

Ciba Specialty Chemicals
USA

Water
Treatments

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December 23, 1998

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Attn: Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460



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Re: TSCA Section 8(e) Notice

CONTAINS NO CBI

Dear Sir or Madam:

Ciba Specialty Chemicals Water Treatments, Inc. is submitting the three mammalian toxicity studies discussed below pursuant to Section 8(e) of the Toxic Substances Control Act ("TSCA"). These studies were conducted on commercial products. Thus, there is the potential for some human and environmental exposure to these substances.

Acute Eye Irritation Test in the Rabbit, Alcopol 0 70PG: Alcopol is a wetting agent used primarily in the textile industry. It contains dioctyl sodium sulfosuccinate, CAS No. 577-11-7, propylene glycol, CAS No. 57-55-6, and ethanol, CAS No. 64-17-5. This test produced opalescent corneal opacity, iridial inflammation, and severe conjunctival irritation in one rabbit. Although severe eye irritation in one rabbit may not be reportable under Section 8(e) absent additional findings, we are submitting this study as a precautionary measure.

Acute Oral Toxicity to Rats, Collafix PP2: Collafix is a wallpaper adhesive containing a blend of a copolymer of acrylamide and sodium acrylate with a copolymer of acrylamide and a cationic quaternary amino ester suspended in a hydrocarbon solvent. A single oral dose of the test substance was administered to five male and five female rats at 5 g/kg bodyweight. No mortalities were observed at this dose. However, pilo-erection, hunched posture, waddling, and pallor of the extremities were observed in all animals shortly after dosing. One animal also showed lethargy, decreased respiratory rate, ptosis and gasping respiration on Day 3. Recovery of all animals was complete by Day 6, and terminal autopsy findings were normal. While this study is not reportable under Section 8(e) for acute oral toxicity, the

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Allied Colloids
Ciba Specialty Chemicals Water Treatments, Inc.
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Suffolk, Virginia 23439-0820
Tel. 757 538 3700
Fax 757 538 3989

Value beyond chemistry

Document Processing Center
Attn: Section 8(e) Coordinator
December 23, 1998
Page 2

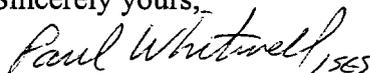
neurological findings may be reportable under Section 8(e). Therefore, we are submitting this study.

Acute Oral Toxicity to Rats, CFR 5651/Magnafloc 1697: The material tested is the same as Percol LT35, a homopolymer of diallyldimethylammonium chloride, CAS No. 26062-79-3, in aqueous solution, that is used as a coagulant in treating potable water. A single oral dose of the test substance was administered to five male and five female rats at 5 g/kg bodyweight. While no mortalities were observed, pilo-erection, hunched posture, waddling, pallor of the extremities, and diarrhea were observed in all animals shortly after dosing. These effects were no longer apparent at Day 7, and terminal autopsy findings were normal. As with the Collafix PP2 study, this study is being submitted as a precautionary measure.

Ciba Specialty Chemicals Water Treatments, Inc., formerly known as Allied Colloids, Inc. ("Allied Colloids"), is a subsidiary of Ciba Specialty Chemicals Corporation ("Ciba"). Ciba has a worldwide policy for environmental and safety audits and due diligence that is designed to meet the standards of EPA's policy on "Incentives for Self-Policing: Discovery, Disclosure, Correction and Prevention of Violations," 60 Fed. Reg. 66706 (Dec. 22, 1995). Ciba undertook a program of TSCA management systems audits in 1997, and these audits are continuing. Earlier this year, Ciba acquired the business of Allied Colloids and has been incorporating it into Ciba's audit and due diligence program. As a part of this program, a targeted toxicology self-audit of the former Allied Colloids facility in Bradford, England, was recently completed to ensure that any studies potentially reportable under Section 8(e) would be submitted to EPA. During the course of this review of toxicological files in England, the studies discussed above were identified. To the best of our knowledge, these studies were not previously known to U.S. employees of Allied Colloids, Ciba, or their subsidiaries. We are also participating in EPA's "Compliance Incentive Program" for the Industrial Organic Chemical sector (SIC Code 2869), and will submit to EPA by January 31, 1999, a final report identifying all potential areas of noncompliance uncovered pursuant to this program.

Please call me at (757) 538-3700 if you have any questions regarding this matter.

Sincerely yours,



Paul Whitwell
Technical Manager
Ciba Specialty Chemicals Water Treatments, Inc.

