling of dangerous substances.

The test material will be classified and assigned the appropriate symbol and risk phrase as follows:

CATEGORY	ACUTE ORAL LD ₅₀ mg/kg	SYMBOL	RISK PHRASE
VERY TOXIC	≤25	T+	R 28 "VERY TOXIC IF SWALLOWED"
TOXIC	>25 to 200	T	R 25 "TOXIC IF SWALLOWED"
HARMFUL	>200 to 2000	X _n	R 22 "HARMFUL IF SWALLOWED"

Test materials with acute oral LD₅₀ values greater than 2000 mg/kg require no symbol and risk phrase.

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 five years. After this period, the Sponsor's instructions will be sought.

5. RESULTS

5.1 Range-finding Study

Individual clinical observations and mortality data are given in Table 1.

Animals treated with 200 or 500 mg/kg and the male treated with 100 mg/kg were found dead one or three days after dosing. Common signs of systemic toxicity noted were ataxia, hunched posture, lethargy, decreased respiratory rate, laboured and noisy respiration and red/brown stains around the eyes, mouth or snout with incidents of increased salivation.

Based on this information, dose levels of 10, 22 and 50 mg/kg bodyweight were selected for the main study.

5.2 Main Study

5.2.1 Mortality Data

The mortality data are given in Table 2.

All males treated with 50 mg/kg were found dead one to three days after dosing.

5.2.2 Clinical Observations

Individual clinical observations are given in Tables 3 to 6.

- Common signs of systemic toxicity noted in females treated with 10 mg/kg and males treated with 22 or 50 mg/kg were hunched posture, lethargy and decreased respiratory rate. Common signs of systemic toxicity noted in males treated with 50 mg/kg were ataxia and laboured and noisy respiration. Isolated incidents of systemic toxicity noted in one male treated with 50 mg/kg were ptosis, gasping respiration and red/brown stains around the eyes or snout. No signs of toxicity were noted in one female and all males treated with 10 mg/kg.

Surviving animals appeared normal throughout the study or recovered one or two days after dosing.

5.2.3 Bodyweight

Individual bodyweights and weekly bodyweight changes are given in Tables 7 to 10.

Surviving animals showed expected gain in bodyweight during the study.

5.2.4 Necropsy

Individual necropsy findings are given in Tables 11 to 14.

Abnormalities noted at necropsy of animals treated with 50 mg/kg that died during the study were haemorrhagic lungs, dark liver or patchy pallor of the liver, dark kidneys, gaseous distention of the stomach, haemorrhage of the gastric mucosa and sloughing of the non-glandular epithelium of the stomach. No abnormalities were noted at necropsy of animals that were killed at the end of the study.

6. CONCLUSION

The acute oral median lethal dose (LD₅₀) and 95% confidence limits of the test material, ACETYL FURAN, in the Sprague-Dawley CD strain rat were calculated by the method of Thompson W R to be:

Males only : 33 (22 - 50) mg/kg bodyweight

The test material was classified as TOXIC and the symbol "T" and risk phrase R 25 "TOXIC IF SWALLOWED" are therefore required according to EU labelling regulations.

Female animals were considered not to be markedly more sensitive to the test material than male animals.

ACETYL FURAN : ACUTE ORAL TOXICITY TEST IN THE RAT
KEY FOR CLINICAL OBSERVATIONS

- A = ataxia
- H = hunched posture
- L = lethargy
- Pt = ptosis
- Rd = decreased respiratory rate
- Rg = gasping respiration
- RI = laboured respiration
- Rn = noisy respiration
- S = increased salivation
- Se = red/brown staining around eyes
- Sm = red/brown staining around mouth
- Ss = red/brown staining around snout
- O = no signs of systemic toxicity
- X = animal dead
- X* = animal found dead at afternoon death check

ACETYL FURAN : ACUTE ORAL TOXICITY TEST IN THE RAT
T A B L E 1
INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN THE RANGE-FINDING STUDY

Dose Level mg/kg	Animal Number and Sex	Effects Noted After Dosing (Hours)					Effects Noted During Period After Dosing (Days)						
		1/2	1	2	4	1	2	3	4	5			
500	1-0 Male	0	HSRdRI	HSARdRI	HARdRIRn SmSs	X							
	2-0 Female	0	HRdRIRn	HARdRIRn	HLARdRIRn	X							
200	1-1 Male	0	HRdRIRn	HRdRLRn	HRdRIRnL	HLRdRIRn SmSs	HLARdRIRs SmRn	X					
	2-1 Female	0	HRdRI	HRdRI	HRdRIRn	HLRdRIRn SsSe5m	HLARdRIRn SsSe5m	X					
100	1-2 Male	0	HRdRI	HRdRI	HRdRIRn	HLRdRIRn SmSs	HLARdRIRs SmRn	X					
	2-2 Female	0	HRdRI	HRdRI	HRdRIRn	HLRdRIRn	HLRnRd	HLRdRn	HRd				0

ACETYL FURAN : ACUTE ORAL TOXICITY TEST IN THE RAT
 TABLE 2
 MORTALITY DATA IN THE MAIN STUDY

Dose Level mg/kg	Sex	Number of Animals Treated	Deaths During Day of Dosing (Hour)				Deaths During Period After Dosing (Days)								Deaths	%				
			1/2	1	2	4	1	2	3	4	5	6	7	8-14						
10	Male	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Female	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
22	Male	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
50	Male	5	0	0	0	0	3	1	0	0	1	0	0	0	0	0	0	0	5	100

