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Chemical Category	LETTER DATED 12/19/94		



AlliedSignal Inc.
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Morristown, NJ 07962-1139

FYI-1294-1060
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December 19, 1994

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Office of Toxic Substances
US. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460



INIT ~~07/21/94~~ 12/21/94

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DOCUMENTS



04950000007

Dear Sir:

RE: TSCA FYI Submission for NFTh
1-hydroxy-4-fluoro-1,4-diazonia-bicyclo(2,2,2)octane bis (tetrafluoroborate)

AlliedSignal is submitting summary information contained in a draft report of a rabbit eye irritation study for NFTh. The test resulted in corneal opacification and conjunctival irritation. Sufficient information is not available at this time to determine if significant risk is present from the use of this chemical.

AlliedSignal is reporting this information as a "For Your Information" (FYI) submission and is submitting the attached summary. This chemical is currently under Research & Development evaluation. Hazard information has been forwarded to all personnel handling this material.

We do not claim confidentiality for this report.

Very truly yours,

R. Greg Watson
Supervisor, Product Safety

Contains No CBI

Attachment: Draft Report of Rabbit Eye Irritation Study

DEC 23 1994

NFTB
EYE IRRITATION TO
THE RABBIT

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CONFIDENTIAL

AJS 49/340548/SE
Sponsor Project Number: 94007/TOX-065A

NOTE
This report is considered by the Study Director to be the 'final draft'. It has been sealed by the HRC Quality Assurance Department.
The sponsor is requested to review this document and communicate any comments to the Study Director as soon as possible. When these comments have been received, the FINAL REPORT containing Study Director and QA comments will be issued.
PLEASE NOTE
In compliance with OLP any changes to the final report after the date of issue will be to the form of a separate amendment to the report.
Date: 21 November 1994

NF1b

EYE IRRITATION TO THE RABBIT

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Sponsor

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Report issued

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COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The study described in this report was conducted in compliance with the following Good Laboratory Practice standards and I consider the data generated to be valid.

Good Laboratory Practices, The United Kingdom Compliance Programme, Department of Health & Social Security 1986 and subsequent revision, Department of Health 1989.

EC Council Directive, 87/18 EEC of 18 December 1986, (No. L 15/29).

Good Laboratory Practices in the testing of Chemicals OECD, ISBN 92-64-12367-9, Paris 1982, subsequently republished OECD Environment Monograph No. 45, 1992.

United States Environmental Protection Agency, (FIFRA), Title 40 Code of Federal Regulations Part 160, Federal Register, 29 November 1983 and subsequent amendment Federal Register 17 August 1989.

Japan Ministry of Agriculture, Forestry and Fisheries, 59 Nohsan, Notification No. 3850, Agricultural Production Bureau, 10 August 1984.

United States Environmental Protection Agency, (TSCA), Title 40 Code of Federal Regulations Part 792, Federal Register, 29 November 1983 and subsequent amendment Federal Register 17 August 1989.

Japan Ministry of International Trade and Industry, Directive 31 March 1984 (Kanpogyo No. 39 Environmental Agency, Kikyoku No. 85-MIT)

United States Food and Drug Administration, Title 21 Code of Federal Regulations Part 58, Federal Register, 22 December 1978, and subsequent amendments.

Japan Ministry of Health and Welfare, Notification No. Yakuhatsu 313 Pharmaceutical Affairs Bureau, 31 March 1982 and subsequent amendment Notification No. Yakuhatsu 870, Pharmaceutical Affairs Bureau, 5 October 1988.

Brenda I. Parcell, M.I.A.C.
Study Director,
Huntingdon Research Centre Ltd.

Date

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QUALITY ASSURANCE STATEMENT

This report has been audited by the Huntingdon Research Centre Quality Assurance Department. The methods, practices and procedures reported herein are an accurate description of those employed at HRC during the course of the study. Observations and results presented in this final report form a true and accurate representation of the raw data generated during the conduct of the study at HRC.

Certain studies such as that described in this report, are conducted at HRC in a setting which involves frequent repetition of similar or identical procedures. At or about the time the study described in this report was in progress, 'process-based' inspections were made by the Quality Assurance Department of critical procedures relevant to this study type. The findings of these inspections were reported promptly to the Study Director and to HRC Management.

Date(s) of inspection

27 June-1 July 1994

Date(s) of reporting inspection findings
to the Study Director and HRC Management

4 July 1994

Date of reporting audit findings to the
Study Director and HRC Management

30 August 1994

P. Watson,
Systems Compliance Auditor,
Department of Quality Assurance,
Huntingdon Research Centre Ltd.

Date

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ALS 49/940548/SE
Sponsor Project Number: 94007/TOX-065A

RESPONSIBLE PERSONNEL

Brenda I. Purcell, M.I.A.T.,
Study Director,
Department of Industrial Toxicology.