Enclosures

cc: Aquanetta Dickens, U.S. EPA, Region III

CONFIDENTIAL

'ALCOPOL' 0 70PG: ACM 293:

ACUTE EYE IRRITATION

TEST IN THE RABBIT

PROJECT NUMBER 3/44

Experimental Procedures:

Date Started: 18 April 1988

Date Completed: 21 April 1988

AUTHOR: J.R. Jones

STUDY SPONSOR:

Allied Colloids Limited
P.O. Box 38
Low Moor
BRADFORD
West Yorkshire
BD12 0JZ

ISSUED BY:

Safepharm Laboratories Limited
P.O. Box No. 45
DERBY
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U.K.

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Facsimile: (0332) 799018

Telex: 377079 SAFPHM G

SAFEPHARM LABORATORIES LIMITED

QUALITY ASSURANCE UNIT REPORT

The routine inspection of short term toxicity studies at Safepharm Laboratories is carried out as a continuous process designed to ensure that where possible all critical phases of a particular study type are inspected at least once per month. Dates of inspection for this study type are given below:

<u>STUDY TYPE</u>	<u>DATE(S) OF INSPECTION</u>
Eye Irritation:	08/03/88, 16/03/88
General Facilities Audit conducted:	29/03/88
All findings reported to management:	30/03/88

This report has been audited by Safepharm Laboratories Quality Assurance Unit and is an accurate account of the procedures followed and accurately records the original raw laboratory data generated in this study.

Date of report audit: 29/04/88

J.M. Crowther M.I.S.T.
ASSISTANT QUALITY ASSURANCE MANAGER

..... J.M. Crowther

DATE:

..... 04/05/88

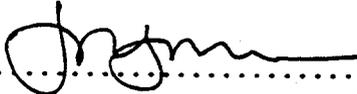
AUTHENTICATION

I, the undersigned, hereby declare that this study was performed under my supervision, as Study Director, according to the procedures herein described, and that this report provides an accurate and faithful record of the results obtained.

 DATE: 04/05/88

R.L. Guest H.TEC
Study Director

This study was performed in compliance with the Organisation for Economic Co-operation and Development (OECD) General Principles of Good Laboratory Practice (GLP).

 DATE: 04/05/88

J.R. Jones H.N.C.
Head of General Toxicology
for Safepharm Laboratories

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

C. Guest
P.A. Warner F.I.A.T., B.A. (Open)

SUMMARY OF RESULTS

STUDY SPONSOR : ALLIED COLLOIDS LIMITED

PROJECT NUMBER : 3/44

TEST MATERIAL : 'ALCOPOL' 0 70PG: ACM 293

1. A study was performed to assess the irritancy potential of the test material to the eye of the New Zealand White rabbit. The method used followed that described in the OECD Guidelines for Testing of Chemicals (1981) No. 405 "Acute Eye Irritation/Corrosion".
2. A single application of the test material to the non-irrigated eye of one rabbit produced opalescent corneal opacity, iridial inflammation and severe conjunctival irritation.
3. The test material produced a maximum total score of 83 and was regarded as a very severe to extremely severe irritant (Class 7 - 8 on a 1 to 8 scale) to the rabbit eye according to a modified Kay and Calandra scoring system (based on one rabbit only).

The test material was also regarded as irritant according to EEC labelling regulations. It is considered reasonable to assume that the symbol "Xi" and risk phrase R 41 "RISK OF SERIOUS DAMAGE TO EYES" are therefore required.

'ALCOPOL' 0 70PC^h ACM 293:

ACUTE EYE IRR. ATION

TEST IN THE RABBIT

PROJECT NUMBER: 3/44

INTRODUCTION

The study was performed according to Safepharm Standard Protocol Number GM 05/84/94B and was carried out in order to assess the irritancy potential of the test material following a single application to the rabbit eye. The study was designed to comply with the recommendations of the OECD Guidelines for Testing of Chemicals (1981) No. 405 "Acute Eye Irritation/Corrosion". The test system was chosen because the rabbit 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 will be used to classify the test material according to the E.E.C. Directive of 29 July 1983 83/467/EEC adapting Council Directive 67/548/EEC on the regulations relating to the classification, packaging and labelling of dangerous substances.

The results of the study are believed to be of value in predicting the likely eye irritancy potential of the test material to man.

METHODS

1. Animals and Animal Husbandry

One male New Zealand White rabbit was supplied by David Percival Ltd., Moston, Sandbach, Cheshire, U.K. At the start of the study the animal weighed 2.59 kg and was approximately twelve to sixteen weeks old. After a minimum acclimatisation period of five days the animal was given a number unique within the study which was written with a black indelible marker-pen on the inner surface of the ear and on a cage label.