- = all animals dead

ACETYL FURAN : ACUTE ORAL TOXICITY TEST IN THE RAT
T A B L E 7
INDIVIDUAL BODYWEIGHTS AND WEEKLY BODYWEIGHT CHANGES IN THE MAIN STUDY - MALES

Dose Level mg/kg	Animal Number and Sex	Bodyweight (g) at Day			Bodyweight Gain (g) During Week	
		0	7	14	1	2
10	4-0 Male	143	208	266	65	58
	4-1 Male	141	200	256	59	56
	4-2 Male	158	219	279	61	60
	4-3 Male	136	201	262	65	61
	4-4 Male	151	228	282	77	54

ACETYL FURAN : ACUTE ORAL TOXICITY TEST IN THE RAT
T A B L E 8
INDIVIDUAL BODYWEIGHTS AND WEEKLY BODYWEIGHT CHANGES IN THE MAIN STUDY - MALES

Dose Level mg/kg	Animal Number and Sex	Bodyweight (g) at Day			Bodyweight Gain (g) During Week	
		0	7	14	1	2
22	5-0 Male	156	230	281	74	51
	5-1 Male	159	226	277	67	51
	5-2 Male	140	204	265	64	61
	5-3 Male	147	222	279	75	57
	5-4 Male	156	229	265	73	36

ACETYL FURAN : ACUTE ORAL TOXICITY TEST IN THE RAT
T A B L E 9
INDIVIDUAL BODYWEIGHTS AND WEEKLY BODYWEIGHT CHANGES IN THE MAIN STUDY - MALES

Dose Level mg/kg	Animal Number and Sex	Bodyweight (g) at Day			Bodyweight (g) at Death	Bodyweight Gain (g) During Week	
		0	7	14		1	2
50	3-0 Male	145	-	-	127	-	-
	3-1 Male	132	-	-	125	-	-
	3-2 Male	134	-	-	125	-	-
	3-3 Male	135	-	-	127	-	-
	3-4 Male	141	-	-	131	-	-

- = animal dead

ACETYL FURAN : ACUTE ORAL TOXICITY TEST IN THE RAT
T A B L E 10
INDIVIDUAL BODYWEIGHTS AND WEEKLY BODYWEIGHT CHANGES IN THE MAIN STUDY - FEMALES

Dose Level mg/kg	Animal Number and Sex	Bodyweight (g) at Day			Bodyweight Gain (g) During Week	
		0	7	14	1	2
10	6-0 Female	148	175	201	27	26
	6-1 Female	150	176	203	26	27
	6-2 Female	146	163	199	17	36
	6-3 Female	142	171	189	29	18
	6-4 Female	135	156	171	21	15

ACETYL FURAN : ACUTE ORAL TOXICITY TEST IN THE RAT
T A B L E 11
INDIVIDUAL NECROPSY FINDINGS IN THE MAIN STUDY - MALES

Dose Level mg/kg	Macroscopic Observations	Animal Number and Sex				
		4-0 Male	4-1 Male	4-2 Male	4-3 Male	4-4 Male
10	No abnormalities detected (N)	N	N	N	N	N

ACETYL FURAN : ACUTE ORAL TOXICITY TEST IN THE RAT
T A B L E 12
INDIVIDUAL NECROPSY FINDINGS IN THE MAIN STUDY - MALES

Dose Level mg/kg	Macroscopic Observations	Animal Number and Sex			
		5-0 Male	5-1 Male	5-2 Male	5-4 Male
22	No abnormalities detected (N)	N	N	N	N

ACETYL FURAN : ACUTE ORAL TOXICITY TEST IN THE RAT
 TABLE 13
 INDIVIDUAL NECROPSY FINDINGS IN THE MAIN STUDY - MALES

Dose Level mg/kg	Macroscopic Observations	Animal Number and Sex				
		3-0 Male*	3-1 Male*	3-2 Male*	3-3 Male*	3-4 Male*
50	Lungs: haemorrhagic	P	P	P	P	P
	Liver: dark	P		P	P	P
	patchy pallor		P			
	Kidneys: dark	P	P	P	P	P
	Stomach: gaseous distension				P	P
Gastric mucosa: haemorrhagic	P	P	P	P	P	
Non-glandular epithelium of stomach: sloughing				P	P	

* = animal died during study P = finding present

ACETYL FURAN : ACUTE ORAL TOXICITY TEST IN THE RAT
T A B L E 14
INDIVIDUAL NECROPSY FINDINGS IN THE MAIN STUDY - FEMALES

Dose Level mg/kg	Macroscopic Observations	Animal Number and Sex				
		6-0 Female	6-1 Female	6-2 Female	6-3 Female	6-4 Female
10	No abnormalities detected (N)	N	N	N	N	N

APPENDIX I



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

TEST TYPE

SafePharm Laboratories Ltd.
P.O. Box No. 45
Derby DE1 2BT

Analytical Chemistry
Environmental Tox.
Environmental Fate
Mutagenicity
Phys/Chem. tests
Toxicology

DATE OF INSPECTION

22 January 1996

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 non-clinical studies performed at these facilities.

27/2/96

D.F. Moore
Director
UK GLP Monitoring Authority

Best Available Copy