FYI-0794-001198
0040
Contains No CBI

FMC Corporation

Industrial Chemical Group
2000 Market Street
Philadelphia Pennsylvania 19103
(215) 299 6000

April 3, 1981

FMC

Mr. Martin Greif
Executive Secretary
TSCA Interagency Testing Committee
Environmental Protection Agency
401 M Street, SW
Washington, D.C. 20460

Re: Federal Register - October 7, 1980
Chemicals to be Reviewed by the
TSCA Interagency Testing Committee

Dear Mr. Greif:

We would like to make some comments on two chemicals appearing on the referenced list. These comments are submitted by FMC Corporation, a publicly owned company which produces machinery and chemicals at 143 plants in the United States and several foreign countries. FMC has more than 46,000 employees.

Our comments concern the following compounds:

CAS No. 15547-17-8
9,10-Anthracenedione, 6-ethyl-1,2,3,4-tetrahydro
Referred to hereafter as H4EAQ

CAS No. 68279-54-9
9,10-Anthracenediol, 6-ethyl-1,2,3,4-tetrahydro
Referred to hereafter as H4EAQH2

We believe it is not appropriate, under TSCA Section 4(c)(1)(A) to recommend these compounds to EPA for priority consideration for further testing because:

(a) These compounds are site-limited intermediates formed, used, and reused in an enclosed system under recycle conditions.

(b) The total production of these compounds was reported in the TSCA inventory of 1978 as between 45.4 and 227 million kg per year. However,

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at any given time there is approximately 120 thousand kg present in the reactor systems and auxiliary storage tanks due to the cyclic nature of the process.

(c) The only employee exposure occurs during transfer of spent catalyst to containers. (Details below).

(d) The amounts lost to the environment to the best of our knowledge are:

(1) none to the air
(2) none to water
(3) less than 1,000 kg in the product hydrogen peroxide per year. (Details below).

(e) H4EAQH2 reacts with the oxygen of the air and converts rapidly into H4EAQ. H4EAQH2 cannot exist for any significant length of time outside the reactor and cannot pose a significant hazard to health or the environment.

(f) H4EAQ has a low degree of toxicity. (Details below).

The following discourse applies to the procedures and conditions prevailing in the FMC plant where these chemicals are used. These two chemicals occur as intermediates in a cyclic process used by FMC Corporation to make hydrogen peroxide. They are generated, used, regenerated over and over again in the operation of the process and in fact they exist only in relatively small quantities or not at all outside process equipment. In order to understand the nature of their generation and use, it is necessary to have some knowledge of the hydrogen peroxide cycling production process.

Process Description

Hydrogen peroxide is manufactured by the sequential reduction and oxidation of 2-ethylanthraquinone. The basic flow sheet is shown in figure 1 and the basic chemistry is presented in equation 1 and 2. 2-ethylanthraquinone (EAQ) is dissolved in a suitable solvent or solvent mixture, which is commonly referred to as the work solution. The EAQ is catalytically reduced to 2-ethyl-antrahydroquinone using hydrogen (EAQH2, equation 1). The hydrogenated work solution is then treated