The animal was individually housed in suspended metal cages. Free access to mains drinking water and food (Rabbit Diet, Preston Farmers Limited, New Leake, Boston, Lincolnshire, U.K.) was allowed throughout the study.

1. Animals and Animal Husbandry (contd)

The animal room was maintained at a temperature of 17 - 22°C and relative humidity of 65 - 70%. The rate of air exchange was approximately 15 changes per hour and the lighting was controlled by a time switch to give 12 hours light and 12 hours darkness.

2. Test Material and Experimental Preparation

The test material was supplied by Allied Colloids Limited, as follows:

Description	:	colourless slightly viscous liquid
Container	:	glass screw-top bottle
Label	:	'ALCOPOL' O 70PG: ACM 293
Date of arrival	:	16 February 1988
Storage conditions	:	room temperature

For the purpose of this study the test material was used as supplied.

The identification and stability of the test material were not determined.

3. Procedure

Immediately before commencement of the test, both eyes of the provisionally selected test rabbit were examined for evidence of ocular irritation or defect using the light source from a standard ophthalmoscope.

On the day of the test the animal was held firmly but gently until quiet. A volume of 0.1 ml of the test material was instilled into the right eye of the rabbit by gently pulling the lower lid away from the eyeball to form a cup into which the test material was dropped. The upper and lower eyelids were held together for about one second immediately after application, to prevent loss of the test material, and then released. The left eye remained untreated and was used for control purposes.

Assessment of damage/irritation was made 1, 24, 48 and 72 hours following treatment, according to the numerical evaluation given in Appendix I, (i.e. Draize J.H. 1959, Association of Food and Drug Officials of the United States, Austin, Texas, "The Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics"). Examination of the eye was facilitated by use of the light source from a standard ophthalmoscope.

3. Procedure (contd)

Severe ocular reactions were noted at the 72-hour observation and for humane reasons no further animals were treated.

4. Interpretation of Results

The numerical values corresponding to each animal, tissue and day were recorded. The data relating to the conjunctivae were designated by the letters A (redness), B (chemosis) and C (discharge), those relating to the iris designated by the letter D and those relating to the cornea by the letters E (degree of opacity) and F (area of opacity). For each tissue the total score was calculated as follows:

$$\begin{aligned} \text{Total score for conjunctivae} &= (A + B + C) \times 2 \\ \text{Total score for iris} &= D \times 5 \\ \text{Total score for cornea} &= (E \times F) \times 5 \end{aligned}$$

Using the numerical data obtained a modified version of the system described by Kay J.H. and Calandra J.C., J. Soc. Cosmet. Chem., 1962 13 281 - 289 (see Appendix II) was used to classify the ocular irritancy potential of the test material. The highest maximum total score enabled assessment of the eye irritancy potential of the test material using the table given in Appendix II.

The results were also interpreted according to the EEC Directive of 29 July 1983 83/467/EEC adapting Council Directive 67/548 EEC on the regulations relating to the classification, packaging and labelling of dangerous substances, as follows:

i) Interpretation according to Annex VI Part II (B) Eye Irritation

Criteria

The test material will be classified as irritant and will require the appropriate "Xi" symbol if ocular lesions occur within 72 hours after exposure, persist for at least 24 hours and correspond to one or more

- corneal opacity 2 or more
- iridial lesion 1 or more
- redness of conjunctivae 2.5 or more
- chemosis of conjunctivae 2 or more

4. Interpretation of Results (contd)

i) Interpretation according to Annex VI Part II (B) Eye Irritation
Criteria (contd)

The 24, 48 and 72-hour readings for each animal will be used to calculate the mean values.

ii) Interpretation according to Annex VI Part II (D)

In addition the following risk (R) phrases will be assigned to the test material, if appropriate, according to the criteria indicated below:

R 36 "IRRITATING TO EYES"

If, when applied to the eye of three rabbits, significant ocular lesions are caused which are present 24 hours or more after the instillation of the test material in two or more animals. Ocular lesions are significant if the mean of the 24, 48 and 72-hour readings comply with any of the following criteria:

- | | |
|-------------------------|---|
| - corneal opacity | equal to or greater than 2
but less than 3 |
| - iridial lesion | equal to or greater than 1 |
| - conjunctival redness | equal to or greater than 2.5 |
| - conjunctival chemosis | equal to or greater than 2 |

R 41 "RISK OF SERIOUS DAMAGE TO THE EYES"

If, when applied to the eye of three rabbits, severe ocular lesions are caused in two or more animals which are present 24 hours or more after instillation of the test material. Ocular lesions are severe if the mean of the 24, 48 and 72 hour readings comply with either of the following criteria:

- | | |
|-------------------|----------------------------|
| - corneal opacity | equal to or greater than 3 |
| - iridial lesion | equal to 2 |

ARCHIVES

On completion of the study, all raw laboratory data and a copy of the final report were transferred to Safeparm Laboratories Central Archives, London Road, Shardlow, Derbyshire, U.K., where they will be retained for a period of ten years.

