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8EHQ-0993-12431

September 13, 1993



INIT 09/17/93

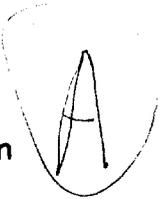
**FEDERAL EXPRESS
RETURN RECEIPT REQUESTED**

Document Processing Center (TS-790)
Office of Toxic Substances
Environmental Protection Agency
401 M St. S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator



88930000448

Subject: TSCA Section 8(e) Submission



93 SEP 17 AM 11:55

Dear Sir/Madam:

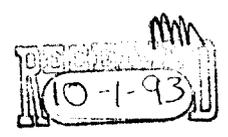
Elf Atochem North America Inc. is submitting the attached studies to the Environmental Protection Agency (EPA) pursuant to Toxic Substances Control Act (TSCA) Section 8(e). These studies do not involve effects in humans.

The enclosed studies recently came into our possession via our parent company in France and provide information on ADAMQUAT 80 MC. ADAMQUAT 80 MC is 2-(dimethylamino)ethyl acrylate methochloride (CAS No. 44992-01-0). This product is manufactured by Elf Atochem for use as a monomer in polymer synthesis.

Nothing in this letter or the enclosed study summary reports is considered confidential business information of Elf Atochem.

The titles of the enclosed study reports are OECD Acute Eye Irritation/Corrosion Test in the Rabbit and Magnusson & Kligman Maximization Test in the Guinea Pig. The following is a summary of the adverse effects observed in the above-referenced studies.

Magnusson & Kligman Maximization Test - ADAMQUAT 80 MC was tested for potential to produce allergic skin reaction by intradermal injection and skin application to guinea pigs using a modified Magnusson and Klingman method. The test material produced a 100% (19/19) sensitization rate and was classified as a strong sensitizer.



39 pgs.

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TSCA 8(e) Submission
ADAMQUAT 80 MC
September 13, 1993
Page 2

Eye Irritation/Corrosion Test - Due to the severity of the reactions observed the study was confined to one rabbit. The test material produced moderate corneal and iridial reactions and severe conjunctival reactions.

Elf Atochem has not previously filed any 8(e) notices or Premanufacture Notifications (PMNs) on the subject material.

Results from the enclosed study report are being included in the current Elf Atochem Material Safety Data Sheet for ADAMQUAT 80 MC.

Further questions regarding this submission may be directed to me at (215) 337-6892.

Sincerely,



C.H. Farr, PhD, DABT
Manager, Product Safety
and Toxicology

Enclosure

2

CONFIDENTIAL

ADQUAT 80 MC:

1. RANGE FINDING ACUTE ORAL TOXICITY TEST IN THE RAT.
2. OECD ACUTE DERMAL IRRITATION/CORROSION TEST IN THE RABBIT.
3. OECD ACUTE EYE IRRITATION/CORROSION TEST IN THE RABBIT.
4. MAGNUSSON & KLIGMAN MAXIMIZATION TEST IN THE GUINEA PIG.

Authors: T. A. Collier
R. L. Guest
D. S. Hewitt

Addressee:

Norsolor S.A.
B.P. 109
57503 St. Avoild Cedex
FRANCE

Issued by:

Safeparm Laboratories Limited
P.O. Box No. 45
DERBY
DE1 2BT
ENGLAND

Telephone: DERBY (0332) 792789/
792896

Telex: 377079 SAFPHM G

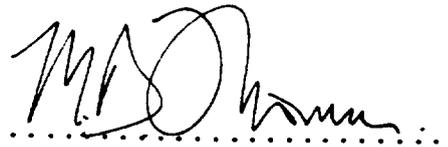
STATEMENT OF COMPLIANCE

This study was carried out in compliance with OECD Principles of Good Laboratory Practice.

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.

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.

M.B. Thomas B.Sc., M.I. Biol.
QUALITY ASSURANCE MANAGER


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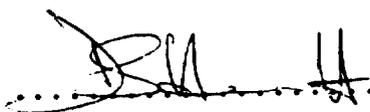
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11/7/85
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V A L I D A T I O N

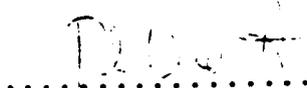
We the undersigned hereby declare that this study was performed under our supervision according to the procedures herein described, and that this report provides an accurate and faithful record of the results obtained.

Study Supervisors:

.....

Date: 11.7.85.....

D.S. Hewitt B.Sc. (Hons)

.....

Date: 11.7.85.....

R.L. Guest HTEC

Study Director:

.....

Date: 11/7/85.....

T.A. Collier HNC

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MAGNUSSON & KLIGMAN MAXIMIZATION STUDY:
DETERMINATION OF THE CONTACT SENSITIZATION
POTENTIAL OF ADQUAT 80 MC IN THE GUINEA PIG
EXPERIMENT NUMBER 84/8505

INTRODUCTION

This study was performed according to Safepharm Standard Protocol Number GM 09/83/85B "The Magnusson & Kligman Maximization Test" and was designed to assess the contact sensitization potential of the test material. The results of the study will be of value in predicting the contact sensitization potential of the test material to man.