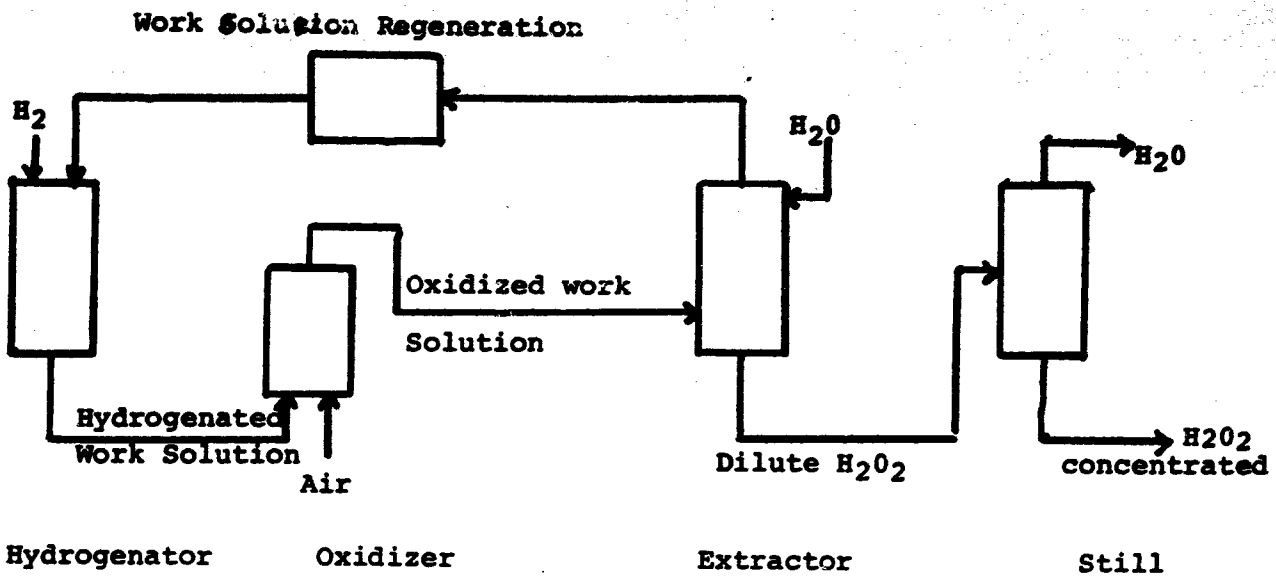
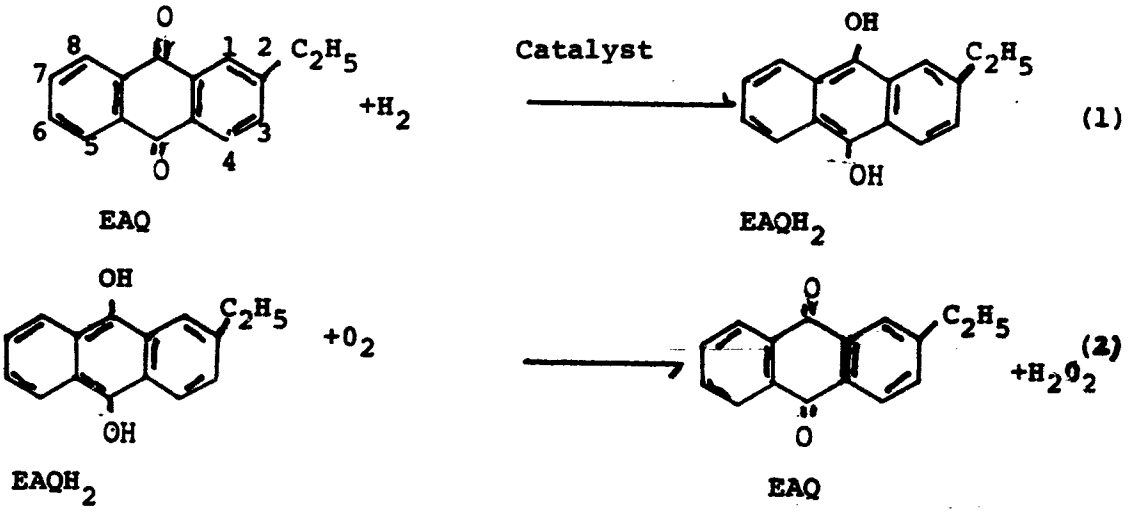

Work Solution Regeneration
H_2
H_2O
H_2O
Oxidized work
Solution
Hydrogenated
Work Solution
Air
Dilute H_2O_2
H_2O_2
concentrated
Hydrogenator
Oxidizer
Extractor
Still

FIGURE 1


O
8
1
2
C_2H_5
7
6
5
3
O
4
$+H_2$
EAQ
Catalyst
OH
C_2H_5
OH
(1)
$EAQH_2$
OH
C_2H_5
$+O_2$
OH
$EAQH_2$
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C_2H_5
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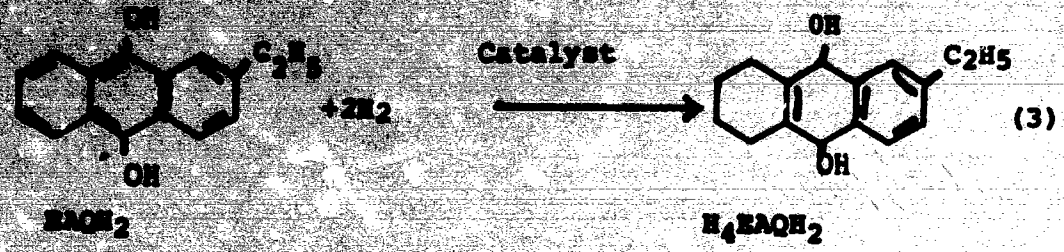
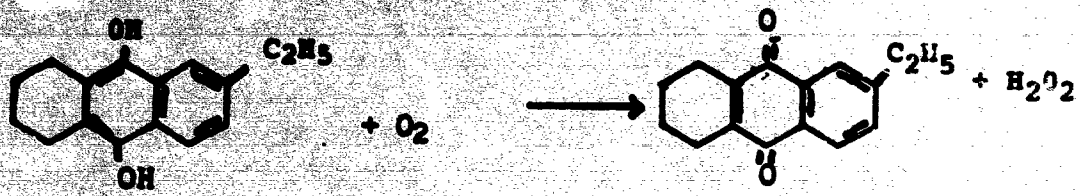
(2)
O
EAQ

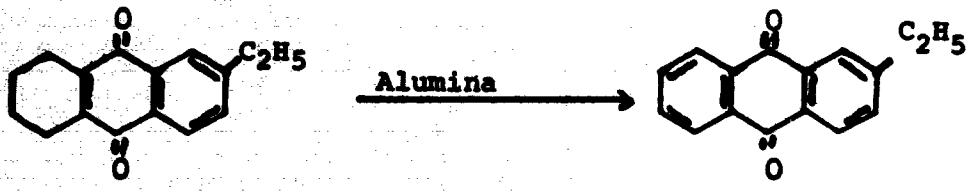


EAQH$_2$ H_4EAQH$_2$ (3)



H_4EAQH$_2$ H_4EAQ (4)

H_4EAQ H_4EAQH$_2$ (5)



(6)

with air to oxidize the hydroquinone to quinone and simultaneously yield one mole of hydrogen peroxide (equation 2). The oxidized work solution is extracted with water and the dilute hydrogen peroxide in the water extract is concentrated by distillation. The work solution is returned to the hydrogenator and the cycle is repeated.