RESULTS

Individual and total scores for ocular irritation are given in Table 1. The individual mean scores, as required for EEC labelling regulations, are presented in Table 2.

Diffuse corneal opacity, iridial inflammation and moderate conjunctival irritation were noted one hour after treatment. The ocular irritation increased at subsequent observations and was identified as translucent or opalescent corneal opacity, iridial inflammation and severe conjunctival irritation. Due to the persistence of the severe ocular reactions the study was terminated after the 72-hour observation. No further animals were treated.

The test material produced a maximum total score of 83 and was regarded as a VERY SEVERE TO EXTREMELY SEVERE IRRITANT (CLASS 7 - 8 ON A 1 TO 8 SCALE) to the rabbit eye (based on one rabbit only).

The test material was also regarded as irritant according to EEC labelling regulations. It is considered reasonable to assume that the symbol "Xi" and risk phrase R 41 "RISK OF SERIOUS DAMAGE TO EYES" are therefore required.

CONCLUSION

The test material, 'ALCOPOL' O 70PG: ACM 293, was regarded as a very severe to extremely severe irritant to the rabbit eye (based on one rabbit only).

The test material was also regarded as irritant according to EEC labelling regulations. It is considered reasonable to assume that the symbol "Xi" and risk phrase R 41 "RISK OF SERIOUS DAMAGE TO EYES" are therefore required.

TABLE 1

INDIVIDUAL SCORES AND TOTAL SCORES FOR OCULAR IRRITATION

TEST MATERIAL: 'ALCOPOL' 0 70PG: ACM 293

RABBIT NUMBER	31			
TIME AFTER TREATMENT	1 hr	24 hr	48 hr	72 hr
<u>CORNEA</u>				
E = Degree of opacity	1	2	2	3
F = Area of opacity	4	4	4	4
Score (E x F) x 5	20	40	40	60
<u>IRIS</u>				
D	1	1	1	1
Score (D x 5)	5	5	5	5
<u>CONJUNCTIVAE</u>				
A = Redness	2	3	3	3
B = Chemosis	2	3	4	4
C = Discharge	3	2	3	2
Score (A+B+C) x 2	14	16	20	18
TOTAL SCORES	39	61	65	83

Key: hr = hour(s)

TABLE 2

INDIVIDUAL MEAN SCORES FOR CORNEA, IRIS & CONJUNCTIVAE

REQUIRED FOR EEC LABELLING REGULATIONS

TEST MATERIAL: 'ALCOPOL' 0 70PG: ACM 293

RABBIT NUMBER	TIME AFTER TREATMENT	CORNEAL OPACITY	IRIDIAL INFLAMMATION	CONJUNCTIVAL REDNESS	CONJUNCTIVAL CHEMOSIS
	24 HOURS	2	1	3	3
31	48 HOURS	2	1	3	4
	72 HOURS	3	1	3	4
TOTAL (24, 48 & 72 HOURS)		7	3	9	11
MEAN		2.3+	1.0+	3.0+	3.7+

+ = positive criteria

A P P E N D I C E S

A P P E N D I X I

DRAIZE SCALE FOR SCORING OCULAR IRRITATION

1. CONJUNCTIVAE

(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

- Vessels normal 0
- Vessels definitely injected above normal 1
- More diffuse, deeper crimson red, individual vessels not easily discernible 2
- Diffuse beefy red 3

(B) Chemosis

- No swelling 0
- Any swelling above normal (includes mictitating membrane) 1
- Obvious swelling with partial eversion of lids 2
- Swelling with lids about half closed 3
- Swelling with lids half closed to completely closed 4

(C) Discharge

- No discharge 0
- Any amount different from normal (does not include small amounts observed in inner canthus of normal animals) 1
- Discharge with moistening of the lids and hairs just adjacent to lids 2
- Discharge with moistening of the lids and hairs a considerable area around the eye 3

THE TOTAL SCORE = (A + B + C) x 2

MAXIMUM TOTAL = 20

2. IRIS

(D) Values

- Normal 0
- Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive) 1
- No reaction to light, haemorrhage, gross destruction (any or all of these) 2