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SUMMARY

A study was performed to assess the eye irritation potential of NPTh to the rabbit. The method followed was that described in EEC Methods for the determination of toxicity, Annex to Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part B, Method B.5. Acute toxicity (eye irritation).

Four rabbits were each administered a single ocular dose of 64 mg of the test substance and observed for a maximum of 17 days after instillation. The eyes of three rabbits were rinsed with water immediately after instillation for 30 seconds.

A single instillation of NPTh into the eye of the rabbit elicited persistent corneal opacification and considerable conjunctival irritation. Rinsing of the eyes immediately after dosing reduced the irritant potential of NPTh although corneal opacification and well-defined conjunctival irritation was seen. Following rinsing, all reactions had resolved 2, 4 or 7 days after instillation.

Although the full criteria has not been met (i.e. only one animal has been used), consideration should be given to labelling NPTh with the risk phrase R41 "Risk of serious damage to eyes", in accordance with Council Directive 79/831/EEC, Annex VI, Part II(D) as described in Commission Directive 93/21/EEC, based on the data generated for one animal.

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INTRODUCTION

The study was designed to assess eye irritation potential of NITh following a single instillation into the eye of the rabbit. The test substance may come into contact with the eye during handling or use.

The study was conducted in compliance with EEC Methods for the determination of toxicity, Annex to Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part B, Method B.5. Acute toxicity (eye irritation).

The albino rabbit was chosen as it has been shown to be a suitable model for eye irritation studies and is the animal recommended in the test guideline.

The amount of test substance instilled was chosen in compliance with the guideline.

The protocol was approved by the Study Director and HRC Management on 24 January 1994 and by the Sponsor on 18 February 1994.

The experimental phase of the study was undertaken between 23 May and 23 June 1994.

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ALS 49/940548/SE
Sponsor Project Number: 94007/TOX-065A

TEST SUBSTANCE

Identity: NITh

Chemical name: 1-hydroxy-4-fluoro-1,4-diazoni-
abicyclo(2,2,2)octane bis (tetrafluoroborate)

Lot number: 449-94A

Expiration: 30 March 1995

Purity: ~ 94%

Appearance: Free flowing white-tan powder

Storage conditions: 4°C in dry conditions

Date received: 30 March 1994

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EXPERIMENTAL PROCEDURE

ANIMAL MANAGEMENT

Four healthy adult rabbits of the New Zealand White strain were obtained from Froxfield (U.K.) Ltd., Petersfield, Hampshire, England.

The animals were in the weight range of 2.2 to 3.5 kg and approximately 10 to 15 weeks of age, prior to treatment (Day 1). All rabbits were acclimatized to the experimental environment.

The rabbits were selected without conscious bias for the study. They were housed individually in metal cages with perforated floors in Building R 14 Room 5 and 1.

A standard laboratory diet SDS Stanrab (P) Rabbit Diet and drinking water were provided *ad libitum*.

The batch of diet used for the study was not analysed for nutrients, contaminants or micro-organisms.

Results of routine physical and chemical examination of drinking water at source as conducted usually weekly by the supplier, are made available to Huntingdon Research Centre Ltd. as quarterly summaries.

Animal room temperature was maintained at approximately 19°C and relative humidity at 30 - 70%. These environmental parameters were recorded daily. Air exchange was maintained at approximately 19 air changes per hour and lighting was controlled by means of a time switch to give 12 hours of artificial light (0700 - 1900 hours) in each 24 hours period.

Each animal was identified by a numbered aluminium tag placed through the edge of one ear. This number was unique within the HRC Industrial Toxicology Department throughout the duration of the study. Each cage, was identified by a coloured label displaying the study schedule number, animal number and initials of the Study Director and Home Office licensee.

TEST SUBSTANCE PREPARATION

NFTh was administered as supplied by the Sponsor.

The absorption of the test substance was not determined.

The homogeneity, stability and purity of the test substance were the responsibility of the Sponsor.

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TREATMENT PROCEDURE

The eyes of each animal were examined prior to instillation of the test substance to ensure that there was no pre-existing corneal damage, iridial or conjunctival inflammation.

One animal was treated in advance of the others, to ensure that if a severe response was produced, no further animals would be exposed (pilot animal see Table 1). On this occasion severe ocular reactions were seen in the pilot animal and no further animals were exposed without rinsing the eyes. One further animal was treated in advance of the others to check the effects of rinsing the eyes.

Approximately 64 mg of the test substance, the weight occupying a volume of 0.1 ml, was placed into the lower everted lid of one eye of each animal.