Ethylanthraquinone can also undergo several side reactions. By far the most common side reaction is the overhydrogenation of the hydroquinone to give 2 ethyl-5,6,7,8-tetra hydroanthrahydroquinone (H4EAQH2, equation 3). This compound is very similar to EAQH2 and is also easily oxidized on exposure to air and the product readily converts into hydrogen peroxide and 2 ethyl-5,6,7,8-tetrahydroanthraquinone (H4EAQ, equation 4). The tetrahydroanthraquinone is an effective participant in the process cycle being hydrogenated to the hydroquinone (equation 5) and then oxidized back in a manner analogus to the anthraquinone system (equation 4). As a result a typical work solution used to manufacture hydrogen peroxide will contain EAQ and H4EAQ as the active quinone component. These are both hydrogenated to the intermediate hydroquinones which are then oxidized to give hydrogen peroxide. Formation of H4EAQ is a very slow process but if allowed to remain unchecked would eventually result in an all H4EAQ system. Thus, one part of the process is a work solution regeneation and purification section in which H4EAQ is converted back to EAQ (equation 6) by the use of an activated alumina catalyst.

The cyclic nature of the process is important in considering the fate of H4EAQ and H4EAQH2. All of the hydroquinone H4EAQH2 is oxidized in the course of a cycle. It cannot be isolated from the plant or from the work solution. Any H4EAQH2 occuring in the hydrogenated work solution cannot be maintained outside the reactor since the oxygen in the atmosphere is sufficient to oxidize it to the quinone and hdyrogen peroxide. Because of this property H4EAQH2 cannot threaten people or the environment.

Since H4EAQ is an active component in the work solution it is recycled through the process and its losses must be kept to a minimum to maintain a sound economic process. There are several places where H4EAQ can leave the process cycle. One of these is in the product. Laboratory and pilot work have provided information which shows the concentration of

H4EAQ to be in the range of 3 to 6 ppm in the extractor product which is 25% hydrogen peroxide and 75% water. This represents the total amount of H4EAQ going to the distillation section and is the maximum amount of H4EAQ that could be found in the final hydrogen peroxide. For a plant of FMC's size this would be between 500 and 1,000 kg of H4EAQ lot per year.

The major loss of H4EAQ from the process comes when the alumina used in the work solution regeneration and purification is discarded. During this operation the work force in the area wear full cover clothing, gloves and respirators. This alumina contains approximately 2% H4EAQ prior to treatment as follows. It is washed with solvent to remove work solution components which are returned to the process. The alumina is then treated with steam to remove the residual solid; the organic phase for this treatment is returned to the process. The aqueous phase which is diverted to an impoundment pond contains no H4EAQ. The final alumina product to be discarded contains approximately 0.5% by weight residual H4EAQ. This material is sold to another company for use as a raw material. Their process includes a high temperature treatment in which the residual H4EAQ is converted into carbon dioxide and water, meaning that no H4EAQ is discarded to the environment.

The amount of H4EAQ that leaves the hydrogen peroxide process and enters the environment amounts to no more than 1,000 kg per year in the product hydrogen peoxide. A modification of the distillation step in the production procedure is being introduced shortly and is expected to reduce the amount of H4EAQ remaining in the product to less than 80 kg per year.

Toxicology

The H4EAQ component of the work solution has been isolated and several of the more common toxicological and potential mutagenic effects have been determined. The samples of H4EAQ used in this test gave the following results:

Acute Oral LD 50 in rats:	Above 10 g/kg
Acute Dermal LD 50 in rabbits:	Above 5 g/kg
Primary Dermal irritation on rabbits: (primary irritation index 0.0/8.0)	Non-irritant
Ocular irritation on rabbits	Non-irritating with or without a 4 second washout
Salmonella/microsomal assay (AMES test): with or without activation by liver enzymes	Not mutagenic

A copy of the reports giving these results and other information are attached.

Conclusion

1. The H4EAQH2 is not released to the environment and does not pose a hazard since it converts immediately on exposure to air to H4EAQ.

2. The workplace exposure to H4EAQ in the FMC plants is low since it is made, used, and regenerated in a closed reactor system.

3. The losses of H4EAQ to the environment are low.

   a) Less than 1,000 kg/yr. is lost with the product hydrogen peroxide and modifications presently underway at the plant in the distillation step are expected to reduce this further.

   b) A major removal of H4EAQ from the process by way of the alumina is recovered for reintroduction to the process as explained above. The 0.5% H4EAQ remaining on the alumina and unrecovered in our plant is pyrolyzed to carbon dioxide and water.

In conclusion it is believed the Inter-Agency Testing Committee of TSCA does not need to recommend further testing for these two compounds. If the committee feels the need for further discussion we will be glad to accept such an invitation. In fact FMC would welcome such a chance for an informal discussion of this rather complex process. Thank you for your attention.