THE TOTAL SCORE = D x 5

MAXIMUM TOTAL = 10

3. CORNEA

(E) Degree of Opacity (most dense area used)

- No opacity 0
- Scattered or diffuse areas, details of iris clearly visible 1
- Easily discernible translucent areas, details of iris slight obscured 2
- Opalescent areas, no details of iris visible, size of pupil barely discernible 3
- Opaque, iris invisible 4

(F) Area of Cornea involved

- One quarter (or less) but not zero 1
- Greater than one quarter but not less than half 2
- Greater than half but less than three quarters 3
- Greater than three quarters, up to whole area 4

THE TOTAL SCORE = (E x F) x 5

MAXIMUM TOTAL = 80

MAXIMUM TOTAL SCORE POSSIBLE = 110

APPENDIX II

MODIFIED KAY AND CALANDRA INTERPRETATION OF EYE IRRITATION TEST

MAXIMUM MEAN SCORE	PERSISTENCE OF SCORE	DESCRIPTION RATING (AND CLASS)	
0.0 to 0.5	Group mean score at 24 hours = 0	Non-irritating (1)	
	Group mean score at 24 hours > 0	Practically non-irritating (2)	
0.5 to 2.5	Group mean score at 24 hours = 0	Non-irritating (1)	
	Group mean score at 24 hours > 0	Practically non-irritating (2)	
2.5 to 15	Group mean score at 48 hours = 0	Minimal irritant (3)	
	Group mean score at 48 hours > 0	Mild irritant (4)	
15 to 25	Group mean score at 72 hours = 0	Mild irritant (4)	
	Group mean score at 72 hours > 0	Moderate irritant (5)	
25 to 50	Group mean score at 7 days 20 or less	More than half of the individual total scores at 7 days 10 or less	Moderate irritant (5)
		More than half of the individual total scores at 7 days > 10 but no individual total score at 7 days > 30	Moderate irritant (5)
		More than half of the individual total scores at 7 days > 10 and any individual score at 7 days > 30	Severe irritant (6)
		Group mean score at 7 days > 20	Severe irritant (6)
50 to 80	Group mean score at 7 days 40 or less	More than half of the individual total scores at 7 days 30 or less	Severe irritant (6)
		More than half of the individual total scores at 7 days > 30 but no individual total scores at 7 days > 60	Severe irritant (6)
		More than half of the individual total scores at 7 days > 30 and any individual total score at 7 days > 60	Very severe irritant (7)
		Group mean total score at 7 days > 40	Very severe irritant (7)
80 to 100	Group mean total score at 7 days 80 or less	More than half of the individual total scores at 7 days 60 or less	Very severe irritant (7)
		More than half of the individual total scores at 7 days > 60 but no individual total score at 7 days > 100	Very severe irritant (7)
		More than half of the individual total scores at 7 days > 60 and any individual total score at 7 days > 100	Extremely severe irritant (8)
		Group mean total score at 7 days > 80	Extremely severe irritant (8)
100 to 110	Group mean total score at 7 days 80 or less	Very severe irritant (7)	
	Group mean total score at 7 days > 80	Extremely severe irritant (8)	

ACUTE ORAL TOXICITY TO
RATS OF
COLLAFIX PP2

Addressee:

Mr. R. Lisle,
Allied Colloids Limited,
P.O. Box 38,
Low Moor,
BRADFORD.
Yorks,
BD12 0J2.

18 March 1983.
Re-issued 3 May 1983

Author:

Sheena R. Kynoch.
Huntingdon Research Centre,
HUNTINGDON,
Cambridgeshire.

I the undersigned, hereby declare that the work was performed under my supervision according to the procedures herein described, and that this report provides a correct and faithful record of the results obtained.

Sheena R. Kynoch

Sheena R. Kynoch, B.Sc.,
Head of Department of Industrial Toxicology

QUALITY ASSURANCE AUDIT STATEMENT

HRC REPORT NO. 83170D/AL-6/AC

This report has been audited by HRC Quality Assurance Unit and is considered to be an accurate presentation of the data produced during the course of the study.

Kenneth W.G. Shillam
14.3.83

Kenneth W.G. Shillam, B.Sc., Ph.D., F.I. Biol.,
Director, Quality Assurance

Audit notes

An audit by the QAU consists of (a) a comparison of the reported findings with the raw data as recorded in notebooks and worksheets, and (b) a comparison of derived data and statements of fact with the reported raw data. Any computerized presentations which are the outcome of verified entry direct from the raw data and which are secure against manual alteration are not normally audited.