The test system was chosen because the guinea pig has been shown to be a suitable model for this type of study and is recommended in the test method.

METHODS

1. Animals and Animal Husbandry

Forty-eight female, albino Dunkin-Hartley guinea pigs supplied by A. Tuck & Sons Limited, Battlesbridge, Essex, in the weight range 324-490g and approximately six to twelve weeks of age at the start of the study, were used. This strain of guinea pig has been shown to produce a satisfactory sensitization rate using known positive sensitizers; the sensitivity of these animals is checked at regular intervals at this laboratory.

All the guinea pigs were acclimatized to the laboratory environment for a minimum period of five days prior to the start of the study.

The guinea pigs were allocated at random to cages within treatment groups. They were housed in groups of up to four in solid-floor polypropylene cages (supplied by NKP Limited, Dartford, Kent) and furnished with softwood shavings. A standard laboratory guinea pig diet (Guinea Pig FD1 Diet supplied by Special Diet Services Limited, Witham, Essex) and mains tap water, were supplied ad libitum.

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METHODS/Contd

1. Animals and Animal Husbandry (contd)

The animal room temperature was maintained at $22 \pm 3^{\circ}\text{C}$ recorded daily on a maximum and minimum thermometer. The rate of air exchange was approximately 10 changes per hour and lighting was controlled by means of a time switch to give a 12 hour light/dark cycle. Humidity remained within a range of 45-65%RH recorded daily on a wet and dry bulb hygrometer.

Each animal was uniquely identified for this study by experimental cage label and indelible ink marks on the rump.

2. Test Material and Experimental Preparation

Clear pale straw coloured liquid ADQUAT 80 MC supplied by Norsolor SA in a plastic screw-top container was received at these laboratories on 29 April 1985. The test material was stored at ambient temperature in the dark.

For the purpose of this study the following concentrations of the test material were freshly prepared as required:-

Intradermal Induction : 0.1% in water for injection B.P.
Topical Induction : 25% in water for injection B.P.
Topical Challenge : 100% as supplied.

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

3. Procedures

The test method is based on that originally described by Magnusson B. and Kligman A.M., J. Invest. Derm. 1969, 52, 268-276 with modifications as indicated in the U.K. Health and Safety Commission publication "Approved Code of Practice: Methods for determination of toxicity" to comply with the Notification of New Substances Regulations 1982.

Before commencing the Main Study a preliminary screen was carried out on the test material in order to determine its primary cutaneous irritation and systemic toxicity properties following both topical application and intradermal injection.

- 1) Procedures for Preliminary Siting Test
- a) Intradermal Injection

An area measuring 4cm x 6cm in the shoulder region of each of two guinea pigs was clipped free of hair using Oster A5 electric animal clippers (Oster Inc, Wisconsin, USA). Into the clipped area of one of these animals four 0.1ml intradermal injections of the test material at a concentration of 1% in a suitable vehicle were administered simultaneously; similarly four 0.1ml aliquots of a 5% concentration of the test material were injected into the second guinea pig.

Animals were observed 24, 48 and 72 hours and 7 days following treatment and any evidence of localized necrosis or systemic toxicity was recorded.

This procedure was repeated at concentrations of 0.1% and 0.5% using a further two guinea pigs.

Using the information obtained from this preliminary test, a concentration of the test material which was well

METHODS/Contd

3. Procedures (contd)

i) Procedures for Preliminary Siting Test (contd)

a) Intradermal Injection (contd)

tolerated both locally and systemically was selected for the Intradermal Induction stage of the Main Study.

b) Topical Application

Both flanks of each of two guinea pigs were closely clipped free of hair using Oster A5 electric animal clippers. These animals had been intradermally injected with Freund's complete adjuvant (Difco Laboratories, Detroit, Michigan, USA) between one and three weeks previously. The test material at a number of different concentrations in a suitable vehicle was applied to the clipped flanks under occlusive patches; the test material preparation was applied to a 2cm x 2cm square of Whatman No 4 filter paper and placed into position on the skin. The patch was secured with two strips of Slek waterproof adhesive strapping (Smith & Nephew Limited) in the form of a cross. Up to four patches were applied to each guinea pig. The loaded patches were covered with an overlapping length of aluminium foil. Both patches and foil were then firmly secured by a 7.5cm x 25cm length of Elastoplast elastic adhesive bandage (Smith & Nephew Limited) wound in a double layer around the torso of the animal. The patches were left in position for 24 hours.

Following the 24 hour exposure period the dressings and patches were removed and any residual test material

METHODS/Contd

3. Procedures (contd)

i) Procedures for Preliminary Siting Test (contd)

b) Topical Application (contd)

was washed from the application sites using cotton wool soaked in lukewarm water or ether. Approximately one hour following removal of the patches and 24 and 48 hours later, the reactions at the application sites were evaluated and scored according to the following scheme:-

No reaction	0
Scattered mild redness	1
Moderate and diffuse redness	2
Intense redness and swelling	3

The concentrations of the test material to be used on a further two guinea pigs were chosen, applied and then evaluated after similar time intervals.