Very truly yours,

C. E. Price

C.E. Price
Regulatory Affairs Specialist
Specialty Chemicals Division

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BA42a

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1530 EAST JEFFERSON STREET, ROCKVILLE, MARYLAND 20852
Tel. (301) 770-4400

SALMONELLA/MAMMALIAN-MICROSOME PLATE INCORPORATION MUTAGENESSIS ASSAY OF FMC CORPORATION COMPOUND 4H-EAQ C8544-72 (MRI #90)

Notebook #MRI-WL-21

Pages 99, 100, 117

Compound Description: Yellow Powder

Storage Conditions: Room Temperature with Desiccation

Date Received: May 31, 1978

Report Date: September 1, 1978

Principal Investigator: Tito Cascieri, Ph.D.

Scientific Investigator: Steve R. Haworth, Ph.D.

Steve R. Haworth
Steve R. Haworth, Ph.D.
Scientific Investigator

Timothy E. Lawlor
Timothy E. Lawlor
Sr. Technician

Jeanene Smith
Jeanene Smith
Technician

Introduction

FMC Corporation compound 4H-EAQ C8544-72 (MRI #90) was received on May 31, 1978 for testing in the Salmonella plate incorporation mutagenesis assay using five tester strains, TA98, TA100, TA1535, TA1537 and TA1538, with and without metabolic activation by rat liver microsomes.

Materials and Methods

The experimental protocol (see Appendix) is a modification of that described by Ames, B. N., et al. Methods for detecting carcinogens and mutagens with the Salmonella/ mammalian-microsome mutagenicity test. Mutation Research 31:347-364, 1975.

RESULTS

Table 1

DETERMINATION OF FMC CORPORATION COMPOUND 4H-EAQ C8544-72 (MRI #90)

TOXICITY TO TESTER STRAINS

Test Compound Concentration µg/Plate	Viable Count/ Plate	Revertants/Plate	Background Bacterial Lawn
50) Solvent	588	289	NORMAL
0.2 ug.	596	280	NORMAL
0.6 ug.	548	295	NORMAL
2.0 ug.	591	253	NORMAL
6.4 ug.	611	243	NORMAL
20.3 ug.	610	291	NORMAL
65.1 ug.	575	272	NORMAL
208.3 ug.	615	285	NORMAL WITH PRECIPITATE
666.7 ug.	485	220	NORMAL WITH PRECIPITATE
1333.3 ug.	534	278	NORMAL WITH PRECIPITATE

Eight serial half-log dilutions of the test compound are plated with TA100 on minimal agar plus 10XSA and on minimal agar plus 1XSA. Equal numbers of cells are seeded on each plate in the presence of the test compound. The percent survival of an appropriately diluted TA100 culture on the 10XSA supplemented plates is determined by comparing numbers of colonies on the solvent control with those on the plates containing test compound. Toxicity on the 1XSA supplemented plates is detectable by a decrease in the number of revertant colonies occurring per plate and by a thinning or disappearance of the background bacterial lawn. The highest concentration of test compound used in the broad range mutagenesis assay is that which gives approximately 35% survival on the 10XSA supplemented plates and a detectable reduction of spontaneous revertants on the 1XSA supplemented plates.

Timothy E. Lawlor
Investigator

EG&G MASON RESEARCH INSTITUTE

Table 2

SALMONELLA MUTAGENESIS ASSAY

RAW EXPERIMENTAL DATA

FMC CORPORATION
Client

Jeanene Smith
Investigator

13.34 µg - 1333.8 µg
Dose Range

4H-EAQ C8544-72 (MRI #90)
Test Compound Identity

DMSO
Solvent

None
Metabolic Activation

STRAIN	DATE	SOLVENT CONTROL			FIRST CONCENTRATION 13.34 µg			SECOND CONCENTRATION 66.69 µg			THIRD CONCENTRATION 333.4 µg			FOURTH CONCENTRATION 666.9 µg			FIFTH CONCENTRATION 1333.8 µg		
TA98	8/21/78	56	48	52	58	55	56	43	61	40	36	62	49	46	55	52	35	41	53
TA100	8/21/78	221	212	216	215	225	220	199	192	180	210	201	193	195	198	180	217	240	212
TA1535	8/21/78	44	43	26	48	36	37	41	39	47	61	36	30	28	31	31	27	26	34
TA1537	8/21/78	8	8	9	5	5	6	4	6	5	6	8	7	4	7	6	2	5	3
TA1538	8/21/78	22	16	17	17	13	12	15	12	18	11	19	22	15	13	17	11	12	15

POSITIVE CONTROLS

TA98 2AA @ 0.4µg/plate with activation			TA100 2AA @ 0.4µg/plate with activation			TA1538 2AA @ 0.4µg/plate with activation			TA1535 PS @ 0.02µl/plate without activation			TA1537 9AAD @ 75µg/plate without activation		
1413	1369	1241	963	883	870	1227	1242	1508	1448	1451	1341	213	241	223