Short reports and some parts of longer reports are audited completely. Reports containing large amounts of data are divided into sections liable to have similar error rates and each is subjected to a sampling procedure according to the methods described in British Standards Institution, BS 6000, 6001 (1972) and US Military Standard 105D (1963). The Acceptable Quality Level (the maximum percentage errors considered satisfactory as a process average) is 0.4. Reports with any section not meeting the acceptance criteria are revised by the Study Director and this is followed by QAU re-audit.

The results of any investigations made by the sponsor and which are included in HRC reports are audited using the sponsor's report to HRC.



QAU STUDY INSPECTIONS

HRC Report No. 83170D/ALC 6/AC

Acute studies are conducted at HRC in a setting which involves frequent repetition of similar or identical procedures. At or about the time of this study, 'process-based' inspections were made by the QAU of the critical procedures relevant to this study type. For the inspection of each procedure, at least one study was selected at random.

The findings of these inspections were reported promptly to the Study Director and to HRC Management.

A handwritten signature in black ink, appearing to read 'K. W. G. Shillam', is written above the printed name.

K. W. G. Shillam
Director, Quality Assurance

Sample designation:

Collafix PP2

Examination for:

Acute oral toxicity to rats.

1. INTRODUCTION

- 1.1. The study was designed to assess the toxicity following a single oral dose. The test sample may be ingested accidentally.
- 1.2. The rat has been shown to be a suitable model for this type of study and is the animal recommended in the test protocol.
- 1.3. The study plan of the main study was agreed by the Study Director on 9 February 1983 and the study was undertaken between 17 February - 3 March 1983.

2. TEST SUBSTANCE

- 2.1. Collafix PP2, a white mobile dispersion was received on 7 February 1983 and stored at ambient temperature.
- 2.2. Collafix PP2 was administered as supplied by the sponsor at a volume not exceeding 5.3 ml/kg (S.G. 0.95).
- 2.3. The test substance was prepared on the day of dosing.
- 2.4. The stability and absorption of the test substance were not determined.

3. EXPERIMENTAL PROCEDURE3.1 Protocol

The procedure was based on that recommended under the OECD Guideline for Testing Chemicals No. 401 "Acute Oral Toxicity".

3.2. Animal management

- 3.2.1. An equal number of male and female HC/CFY (Remote Sprague-Dawley) rats was obtained from Hacking and Churchill Limited, Abbots Ripton Road, Wyton, Huntingdon, Cambridgeshire, England. They were in a weight range of 91 to 121 g in the main study and approximately four to six weeks of age. All the rats were acclimatised to the experimental environment for a minimum period of 6 days prior to the start of the main study.
- 3.2.2. The rats were randomly allocated to cages within treatment groups. They were housed in groups in metal cages with wire mesh floors. A standard laboratory rodent diet (Laboratory Diet No. 1, Spratt's Rodent Breeding Diet (LAD 1) Expanded obtained from Spratt's Specialist Services Division, New Malden, Surrey, England) and water were provided ad libitum. The batch of diet used for the study was analysed for certain chemical and microbiological contaminants. Access to food only was prevented overnight prior to and approximately 4 hours after dosing.
- 3.2.3. Results of routine chemical examination of water at source (Sapley Reservoir) as conducted quarterly by the Anglian Water Authority, are made available to Huntingdon Research Centre.
- 3.2.4. Animal room temperature was maintained at $21.5 \pm 3.5^{\circ}\text{C}$, recorded daily on a maximum and minimum thermometer. The rate of air exchange was maintained at approximately 15 air changes/hour. Lighting was controlled by means of a time switch to 12 hours artificial light in each 24 hours period. Humidity was not controlled but remained within a range of 25 - 59%RH recorded daily on a wet and dry bulb hygrometer.
- 3.2.5. Each animal at each dose level was identified by cage number and ear punching.

3.3. Experimental design

3.3.1. Preliminary study

A trial test was carried out by dosing two male and two female rats at 5.0 g/kg bodyweight.

3.3.2. Main study

A group of ten rats (five males and five females) was treated at 5.0 g/kg bodyweight.

3.4. Treatment procedure

The appropriate dose volume of the test substance was administered to each rat using a syringe and plastic catheter.

3.5. Observation

- 3.5.1. Animals were observed soon after dosing; then at frequent intervals for the remainder of Day 1. On subsequent days the animals were observed at least twice. Clinical signs were recorded at each observation.
- 3.5.2. The animals on the preliminary and main studies were observed for 5 and 14 days respectively, after dosing.
- 3.5.3. The following were recorded on the main study:
- 3.5.3.1. The nature, severity, approximate time of onset and duration of each toxic sign.
- 3.5.3.2. Individual bodyweights of rats on Days 1 (day of dosing), 8 and 15.