Using the irritancy data obtained from all four animals used in the siting test the maximum concentration of the test material that was well tolerated was chosen for the Topical Induction stage of the Main Study. In addition the maximum non-irritant concentration of the test material ie that which caused no reactions at the 24 or 48 hour readings in any of the siting test animals, was chosen for the Topical Challenge stage of the Main Study.

ii) Procedure for Main Study

a) Induction

DAY 0: EXPERIMENTAL GROUP. An area measuring 4cm x 6cm in the shoulder region of each of 20 guinea pigs

METHODS/Contd

3. Procedures (contd)

ii) Procedure for Main Study (contd)

a) Induction (contd)

Day 0: EXPERIMENTAL GROUP. (contd)

was closely clipped free of hair. Into this area three pairs of intradermal injections were given simultaneously as follows:-

(1)	(1)
(2)	(2)
(3)	(3)

- (1) 0.1ml of Freund's complete adjuvant (Difco Laboratories, Detroit, Michigan USA).
- (2) 0.1ml of a 0.1% concentration of the test material.
- (3) 0.1ml of a 50:50 mixture of a 0.1% concentration of the test material emulsified in the adjuvant.

DAY 0: CONTROL GROUP. A further group of 20 guinea pigs was treated in a similar manner to the Experimental Group except that they were not exposed to the test material but received three pairs of intradermal injections as follows:-

- (1) 0.1ml of Freund's complete adjuvant
- (2) 0.1ml of vehicle alone
- (3) 0.1ml of a 50:50 mixture of vehicle emulsified in Freund's complete adjuvant

DAY 7: EXPERIMENTAL GROUP. The same area in the shoulder region of each guinea pig used

METHODS/Contd

3. Procedures (contd)

ii) Procedure for Main Study (contd)

a) Induction (contd)

DAY 7: EXPERIMENTAL GROUP. (contd)

previously for intradermal inductions was again closely clipped free of hair. The test material at a concentration of 25% was applied to a 2cm x 4cm patch of Whatman No 4 filter paper. This patch was applied to the clipped shoulder region and held in position with two strips of Slek waterproof adhesive strapping in the form of a cross. The patch was further secured by a 3.5cm x 25cm length of Elastoplast elastic adhesive bandage which was wound in a double layer around the torso of the animal. The dressing and patches were removed following a 48 hour exposure period.

DAY 7: CONTROL GROUP. The control group guinea pigs were treated in an identical manner to the Experimental Group animals except that the vehicle alone was applied to the induction site.

b) Challenge

DAY 21: EXPERIMENTAL AND CONTROL GROUPS. An area measuring 5cm x 5cm on both flanks of each Experimental and Control Group guinea pig was closely clipped free of hair. The test material, at the highest non-irritant concentration indicated by the topical siting test (100 %) was applied to

METHODS/Contd

3. Procedures (contd)

ii) Procedure for Main Study (contd)

b) Challenge (contd)

DAY 21: EXPERIMENTAL AND CONTROL GROUPS. (contd)

the clipped right flank of each animal under an occlusive patch in a similar manner to that used in the topical siting test. The vehicle alone was similarly applied to the clipped left flank. Both patches were covered with an overlapping length of aluminium foil and then held firmly in position for 24 hours by means of a 7.5cm x 25cm length of Elastoplast elastic adhesive bandage wound in a double layer around the torso of the animal.

DAY 22: Following the 24 hour exposure period the dressing and patches were removed from all Experimental and Control Group guinea pigs and any residual test material or vehicle was washed from the challenge sites using cotton wool soaked in lukewarm water or ether. The sites were marked using an indelible pen.

DAY 23: Twenty-one hours following removal of the patches the challenge sites of all Experimental and Control Group guinea pigs were lightly clipped free of hair. Three hours later (ie 24 hours following removal of the patches) the reactions observed at the test material and vehicle control sites were evaluated and scored using the same scheme used in the topical application siting test (see Methods 3 i b).

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METHODS/Contd

3. Procedure (contd)

ii) Procedure for Main Study (contd)

b) Challenge (contd)

DAY 24: The reactions observed at the challenge sites were again observed and scored i.e. 48 hours following removal of the patches.

c) Interpretation of Results

The number of guinea pigs in the Experimental Group showing a more severe reaction at the test material challenge site, than the most severe reaction observed at the test material challenge site of any of the Control Group animals, was noted. These reactions in the Experimental Group were attributed to contact sensitization caused by the test material. The test material was assigned a sensitization classification based on the percentage of animals showing a positive reaction according to the following modification of a scheme originally designed by Magnusson:-

Percentage of animals sensitized	Classification of sensitization potential
0	Non-sensitizer
1 - 28	Mild sensitizer
29 - 65	Moderate sensitizer
66 - 100	Strong sensitizer

METHODS/Contd

3. Procedure (contd)

ii) Procedure for Main Study (contd)

The results of this study provides an assessment of whether or not a test material could be a likely sensitizer. Extrapolation of these results to man is valid only to a very limited degree. The only generalisation that can be made is that test materials which are strong sensitizers in guinea pigs also cause a substantial number of sensitization reactions in man, whereas mild sensitizers in guinea pigs may or may not cause reactions in man.