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Table 3

SALMONELLA MUTAGENESIS ASSAY

AVERAGED PLATE COUNTS AND REVERSION INDEX*

FMC CORPORATION — Client

Jeanene Smith — Investigator

13.34 µg - 1333.8 µg — Dose Range

4H-EAQ C8544-72 (MRI #90) — Test Compound Identity

DMSO — Solvent

None — Metabolic Activation

STRAIN	DATE	SOLVENT CONTROL AVG. REVERT.	SOLVENT CONTROL REVERSION INDEX	1st CONCENTRATION 13.34ug. AVG. REVERT.	1st CONCENTRATION REVERSION INDEX	2nd CONCENTRATION 66.69ug. AVG. REVERT.	2nd CONCENTRATION REVERSION INDEX	3rd CONCENTRATION 333.4ug. AVG. REVERT.	3rd CONCENTRATION REVERSION INDEX	4th CONCENTRATION 666.9ug. AVG. REVERT.	4th CONCENTRATION REVERSION INDEX	5th CONCENTRATION 1333 ug. AVG. REVERT.	5th CONCENTRATION REVERSION INDEX
TA98	8/21/78	52	30.6	56	32.9	48	28.2	49	28.8	51	30.0	45	26.5
TA100	8/21/78	216	86.4	220	88.0	190	76.0	201	80.4	191	76.4	223	89.2
TA1535	8/21/78	38	17.3	40	18.2	42	19.1	42	19.1	30	13.6	29	13.2
TA1537	8/21/78	8	5.7	5	3.6	5	3.6	7	5.0	6	4.3	3	2.1
TA1538	8/21/78	18	5.8	14	4.5	15	4.8	17	5.5	15	4.8	14	4.5

POSITIVE CONTROLS

TA98 2AA @ 0.4µg/plate with activation		TA100 2AA @ 0.4µg/plate with activation		TA1538 2AA @ 0.4µg/plate with activation		TA1535 PS @ 0.02µl/plate without activation		TA1537 9AAD @ 75µg/plate without activation	
Avg. Revert.	Revers. Index	Avg. Revert.	Revers. Index	Avg. Revert.	Revers. Index	Avg. Revert.	Revers. Index	Avg. Revert.	Revers. Index
1341	788.8	905	362.0	1326	427.7	1413	642.3	226	161.4

TOTAL CELLS PLATED PER PLATE

TA98	1.7×10^8
TA100	2.5×10^8
TA1535	2.2×10^8
TA1537	1.4×10^8
TA1538	3.1×10^8

* Revertants observed per 10^8 cells plated.

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Conclusions

The results of the Salmonella/mammalian-microsome mutagenicity assay indicate that FMC Corporation compound 4H-EAQ C8544-72 (NRI #90) did not cause a significant increase in the reversion index of any of the tester strains with or without metabolic activation by rat liver microsomes.

APPENDIX

Consumer Product Testing
Company Incorporated

Bldg. No. 2-158
1275 Bloomfield Avenue
Fairfield, New Jersey 07006

(201) 575-7688
(201) 575-7689

FINAL REPORT

CLIENT: FMC Corporation
Bo. 8
Princeton, New Jersey 08540

ATTENTION: Tito Cascieri, Ph.D.
Product Safety & Toxicology

TESTS: Primary Dermal Irritation (Rabbit)
Ocular Irritation (Rabbit)
Acute Dermal Toxicity (Rabbit)
Oral LD_{50} (Rat)

TEST MATERIAL: 4H-EAQ, C8544-72

EXPERIMENT REFERENCE NO.: 78193 - 10

Christine A. Lewis, B.S.
Laboratory Supervisor
Project Director

Allen L. Palanker
President

Date July 13, 1978
CAL/emk

This report is submitted for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the report nor the name of these Laboratories nor of any member of its staff, may be used in connection with the advertising or sale of any product or process without written permission.

This report details :

a primary dermal irritation study,
an ocular irritation study, and
a dermal toxicity study in albino rabbits, and
an oral LD_{50} study in albino rats,

performed at the behest of :

FMC Corporation
Box 8
Princeton, New Jersey 08540

The test material, supplied by :

FMC Corporation

was received on :

May 9, 1978

and identified as :

411-EAQ, C8544-72

and was used as indicated in the Final Report Summaries.

Study Interval : June 6, 1978 to June 29, 1978

All animals are fed and watered ad libitum; with Wayne animal feeds used exclusively. Animals are received from Summit View Farm, Belvidere, New Jersey and are conditioned prior to use. Samples, raw data and final report copies are retained at these laboratories unless otherwise indicated.

Project Director and study supervisor are signatory to this report. Date of submission is recorded on title page. Names of persons performing these tests are recorded on raw data sheets and laboratory log books and are available upon request.

Final Report Summary

DATE: July 13, 1978
CLIENT: FMC Corporation
STUDY NO.: 78193 - 10
REFERENCE NO.: P.O. #PR11403V
MATERIAL: 4H-EAQ, C8544-72

Primary Dermal Irritation

Method: Six rabbits, 1/2 male, 1/2 female, each abraded and non-abraded, 0.5 ml single application under occluded patch, 24 and 72 hour observation. Test material used as received.

Result: Primary Irritation Index: *

0.0

Not a primary dermal irritant under conditions of this test.