The eyelids were then gently held together for one second before releasing. The contralateral eye remained untreated.

To investigate the effects of remedial irrigation the treated eyes of three rabbits were washed with water immediately after instillation for a duration of 30 seconds.

OBSERVATIONS

Clinical signs

All animals were observed daily for signs of ill health or toxicity.

Ocular responses

Examination of the eyes was made after 1 hour and 1, 2, 3 (equivalent to 24, 48 and 72 hours after instillation), 4, 7, 14 and 17 days after instillation. Observation of the eyes was aided by the use of a handheld light.

Ocular irritation was assessed using the prescribed numerical system:

Cornea

Opacity: degree of density (area most dense taken for reading)

No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal lustre), details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Nacreous areas, no details of iris visible, size of pupil barely discernible	3
Opaque cornea, iris not discernible through the opacity	4

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Iris

Normal	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperaemia or injection, any 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

Conjunctivae

Redness (refers to the most severe reading of palpebral and bulbar conjunctivae, as compared to the control eye)

Blood vessels normal	0
Some blood vessels definitely hyperaemic (injected)	1
Diffuse, crimson colour, individual vessels not easily discernible	2
Diffuse beefy red	3

Chemosis (lids and/or nictating membranes)

No swelling	0
Any swelling above normal (includes nictating membranes)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half-closed	3
Swelling with lids more than half-closed	4

Any other lesion not covered by this scoring system, was described.

ARCHIVES

All raw data and study related documents generated during the course of the study at HRC, together with a copy of the final report will be lodged in the Huntingdon Research Centre Ltd., Archives.

Such records will be retained for a minimum period of five years from the date of issue of the final report. At the end of the five year retention period the client will be contacted and advice sought on the future requirements. Under no circumstances will any item be discarded without the client's knowledge.

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RESULTS

CLINICAL SIGNS

There were no signs of toxicity or ill health in any rabbit during the observation period.

OCULAR RESPONSES

The numerical values given to the ocular reactions elicited by NF7H are shown in Table 1.

Unrinsed eye

A Grade 4 corneal opacity developed 1 hour after instillation and persisted throughout the observation period. Vascularisation over the damaged area was seen.

No iridial inflammation was observed.

A diffuse crimson or beefy red colouration of the conjunctivae was seen accompanied by considerable swelling with the eyelids more than half closed. Necrosis was seen on the nictating membrane. An abscess developed on the conjunctivae 17 days after instillation.

The animal was killed 17 days after instillation due to the severity of the reactions.

Rinsed eyes

Dulling of the cornea was seen in all three animals. Corneal opacification developed in one animal.

No iridial inflammation was seen in any of the animals.

A diffuse crimson colouration of the conjunctivae was seen in two animals accompanied by swelling with partial eversion of the eyelids. Blanching on the nictating membrane was seen in one animal one hour after instillation only.

The eyes were normal 2, 4 or 7 days after instillation.

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ALS 49/940348/SE
Sponsor Project Number: 94007/TOX-065A

CONCLUSION

Instillation of N7Th into the rabbit eye elicited corneal opacification and considerable conjunctival irritation.

Rinsing of the eyes for 30 seconds immediately after instillation reduced the irritant potential of N7Th.

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TABLE I

Ocular reactions observed after instillation of NPTh

Rabbit number and sex	Region of eye	Obs hour	Day after instillation							
			1	2	3	4	7	14	17	
5129*	Cornea	4	4	4	4	4	4	b4	b4	
	Iris	0	0	0	0	0	0	0	0	
	Conjunctiva	Redness	a2	a3	a3	a2	a2	a2	2	c2
		Chemosis	4	4	3	2	1	1	2	3
6329**	Cornea	D	0	0	0	0	0			
	Iris	0	0	0	0	0	0			
	Conjunctiva	Redness	c1	1	0	0	0	0		
		Chemosis	1	0	0	0	0	0		
6439#	Cornea	D	0	0	0	0	0			
	Iris	0	0	0	0	0	0			
	Conjunctiva	Redness	2	1	0	0	0	0		
		Chemosis	2	0	0	0	0	0		
6449#	Cornea	D	1	1	1	0	0			
	Iris	0	0	0	0	0	0			
	Conjunctiva	Redness	2	2	2	2	1	0		
		Chemosis	2	2	2	2	1	0		

- * Pilot animal- unrinsed eye
- ** Pilot animal- rinsed eye
- # Rinsed eye
- a Necrosis on nictating membrane and lower lid
- b Vascularisation
- c Abscess on lower and upper lids
- D Dulling of the cornea
- e Blanching of nictating membrane

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