ARCHIVES

On completion of the study all raw laboratory data and a copy of the final report were transferred to Safepharm Laboratories Central Archives, London Road, Shardlow, Derbyshire, England.

RESULTS

1. Intradermal Injection Siting Test

A summary of the results is given in Table 1 below:-

TABLE 1 : SUMMARY OF RESULTS FOR INTRADERMAL INJECTION

SITING TEST

Guinea Pig Number	Time of observation	Concentration of test material	Evidence of necrosis	Evidence of systemic toxicity
A	24 hour	0.1% ⁺	None	None
	48 hour		None	None
	72 hour		None	None
	7 days		None	None
B	24 hour	0.5% ⁺	Animal died in con- vulsion approximately 4 minutes following dosing.	
	48 hour			
	72 hour			
	7 days			
C	24 hour	1%*	Animal died in con- vulsion approximately 2 minutes following dosing.	
	48 hour			
	72 hour			
	7 days			
D	24 hour	5%*	Animal died in con- vulsion approximately 1 minute following dosing.	
	48 hour			
	72 hour			
	7 days			

* Vehicle : arachis oil B.P.

+ Vehicle : water for injection B.P.

Using the information given in Table 1 the concentration of the test material to be used for the intradermal induction stage of the Main Study was selected as follows:-

Intradermal Induction : 0.1% in water for injection B.P.

RESULTS/Contd

2. Topical Siting Test

An evaluation of the reactions observed at the application sites is given in Table 2 below:-

TABLE 2 : TOPICAL SITING TEST - EVALUATION OF REACTIONS
OBSERVED AT APPLICATION SITES

Guinea Pig Number	Concentration of test Material*%	Evaluation of Application Sites after Removal of Patches		
		1 hour	24 hours	48 hours
E	50	0	0	0
	100	0	0	0
F	50	0	0	0
	100	0	0	0
G	50	0	0	0
	100	0	0	0
H	50	0	0	0
	100	0	0	0

* Vehicle : water for injection B.P.

Using the irritancy data given in Table 2 the test material at a concentration of 100% was indicated as being suitable for the Topical Induction stage of the Main Study. However, this concentration produced death approximately one hour following topical application to a single preliminary guinea pig (No. 5-3) in the Main Study. A concentration of 25% was therefore used for Topical Induction of the remaining nineteen animals.

A concentration of 100% was used for the Topical Challenge.

RESULTS/Contd

3. Main Study

An evaluation of the challenge sites in the Experimental and Control Group guinea pigs is given in Table 3.

TABLE 3 : MAIN STUDY - EVALUATION OF REACTIONS AT CHALLENGE SITE IN THE EXPERIMENTAL AND CONTROL GROUPS

Test material : ADQUAT 80 MC
 Challenge Concentration : 100%
 Vehicle : - *

EXPERIMENTAL GUINEA PIG NUMBER	EXPERIMENTAL GROUP SCORES				CONTROL GUINEA PIG NUMBER	CONTROL GROUP SCORES			
	24 hours		48 hours			24 hours		48 hours	
	Test	Vehicle	Test	Vehicle	Test	Vehicle	Test	Vehicle	
1-0	2	0	2	0	6-0	0	0	0	0
1-1	1	0	1	0	6-1	0	0	0	0
1-2	2	0	2	0	6-2	0	0	0	0
1-3	1	0	1	0	6-3	0	0	0	0
2-0	2	0	2	0	7-0	0	0	0	0
2-1	2	0	2	0	7-1	0	0	0	0
2-2	2	0	2	0	7-2	0	0	0	0
2-3	2	0	1	0	7-3	0	0	0	0
3-0	2	0	1	0	8-0	0	0	0	0
3-1	2	0	2	0	8-1	0	0	0	0
3-2	2	0	1	0	8-2	0	0	0	0
3-3	2	0	1	0	8-3	0	0	0	0
4-0	2	0	2	0	9-0	0	0	0	0
4-1	1	0	1	0	9-1	0	0	0	0
4-2	1	0	1	0	9-2	0	0	0	0
4-3	2	0	2	0	9-3	0	0	0	0
5-0	3	0	2	0	10-0	0	0	0	0
5-1	2	0	2	0	10-1	0	0	0	0
5-2	2	0	2	0	10-2	0	0	0	0
5-3	DIED DAY 7				10-3	0	0	0	0

* Vehicle : water for injection B.P. was applied to all vehicle control sites.