*See Table 1A for evaluation

Final Report Summary

DATE: July 13, 1978
CLIENT: FMC Corporation
STUDY NO.: 78193 - 10
REFERENCE NO.: P.O. #PR11403V
MATERIAL: 4H-EAQ, C8544-72

Ocular Irritation

Method: Nine rabbits, mixed sex, 1.8 - 2.4 kg, 0.1 ml single administration, followed by no wash for 24 hours (6 rabbits) and 4" wash (3 rabbits). Material was used as received.

Result:

	Draize Score				
	---------Day---------				
Group	1	2	3	4	7
No Wash	0.0	0.0	0.0	---	---
4" Wash	0.0	0.0	0.0	---	---

Not an ocular irritant to rabbits under conditions of this test.

Final Report Summary

DATE: July 13, 1978
CLIENT: FMC Corporation
STUDY NO.: 78193 - 10
REFERENCE NO.: P.O. #PR11403V
MATERIAL: 4H-EAQ, C8544-72

Dermal Toxicity

Method: Six rabbits, 1/2 male, 1/2 female, all abraded, 5 g/kg single application under occluded patch, 14 day observation. Material used as received and moistened with saline before application of occlusive wrap.

Result: LD_{50} : > 5 g/kg

Dose Level (g/kg)	Sex	#dead/#dosed	%
5.0	3M:3F	0/3:0/3	0

Not a toxic material dermally to rabbits under conditions of this test.

Final Report Summary

DATE: July 13, 1978
CLIENT: FMC Corporation
STUDY NO.: 78193 - 10
REFERENCE NO.: P.O. #PR11403V
MATERIAL: 4H-EAQ, C8544-72

Oral LD_{50}

Method: Albino rats in groups of ten, 150 - 300 g, single dosed orally, (40 ml/kg top dose mechanically feasible) observed fourteen days. Material used as a 25% w/v suspension in corn oil.

Result: LD_{50} : > 10 g/kg

	Dose Level (g/kg)	Sex	#dead/#dosed	%
Range Finding:	1.0	F	0/1	0
	5.0	F	0/1	0
	10.0	F	0/1	0
Test Dosage:	10.0 (40 ml/kg)	5M:5F	1/5:0/5	10

Not a toxic material orally to rats under conditions of this test.

METHOD:

Primary Dermal Irritation in Rabbits

A group of albino New Zealand rabbits as indicated in the summary were used in this study. The test method was essentially that of Draize et.al.[1]

Briefly paraphrased, it consisted of application of 0.5 ml (0.5 g) of the test material to clipped areas of intact and abraded skin. The abrasions were longitudinal epidermal incisions sufficiently deep to penetrate the stratum corneum, but not so deep as to destroy the integrity of the derma. Applications were made under occlusive patches (1" x 1" gauze, covered by adhesive tape). Following application of the test material the entire trunk of each animal was covered with an impermeable occlusive wrapping. The animals were then immobilized. The wrapping and test material were removed 24 hours following application. The sites were individually examined and scored separately for erythema and edema at 24 and 72 hours. The mean scores for 24 and 72 hour gradings were averaged to determine final irritation indices.

[1] Draize, John H., Woodward, Geoffrey, and Calvery, Herbert O., "Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes", J. Pharm. & Ex. Ther. 82, 377, (1944).

Primary Eye Irritation in Rabbits (Draize)

Nine (9) albino New Zealand rabbits without ocular defects were used. The procedure followed was a modification of that suggested by Dr. J.H. Draize in Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, compiled by the staff of the Division of Pharmacology, Food and Drug Administration - Department of Health, Education and Welfare.

In the technique of determining toxicity of substances to eye mucosa, observation of injuries were made on the cornea, iris and the bulbar and palpebral conjunctivae. Numerical scores were assigned to lesions observed according to the Draize scale. In this system of scoring, the injuries to the cornea and iris account for approximately eighty (80%) percent of the score; these structures are purposely weighted because of their vital role in vision. Healthy New Zealand rabbits were used for this test. One-tenth of a milliliter of the test substance was instilled in the right eye; the left eye, remaining untreated, served as a control. The treated eyes of six rabbits remained unwashed for 24 hours. The eyes of the remaining three (3) rabbits were irrigated 4 seconds following instillation of the test material (30 ml tap water at 37 degrees C). Irrigation is important to determine the effect of washout, either beneficial or detrimental and the extent of that effect.

Readings facilitated by hand-held lenses were made 1, 2, 3, and up to 7 days after treatment.

Acute Dermal Toxicity in Rabbits

A modification of the techniques described in Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, compiled by the staff of the Division of Pharmacology, Food and Drug Administration, was followed. Healthy albino rabbits as indicated in the summary were used. The animals were prepared by clipping the skin of the trunk free of hair and were further prepared by introducing epidermal abrasions over the clipped skin surface, thus enhancing penetrability of the test material through the stratum corneum.

A single dermal application as indicated, according to bodyweight was used. The trunk of each animal was encased in a sleeve of plasticized material to insure contact of the test material and the skin for a 24 hour period.

Following the 24 hour exposure period the sleeve was removed and the skin sites gently cleansed. All animals were then observed for mortality, skin response and general behavior for 14 days subsequent to exposure to the test material.

Acute Oral Toxicity in Rats (LD_{50})

Acute oral toxicity in rats was determined according to the procedure suggested by Hagan.[1] Wistar-derived albino rats, as indicated in the summary were assigned to groups, and maintained under standard laboratory conditions for a minimum of seven days, and fasted overnight prior to administration of the test material.