3.6. Post mortem examination

All animals were killed on Day 15 by cervical dislocation and were subjected to a macroscopic post mortem examination which consisted of opening the abdominal and thoracic cavities. The macroscopic appearance of abnormal organs was recorded.

4. ARCHIVES

All specimens, raw data and other documents generated at HRC during the course of this study, together with a copy of this Final Report, have been lodged in the Huntingdon Research Centre Archives, Huntingdon, England.

5. RESULTS

The results of the preliminary study indicated that the acute median lethal oral dose (LD_{50}) was greater than 5 g/kg bodyweight. A death was recorded on the preliminary study at this level (Table 1).

Dosing was then extended to a larger group of rats (five males and five females) in order to confirm this finding.

There were no mortalities (Table 1).

Signs of reaction to treatment (Table 2) observed shortly after dosing consisted of pilo-erection, abnormal body carriage (hunched posture), abnormal gait (waddling) and pallor of the extremities. One animal also showed lethargy, decreased respiratory rate, ptosis and gasping respiration on Day 3.

Recovery as judged by external appearance and behaviour was apparently complete by Day 6.

A poor bodyweight gain was seen in one male rat on Day 8. Male bodyweights on Day 15 and female bodyweights on Days 8 and 15 were within normal limits.

Terminal autopsy findings were normal.

6. CONCLUSION

The acute median lethal oral dose (LD_{50}) to rats of Collafix PP2 was found to be:

greater than 5.0 g/kg bodyweight.

TABLE 1

Mortality data for groups of rats dosed orally with
Collafix PP2

Study	Dose (g/kg)	Mortality ratio ($\frac{\text{No. of deaths}}{\text{N. dosed}}$)			Time of death after dosing (hours)
		♂	♀	Combined	
Preliminary	5.0	1/2	0/2	1/4	<2
Main	5.0	0/5	0/5	0/10	-

TABLE 2

Signs of reaction to treatment observed in rats dosed orally with
Collafix PF2

Main study

Signs	No. of rats in group of 5 showing signs	
	Dose (g/kg)	
	5.0	
	♂	♀
Pilo-erection	5	5
Abnormal body carriage (hunched posture)	5	5
Abnormal gait (waddling)	5	5
Pallor of extremities	5	5
Lethargy	1	0
Decreased respiratory rate	1	0
Ptosis	1	0
Gasping respiration	1	0

TABLE 3

Group mean bodyweights (g) of rats dosed orally with
Collafix PF2

Main study

Sex	Dose (g/kg)	Bodyweight (g) at Day		
		1	8	15
♂	5.0	104	172	242
		102	142	184
		91	190	260
		98	183	251
		108	176	227
	Mean	101	173	233
♀	5.0	93	142	170
		121	178	210
		108	170	202
		96	148	188
		92	144	173
	Mean	102	156	189

CONFIDENTIAL

ACUTE ORAL TOXICITY
TO RATS OF
CFR 5651

Addressee:

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17 June 1985.

Author:

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STUDY DIRECTOR STATEMENT

This report, which describes a study conducted at HRC under my direction, is considered to be a full and true account of the results obtained.

Sheena R. Kynoch

Sheena R. Kynoch, B.Sc.,
Study Director,
Head, Department of Industrial Toxicology.

QUALITY ASSURANCE STATEMENT

Acute studies are conducted at HRC in a setting which involves frequent repetition of similar or identical procedures. At or about the time of the study described in this report, 'process-based' inspections were made by the Quality Assurance Unit of the critical procedures relevant to this study type. For the inspection of any given procedure, at least one study was selected without bias. The findings of these inspections were reported promptly to the Study Director and to HRC Management.

This report has been audited by the HRC Quality Assurance Unit and is considered to be an accurate presentation of the data produced during the course of the study.

P. Rickell B.Sc.
System Compliance Auditor

PP 14.6.85
K.W.G. Shillam, B.Sc., Ph.D., F.I. Biol.,
Director, Quality Assurance.

Sample designation: CFR 5651.

Examination for: Acute oral toxicity to rats.

1. INTRODUCTION

- 1.1. The study was designed to assess the toxicity following a single oral dose. The test sample may be ingested accidentally.
- 1.2. The rat has been shown to be a suitable model for this type of study and is the animal recommended in the test protocol.
- 1.3. The study plan was agreed by the Study Director on 29 April 1985 and the study was undertaken between 9 and 23 May 1985.