RESULTS/Contd

3. Main Study (contd)

As indicated in Table 3 18/19 guinea pigs in the Experimental Group showed scattered mild redness (score 1) or moderate and diffuse redness (score 2) at the test material challenge site at the 24 hour reading. The remaining animal in this group showed intense redness and swelling (score 3) at this observation. At 48 hours scattered mild redness or moderate and diffuse redness persisted at the test material challenge site of all guinea pigs. As no reactions were observed at the test material challenge site of any of the Control Group animals, at either the 24 or 48 hour observation, the effects seen in the Experimental Group were attributed to contact sensitization caused by the test material.

The test material therefore produced a 100% (19/19) sensitization rate and was classified as a STRONG SENSITIZER.

Mortality

The single mortality observed in the Experimental Group at Day 7 was attributed to systemic toxicity caused by the application of the test material to the pre-injected topical induction site at a concentration of 100%.

Bodyweights

Individual bodyweights at Day 0 and Day 24, together with percentage bodyweight gains are given in the Appendix.

Bodyweight gains of guinea pigs in the Experimental Group between Day 0 and Day 24 were comparable to those observed in the Control Group over the same period.

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CONCLUSION

The test material, ADQUAT 80 MC was found to be a strong sensitizer in the guinea pig.

A P P E N D I X

INDIVIDUAL BODYWEIGHTS AND PERCENTAGE
BODYWEIGHT GAINS OF EXPERIMENTAL AND
CONTROL GROUP GUINEA PIGS

APPENDIX

INDIVIDUAL BODYWEIGHTS OF EXPERIMENTAL AND CONTROL GROUP GUINEA PIGS

AT DAY 0 AND DAY 24

TEST MATERIAL: ADQUAT 80 MC

EXPERIMENTAL GROUP				CONTROL GROUP			
GUINEA PIG NO.	BODYWEIGHT		% BODYWEIGHT INCREASE	GUINEA PIG NO.	BODYWEIGHT		% BODYWEIGHT INCREASE
	DAY 0	DAY 24			DAY 0	DAY 24	
1-0	401	491	22	6-0	395	470	19
1-1	451	540	20	6-1	399	475	19
1-2	443	522	18	6-2	425	540	27
1-3	490	570	16	6-3	365	489	34
2-0	378	450	19	7-0	400	502	26
2-1	430	480	12	7-1	405	515	27
2-2	449	535	19	7-2	434	442	2
2-3	481	580	21	7-3	356	430	21
3-0	410	502	22	8-0	490	560	14
3-1	454	528	16	8-1	395	422	7
3-2	428	487	14	8-2	428	480	12
3-3	455	535	18	8-3	395	455	15
4-0	430	480	12	9-0	326	480	47
4-1	418	508	22	9-1	360	489	36
4-2	430	482	12	9-2	393	450	15
4-3	411	489	19	9-3	371	510	37
5-0	452	545	21	10-0	324	328	1
5-1	419	515	23	10-1	413	505	22
5-2	420	530	26	10-2	355	432	22
5-3	398	DIED DAY 7		10-3	364	495	36

OECD SKIN IRRITATION TEST:
DETERMINATION OF THE DEGREE OF
PRIMARY CUTANEOUS IRRITATION
CAUSED BY
ADQUAT 80 MC
IN THE RABBIT
EXPERIMENT NUMBER 356/8505

INTRODUCTION

The study was performed according to Safeparm Standard Protocol Number GM 04/82/40B and was designed to assess the irritant potential of a test substance following a single semi-occluded application to the intact rabbit skin. The study was based on the recommendations of the OECD Guidelines for testing of Chemicals No. 404 "Acute Dermal Irritation/Corrosion". The test system was chosen because the rabbit has been shown to be a suitable model for this type of study and was recommended by the test method.

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

METHODS

1. Animals and Animal Husbandry

Three albino New Zealand White strain rabbits* in the weight range 2.28 - 2.44 kg and approximately 12 - 16 weeks of age were used. All animals were individually housed in suspended metal cages and had free access to tap water and a standard laboratory diet (Rabbit Diet, A.W. Tindall Limited, Holbeach, Lincolnshire). All animals were acclimatised to the laboratory environment for a minimum period of five days prior to the start of the study.

* Supplied by Nottingham University, School of Agriculture, Sutton Bonington, Leics.

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METHODS/Contd

1. Animals and Animal Husbandry (contd)

The animal room temperature was maintained at $20 \pm 2.0^{\circ}\text{C}$ recorded daily on a maximum and minimum thermometer. The rate of air exchange was approximately 10 changes per hour. Lighting was controlled by means of a time switch to give a 12 hour light/dark cycle. Humidity was not controlled but remained within a range of 50-55 %RH recorded daily on a wet and dry bulb hygrometer.

Each animal was uniquely identified by experimental cage label and an indelible number marked on the inner surface of the pinna.

2. Test Material and Experimental Preparation

Clear pale straw coloured liquid ADQUAT 80 MC supplied by Norsolor SA in a plastic screw-top container was received at these laboratories on 29 April 1985. The test material was stored at ambient temperature in the dark.