The rats were dosed individually by gavage, at graded dose levels (following range finding) after which they were returned to quarters where food and water were available ad libitum.

Animals were observed for signs of pharmacologic activity and drug toxicity at 1, 3, 6 and 24 hours post-dosage. Observations were made daily thereafter to a total of fourteen days.

Animals sacrificed at the end of the 14-day observation period were subjected to complete gross necropsy.

LD_{50} was calculated, (including the 95% confidence limits) where possible, using the method of Litchfield and Wilcoxin[2] except when the highest maximum dose mechanically possible (40 ml/kg) is used.

[1] Hagan, E.C. (1959) Acute Toxicity; Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, pp. 17 - 25.

[2] Litchfield, J.T. and Wilcoxin, F. (1949) J. Pharmacol. Exptl. Therap. pp. 96, 99.

RESULTS:

Primary Dermal Irritation in Rabbits

The scoring scale used is presented in Table 1. The individual results are presented in Table 2.

Primary Eye Irritation in Rabbits

Table 3 details scoring criteria. The individual results are presented in Table 4.

Acute Dermal Toxicity in Rabbits

Individual results are presented in Table 5.

Oral LD_{50} in Rats

Individual results are presented in Tables 6 & 7.

Summaries of all results are found preceeding the text.

Table 1

Scoring Criteria for Skin Reactions

Erythema and Edema Formation	
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
Total possible erythema score = 4	

Edema Formation	
Very slight edema (barely perceptible)	1
Slight edema (edges of area well-defined by definite raising)	2
Moderate edema (area raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Total possible edema score = 4	
Total possible primary irritation score = 8	

Table 1A

Scale of Interpreting
Primary Dermal Irritation Scores
(Draize - Rabbit)

Score	Interpretation
C	Corrosive - highly dangerous, warning labels must be used
5.0 and above	Primary Dermal Irritant - highly dangerous, warning label must be used
3.0 - 4.9	Potential for severe irritation - warning label would be advised
2.0 - 2.9	Potential for moderate irritation - may be irritating to humans under conditions similar to test (may consider warning label)
1.0 - 1.9	Potential for mild irritation - possibly irritating to some people under occlusive wrap conditions - usually no warning required
0.1 - 0.9	Potential for slight irritation - rarely irritating to people - no warning required
0.0	No irritation potential - no warning required

Table 2

Primary Skin Irritation - Rabbits
SUMMARY OF SCORES FOR SKIN IRRITATION

4H-EAQ, C8544-72

Rabbit Number	Skin	Hours: 24 E[1]	/	Ed	72 E	/	Ed
1	NA[2]	0		0	0		0
	A[3]	0		0	0		0
2	NA	0		0	0		0
	A	0		0	0		0
3	NA	0		0	0		0
	A	0		0	0		0
4	NA	0		0	0		0
	A	0		0	0		0
5	NA	0		0	0		0
	A	0		0	0		0
6	NA	0		0	0		0
	A	0		0	0		0
Average	NA	0.0		0.0	0.0		0.0
	A	0.0		0.0	0.0		0.0

Combined Averages: 0.0
Primary Irritation Index: 0.0

[1] E/Ed= Erythema and Edema

[2] NA = Non-abraded skin

[3] A = Abraded Skin

Table 3

Eye Irritation Test
Scale of Weighted Scores for
Grading the Severity of Ocular Lesions

Ocular Tissues	Description	Grading
Cornea	**Opacity (A)**	
	Opacity - degree of density (area which is dense is taken for reading)	
	Scattered or diffuse area, 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
	Area of Cornea Involved (B)	
	One-quarter (or less), but not zero.	1
	Greater than one-quarter, but less than one-half.	2
	Greater than one-half, but less than three-quarters.	3
	Greater than three-quarters, up to whole area.	4
	Score equals A x B x 5	Total maximum = 80
Iris	**Values (A)**	
	Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combinations of any thereof), iris still reacting to light.	
	Sluggish reaction is positive.	1
	No reaction to light hemorrhage, gross destruction, (any or all of these).	2
	Score equals A x 5	Total maximum = 10

Table 3 (cont'd.)

Eye Irritation Test
Scale of Weighted Scores for
Grading the Severity of Ocular Lesions

Ocular Tissues	Description	Grading
Conjunctivae	Redness (A)	
	Redness (refers to palpebral conjunctivae only). Vessels definitely injected above normal.	1
	More diffuse, crimson red, individual vessels not easily discernible.	2
	Diffuse beefy red.	3
	Chemosis (B)	
	Any swelling above normal (includes nictitating membrane).	1
	Obvious swelling with partial eversion of the lids.	2
	Swelling with lids about half-closed.	3
	Swelling with lids about half-closed to completely closed.	4
	Discharge (C)	
	Any amount different from normal (does not include small amount observed in inner canthus of normal animals).	1
	Discharge with moistening of the lids and hairs just adjacent to the lids.	2
	Discharge with moistening of the lids and hairs and considerable area around eye.	3
	Score equals (A + B + C) x 2	Total maximum = 20

Note: The maximum total score is the sum of all scores obtained for the cornea, iris and conjunctivae.