2. TEST SUBSTANCE

- 2.1. CFR 5651, a light brown/yellow liquid, was received on 29 April 1985 and stored at ambient temperature.
- 2.2. CFR 5651 was administered as supplied by the Sponsor at a volume of 4.8 ml/kg (S.G. 1.05).
- 2.3. The stability and absorption of the test substance were not determined.

3. EXPERIMENTAL PROCEDURE

3.1. Protocol

The experimental procedure was based on that recommended under the OECD guideline for Testing of Chemicals No. 401 "Acute Oral Toxicity".

3.2. Animal management

- 3.2.1. Equal numbers of male and female CFY (Remote Sprague-Dawley) rats were obtained from Interfauna UK Ltd., (formerly Hacking and Churchill Ltd.), Huntingdon, Cambridgeshire. They were in a weight range of 106 to 143 g prior to dosing (Day 1) and approximately four to six weeks of age. All the rats were acclimated to the experimental environment for a minimum period of 7 days prior to the start of the study.
- 3.2.2. The rats were randomly allocated to cages within the treatment group. They were housed in groups by sex in metal cages with wire mesh floors. A standard laboratory rodent diet (Scientific Feeds LAD 1 obtained from Special Diet Services Ltd., Witham, Essex, England) and water were provided ad libitum. The batch of diet used for the study was analysed for certain chemical and microbiological contaminants. Access to food only was prevented overnight prior to and approximately 4 hours after dosing.
- 3.2.3. Results of routine chemical examination of water conducted quarterly by the Anglian Water Authority, are made available to Huntingdon Research Centre.
- 3.2.4. The mean daily minimum and maximum temperatures of the animal room were 21°C and 23°C respectively and the mean daily relative humidity value was 55%. The rate of air exchange was maintained at approximately 15 air changes/hour. Lighting was controlled by means of a time switch to 12 hours artificial light in each 24 hour period.
- 3.2.5. Each animal was identified by cage number and ear punching.

3.3. Experimental design

A group of ten rats (five males and five females) was treated at 5.0 g/kg bodyweight.

3.4. Treatment procedure

The appropriate dose volume of the test substance was administered to each rat using a syringe and plastic catheter.

3.5. Observation

- 3.5.1. Animals were observed soon after dosing; then at frequent intervals for the remainder of Day 1. On subsequent days the animals were observed at least twice per day. Clinical signs were recorded at each observation.

3.5.2. All animals were observed for 14 days after dosing.

3.5.3. The following were recorded:

3.5.3.1. The nature, severity, approximate time of onset and duration of each toxic sign.

3.5.3.2. Individual bodyweights of rats on Days 1 (day of dosing), 8 and 15.

3.6. Post mortem examination

All animals were killed on Day 15 by cervical dislocation and were subjected to a macroscopic post mortem examination which consisted of opening the abdominal and thoracic cavities. The macroscopic appearance of abnormal organs when present was recorded.

4. ARCHIVES

All specimens, raw data and other documents generated at HRC during the course of this study, together with a copy of this Final Report, have been lodged in the Huntingdon Research Centre Archives, Huntingdon.

5. RESULTS

A group of ten rats (five males and five females) were dosed orally with CER 5651 at 5.0 g/kg bodyweight.

There were no mortalities.

Clinical signs (Table 1)

Signs of reaction to treatment observed shortly after dosing in all rats were pilo-erection, abnormal body carriage (hunched posture), abnormal gait (waddling), pallor of the extremities and diarrhoea.

Recovery as judged by external appearance and behaviour was apparently complete by Day 7.

Bodyweight (Table 2)

Bodyweight gains were recorded for all rats on Days 8 and 15.

Terminal autopsy

Terminal autopsy findings were normal.

6. CONCLUSION

The acute lethal oral dose to rats of CFR 5651 was found to be:

greater than 5.0 g/^A bodyweight.

TABLE 1

Signs of reaction to treatment observed in rats dosed orally with
CFR 5651

Signs	No. of rats in group of 5 showing signs	
	Dose (g/kg)	
	5.0	
	M	F
Pilo-erection	5	5
Abnormal body carriage (hunched posture)	5	5
Abnormal gait (waddling)	5	5
Pallor of extremities	5	5
Diarrhoea	5	5

TABLE 2

Individual bodyweights (g) of rats dosed orally with CFR 5651

Dose: 5.0 (g/kg)

Sex	Bodyweight (g) at Day		
	1	8	15
M	143	203	285
	141	205	282
	117	188	264
	142	205	276
	141	215	286
F	107	156	191
	108	154	196
	108	165	206
	106	150	185
	106	153	195

M = Male

F = Female