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

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

METHODS/Contd

3. Procedure

Approximately twenty-four hours prior to the commencement of the test, each of a group of three rabbits were prepared by closely clipping the fur from the dorsal/flank areas using Oster A5 electric animal clippers (Oster Inc., Wisconsin, USA) fitted with size 40 cutters. Only animals with a healthy intact epidermis were selected for the study.

On the day of the test a suitable test site was selected on the back of each rabbit. A quantity of 0.5 ml of the test material was introduced under a semi-occlusive patch which consisted of a 2.5 cm square of surgical gauze two layers thick. The test material was held in contact with the skin by the patch which was secured in position with two lengths of Sleek adhesive strapping (Smith & Nephew Limited) in the form of a cross. In addition to prevent access of the animal to the patch, the trunk of each rabbit was wrapped in an elasticated corset (Tubigrip). The animals were then returned to their cages for the duration of the exposure period. The test material was kept in contact with the skin for a period of 4 hours.

At the end of the exposure period the corset was removed from each animal and the patches carefully taken off the test sites. Any residual test material was immediately removed by gentle swabbing with cotton wool soaked in water.

Approximately one hour following removal of the patches, and 24, 48 and 72 hours later the test sites were examined for evidence of primary irritation and scored according to the following scale 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":-

METHODS/Contd

3. Procedure (contd)

EVALUATION OF SKIN REACTIONS

<u>Erythema and Eschar Formation</u>	<u>Value</u>
No erythema	0
Very slight erythema (barely perceptible) ...	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)... ..	4
 <u>Oedema Formation</u>	
No oedema	0
Very slight oedema (barely perceptible) ...	1
Slight oedema (edges of area well defined by definite raising).	2
Moderate oedema (raised approximately 1 millimetre)... ..	3
Severe oedema (raised more than 1 millimetre and extending beyond the area of exposure)... ..	4

As no reactions were apparent at the 72 hours observation the study was terminated at this stage.

METHODS/Contd

4. Interpretation of Results

The scores for erythema and oedema at the 24 and 72 hour readings were totalled for the three test rabbits (12 values). This total was divided by 6 to give the Primary Cutaneous Irritation Index of the test material. This index was used to classify the skin irritation properties of the test material according to the following scheme (after 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"):-

<u>Primary Irritation Index</u>	<u>Classification</u>
0	Non-irritant
>0 - 2	Mild irritant
>2 - 5	Moderate irritant
>5 - 8	Severe irritant

ARCHIVES

On completion of the study a copy of the final report, together with all laboratory raw data were transferred to Safepharm Laboratories Central Archives, London Road, Shardlow, Derbyshire, England.

RESULTS

The individual scores for erythema and oedema, together with the calculated primary cutaneous irritation index of the test material, are given in the following table:-

SUMMARY OF RESULTS FOR PRIMARY CUTANEOUS IRRITATION

TEST MATERIAL: ADQUAT 80 MC

SKIN REACTION	READING (HOURS)	INDIVIDUAL SCORES			TOTAL
		Rabbit Number:			
		1 (435)	2 (597)	3 (599)	
Erythema and Eschar Formation	1	0	0	0	(0)
	24	0	0	0	0
	48	0	0	0	(0)
	72	0	0	0	0
Oedema Formation	1	0	0	0	(0)
	24	0	0	0	0
	48	0	0	0	(0)
	72	0	0	0	0
Group Total*				0	
Primary Cutaneous Irritation Index i.e. <u>Group Total</u>				6	0.0

* Group Total = sum of 24 and 72 hour readings.

As indicated in the above table, none of the rabbits showed any observable response to treatment throughout the 72 hours observation period.

The test material produced a Primary Cutaneous Irritation Index of 0.0 and was classified as NON-IRRITANT to the skin.

CONCLUSION

The test material, ADQUAT 80 MC was found to be non-irritant to rabbit skin.

OECD EYE IRRITATION TEST:
DETERMINATION OF THE DEGREE OF
OCULAR IRRITATION CAUSED BY
ADQUAT 80 MC IN THE RABBIT
EXPERIMENT NUMBER 498/8505

Experimental Procedures:

Date Started: 20.05.85

Date Completed: 21.05.85

OECD EYE IRRITATION TEST:
DETERMINATION OF THE DEGREE OF
OCULAR IRRITATION CAUSED BY
ADQUAT 80 MC IN THE RABBIT
EXPERIMENT NUMBER 498/8505

INTRODUCTION

The study was performed according to Safeparm Standard Protocol Number GM 03/84/94A and was designed to assess the irritant potential of a test material following a single application to the rabbit eye. The study was based on the recommendations of the OECD Guidelines for Testing of Chemicals 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 was recommended by the test method. Due to the severity of the ocular reactions together with the systemic effects observed, the study was confined to one animal only.

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

METHODS

1. Animals and Animal Husbandry

One albino New Zealand White strain rabbit* weighing 2.85 kg and approximately 12 to 16 weeks of age was used. The animal was individually housed in a suspended metal cage and had free access to tap water and a standard laboratory diet (Rabbit Diet, A.W. Tindall Limited, Holbeach, Lincolnshire). The rabbit was acclimatised to the laboratory environment for a minimum period of five days prior to the start of the study.