Table 4

Primary Eye Irritation - Rabbits
SUMMARY OF EYE IRRITATION

4H-EAQ, C8544-72

Rabbit Number	Day	Cornea: A x B x 5 =		Iris: A x 5 =	Conjunctivae: (A + B + C) x 2 =			Total Scores*
				--------No Wash Group----------				
1	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	-	-	-	-	-	-	-
	7	-	-	-	-	-	-	-
2	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	-	-	-	-	-	-	-
	7	-	-	-	-	-	-	-
3	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	-	-	-	-	-	-	-
	7	-	-	-	-	-	-	-
4	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	-	-	-	-	-	-	-
	7	-	-	-	-	-	-	-
5	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	-	-	-	-	-	-	-
	7	-	-	-	-	-	-	-
6	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	-	-	-	-	-	-	-
	7	-	-	-	-	-	-	-
Average	1							0.0
	2							0.0
	3							0.0
	4							---
	7							---

*Total score possible/animal/observation interval = 110

Table 4
(continued)
Primary Eye Irritation - Rabbits
SUMMARY OF EYE IRRITATION

4H-EAQ, C8544-72

Rabbit Number	Day	Cornea: A x B x 5 +	Iris: A x 5 +	Conjunctivae: (A + B + C) x 2 =	Total Scores*
		--------4 Second Wash Group--------			
7	1	0 0	0	0 0 0	0
	2	0 0	0	0 0 0	0
	3	0 0	0	0 0 0	0
	4	- -	-	- - -	-
	7	- -	-	- - -	-
8	1	0 0	0	0 0 0	0
	2	0 0	0	0 0 0	0
	3	0 0	0	0 0 0	0
	4	- -	-	- - -	-
	7	- -	-	- - -	-
9	1	0 0	0	0 0 0	0
	2	0 0	0	0 0 0	0
	3	0 0	0	0 0 0	0
	4	- -	-	- - -	-
	7	- -	-	- - -	-
Average	1				0.0
	2				0.0
	3				0.0
	4				---
	7				---

*Total score possible/animal/observation interval = 110

Table 5

Acute Dermal Toxicity in Rabbits

4H-EAQ, C8544-72

Dose g/kg	Animal Number and Sex	Bodyweight (kg)	Mortality IMMED.	1	6	24*	2	3	4	5	6-14	Bodyweight (kg)
5.0	1 M a	1.75	N	N	N	N	N	N	N	N	N	1.66
	2 M a	2.00	N									2.27
	3 M a	1.69	N									2.18
	4 F a	1.59	N	NO CHANGE OBSERVED								1.21
	5 F a	1.50	N									1.65
	6 F a	1.40	N									1.80

a = abraded skin

N = Normal
D = Depression
SD = Slight Depression
XD = Severe Depression
+ = Animal Death

Comments: Animal #1-3, 5-6: Skins pliable and non-irritated; no gross internal changes observed.

Animal #4: Skin pliable and non-irritated; feces loose; no gross internal changes observed.

*Draize scores at 24 hours:

Animal #:	
1	1/0
2	0/0
3	0/0
4	0/0
5	0/0
6	1/0

Table 6

Acute Oral Toxicity

4H-EAQ, C8544-72

Range Finding:

Dose g/kg	Animal and Sex	Number	Bodyweight (grams)	Hours: 1	3	6	24	Days: 2	3	4	5	6	7-14	Bodyweight (grams)
1.0	1	F	220	N	N	N	N	N	N	N	N	N	N N	262
5.0	2	F	208	N	N	N	N	N	N	N	N	N	N N	252
10.0	3	F	220	N	N	N	N	N	N	N	N	N	N N	290

N = Normal
D = Depression
SD = Slight Depression
XD = Severe Depression
+ = Animal Death

Table 7

Acute Oral Toxicity

4H-EAQ, C8544-72

Dose g/kg	Animal Number and Sex	Bodyweight (grams)	Hours: 1	3	6	24	Days: 2*	3	4	5	6	7--14	Bodyweight (grams)
10.0	1 M	216	SD	SD	SD	N	N	N	N	N	N	N	306
	2 M	190	SD	SD	SD	SD	N	N	N	N	N	N	274
	3 M	194	SD	SD	SD	N	N	N	N	N	N	N	272
	4 M	188	SD	SD	SD	N	N	+	-	-	-	-	162
	5 M	194	SD	SD	SD	N	N	N	N	N	N	N	286
	6 F	214	SD	SD	SD	N	N	N	N	N	N	N	266
	7 F	200	SD	SD	SD	N	N	N	N	N	N	N	242
	8 F	190	SD	SD	SD	N	N	N	N	N	N	N	230
	9 F	200	SD	SD	SD	N	N	N	N	N	N	N	194
	10 F	210	SD	SD	SD	N	N	N	N	N	N	N	258

N = Normal
D = Depression
SD = Slight Depression
XD = Severe Depression
+ = Animal Death

*48 hours: All animals sweating.

Comments: Animal #1-3, 5-8, 10: No gross changes observed.
#4: Fibrous tissue encasing heart and lungs.
#9: All lobes of right lung consolidated.

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