* Supplied by Nottingham University, School of Agriculture, Sutton Bonington, Leicestershire.

METHODS/Contd

1. Animals and Animal Husbandry (contd)

The animal room temperature was maintained at $18.5 \pm 0.5^{\circ}\text{C}$ recorded daily on a maximum and minimum thermometer. The rate of air exchange was approximately 10 changes per hour. Lighting was controlled by means of a time switch to give a 12 hour light/dark cycle. Humidity was not controlled but remained within a range of $60 \pm 0\%$ RH recorded daily on a wet and dry bulb hygrometer.

The rabbit was uniquely identified by experimental cage number and an indelible number marked on the inner surface of the pinna.

2. Test Material and Experimental Preparation

Clear pale straw coloured liquid ADQUAT 80 MC supplied by Norsolor S.A. in a plastic screw-top container was received at these laboratories on 29 April 1985. The test material was stored at ambient temperature in the dark.

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

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

METHODS/Contd

3. Procedure

Within 24 hours of commencement of the test, both eyes of a provisionally selected test rabbit were examined for evidence of ocular irritation or defect. Animals showing evidence of ocular lesions were rejected and replaced.

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. The contralateral eye remained untreated and was used for control purposes.

Assessment of damage/irritation was made 1 hour and 24 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 U.S.A., Austin, Texas "The Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics"). Examination of the eye was facilitated by use of a standard ophthalmoscope (Keeler).

Due to the severity of the conjunctival reactions observed the rabbit was killed immediately following the 24 hours reading.

ARCHIVES

On completion of the study all raw data and a copy of the final report were transferred to Safepharm Laboratories Central Archives, London Road, Shardlow, Derbyshire, England.

RESULTS

The individual scores for the cornea, iris and conjunctivae are given in the following table:-

INDIVIDUAL SCORES FOR OCULAR IRRITATION

RABBIT NUMBER	(420)	
	1 hour	24 hours
<u>CORNEA</u>		
E Degree of Opacity	D	1
F Area of Opacity	4	1
Score (ExF) x 5	0	5
<u>IRIS</u>		
D	1	1
Score (Dx5)	5	5
<u>CONJUNCTIVAE</u>		
A Redness	3	3
B Chemosis	4	4
C Discharge	3	3
Score (A+B+C) x 2	20	20
TOTAL SCORE	25	30

D = dulling of the cornea

Approximately 15 seconds following instillation of the test material into the eye, excessive salivation was displayed by the test animal. This effect persisted for approximately fifteen minutes and was accompanied by increased lacrimation from the test and control eyes.

RESULTS/Contd

A dulling of the normal lustre of the cornea was observed at the one hour reading and by the 24 hours reading a diffuse corneal opacity had developed.

Iritis was apparent at the one hour and 24 hours reading.

A diffuse beefy red colouration of the conjunctivae accompanied by severe swelling and an extensive discharge was observed at the one hour reading. No discharge was seen at the control eye at this stage. Similar reactions persisted at the 24 hours reading and were accompanied by areas of haemorrhage and necrosis over the conjunctivae and nictitating membrane.

Because of the severity of the conjunctival reactions observed, the animal was killed immediately following the 24 hours reading.

CONCLUSION

The test material, ADQUAT 80 MC produced moderate corneal and iridial reactions and severe conjunctival reactions when instilled into the rabbit eye. In addition, the test material produced systemic effects manifested as increased salivation and increased lacrimation shortly following its instillation into the eye.

A P P E N D I X I

DRAIZE SCALE FOR SCORING OCULAR IRRITATION

APPENDIX I

DRAIZE SCALE FOR SCORING OCULAR IRRITATION

1.	<u>CONJUNCTIVAE</u>		
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.	<u>Chemosis</u>		
	No swelling		0
	Any swelling above normal (includes nictitating 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.	<u>Discharge</u>		
	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, and considerable area around the eye		3
	The total score = (A + B + C) x 2	Maximum Total	= 20
2.	<u>IRIS</u>		
D.	<u>Values</u>		
	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

* Starred figures indicate positive effect if reaction present at 24, 48 or 72 hour readings.

APPENDIX I (contd)

DRAIZE SCALE FOR SCORING OCULAR IRRITATION (contd)

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 slightly 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

* Starred figures indicate positive effect if reaction present at 24, 48 or 72 hour readings.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

JAN 18 1994

This letter formally acknowledges EPA's receipt of information submitted by your organization under Section 8(e), the "substantial risk" information reporting provision of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA Section 8(e) Document Control Number (i.e., 8EHQ-0000-0000 Init.) assigned by EPA to your submission(s). Please refer to this cited number when submitting follow-up or supplemental information.

Please note that all submitted correspondence will be placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA Section 8(e) policy statement (43 FR 11110, March 16, 1978).

Confidential submissions submitted pursuant to the TSCA Section 8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims, because substantiation of CBI claims is required at the same time the 8(e) CAP is submitted to EPA. (If not done so already, please ensure that this information is provided to the Agency). When substantiating any/all claims, answer the questions detailed in the following attachment.

For NON-CAP submissions, any confidentiality claims should be supported by submission of information as described in the attachment(s).

12431 A



CATS DATA: 0993-12431 SEQ. A
 TYPE: INT SUPP FLW/E/LF
 VOLUNTER NAME: V. Atochum North
America, Inc.

INFORMATION REQUESTED: FLW/P DATE: _____
 6501 NO INFO REQUESTED
 6502 INFO REQUESTED (TECH)
 6503 INFO REQUESTED (VOL ACTIONS)
 6504 INFO REQUESTED (REPORTING RATIONALE)
 DISP. 2.1.108
 REFER TO CHEMICAL SCREENING
 1478 CAP NOTICE

VOLUNTARY ACTIONS:
 6487 NO ACTION REPORTED
 6488 STUDIES PLANNED IN DERWAY
 6489 NOTIFICATION OF WORK: R411111 H S
 6490 LABELS/CHANGES
 6491 PROCESS/HANDLING CHANGES
 6492 APP USE DISCONTINUED
 6493 PRODUCTION DISCONTINUED
 6494 CONFIDENTIAL

UR. DATE: 09/13/93 OTS DATE: 09/17/93 CRAD DATE: 10/01/93
 CHEMICAL NAME: ADP/M/QUAT 80 MC CASE: 44992-910

INFORMATION TYPE: _____ REFORMATION TYPE: _____ P.F.S. _____

INFORMATION TYPE	P.F.S.	INFORMATION TYPE	P.F.S.	REFORMATION TYPE	P.F.S.
201 ONCO (HUMAN)	01 02 04	EPICLIN	01 02 04	6041 INHIBINO (ANIMAL)	01 02 04
202 ONCO (ANIMAL)	01 02 04	HUMAN EXPOS (PROD CONTAM)	01 02 04	6042 INHIBINO (HUMAN)	01 02 04
203 CELL TRANS (IN VITRO)	01 02 04	HUMAN EXPOS (ACCIDENTAL)	01 02 04	6043 CHEMISTS PROF	01 02 04
204 MUTA (IN VITRO)	01 02 04	HUMAN EXPOS (MONITORING)	01 02 04	6044 CLASTO (IN VITRO)	01 02 04
205 MUTA (IN VIVO)	01 02 04	ECOTOXICOLOGY	01 02 04	6045 CLASTO (ANIMAL)	01 02 04
206 REPROTERATO (HUMAN)	01 02 04	ENV. OCCURRENCE	01 02 04	6046 CLASTO (HUMAN)	01 02 04
207 REPROTERATO (ANIMAL)	01 02 04	EMER SAGE OF ENV CONTAM	01 02 04	6047 DNA DAMAGE/REPAIR	01 02 04
208 NEURO (HUMAN)	01 02 04	RESPONSE REQUEST DELAY	01 02 04	6048 PRODUSE/PROC	01 02 04
209 NEURO (ANIMAL)	01 02 04	PRODCOMP/ID	01 02 04	6049 MISDS	01 02 04
210 ACUTE TOX (HUMAN)	01 02 04	REPORTING RATIONALE	01 02 04	6050 OTHER	01 02 04
211 CHR TOX (HUMAN)	01 02 04	CONFIDENTIAL	01 02 04		
212 ACUTE TOX (ANIMAL)	01 02 04	ALLERG (HUMAN)	01 02 04		
213 SUB ACUTE TOX (ANIMAL)	01 02 04	ALLERG (ANIMAL)	01 02 04		
214 SUB CHRONIC TOX (ANIMAL)	01 02 04	METABPHARMACD (ANIMAL)	01 02 04		
215 CHRONIC TOX (ANIMAL)	01 02 04	METABPHARMACD (HUMAN)	01 02 04		

TRACE DATA: YES (CONTINUE) NO (CONTINUE) DETERMINE REFER.
 SPECIES: RBT GP
 TOXICOLOGICAL CONCERN: LOW skin irritation monomer in polymer synthesis
HIGH skin sensitization eye irritation

COMMENTS: Non-Cop
 Skin sensitization in the guinea pig is high because the test material is a strong sensitizer.
 19/19 guinea pigs exhibited sign of sensitization at 24 + 48h following challenge of the modified Magnusson + Kligman Maximization Test. 1/20 guinea pigs died

[100% conc] 3/4 guinea pigs
on day 7 of the induction period w/ 1 hour of topical application. 3/4 guinea pigs
died during convulsions following intradermal injection during the induction
sensitivity test. (Conc. were 0.5, 1.0 + 5.0%, deaths occurred w/ 4 minutes). Eye irritation
in the rabbit is high concern because the test material caused moderate
corneal + iridial reactions, severe conjunctival irritation + necrosis at 24 hours. The test
material also caused systemic effects (\uparrow salivation + locomotion).
Skin irritation in the rabbit is low concern because the test
material was non-irritating to the rabbit skin.