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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

010476

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

AUG 1 0 1993

MEMORANDUM

SUBJECT: Registrant's Response to a Deficiency Identified in an 8/16/89 Review of an Eye Irritation Study of ADBAC (MRID # 40919701)

Tox Chem No.	16E
Submission No.	S425934
DP Barcode No.	D182926
ID No.	069105
Case No.	819070
MRID Nos.	419475-01 408356-02 408356-03

FROM: Brian Dementi, Ph.D., D.A.B.T. Brian Dementi 1/8/93
Review Section III
Toxicology Branch-I
Health Effects Division (H7509C)

TO: Brigid Lowery, PM Team 72
Reregistration Branch
Special Review and Reregistration Division (H7508W)

THRU: Karen Hamernik, Ph.D., Acting Section Head
Review Section III
Toxicology Branch-I
Health Effects Division (H7509C) K. Hamernik 7/16/93 KB 8/2/93

In August 1989 Toxicology Branch reviewed a primary eye irritation study performed in rabbits using ADBAC as test material (MRID # 409197-01). A copy of that review is appended. The reviewer concluded the study to be core minimum, but noted a deficiency described as a lack of information on the chemical analysis of the test material and its stability.

In attempting to address this deficiency the registrant has submitted information from three sources. These include a chronic/oncogenicity study of ADBAC in rats (MRID # 419475-01); a study on the hydrolysis of ADBAC as a function of pH at 25°C (MRID # 408356-02); and a study of the photolysis of ADBAC at pH 7 and 25°C (MRID # 408356-03).

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The registrant advises that when the eye irritation study was being conducted, the same lot of ADBAC was being used in the rat chronic/oncogenicity study identified above. In that long term study, according to the registrant, periodic analyses showed that technical ADBAC was stable over the two year study period. An independent Tox Branch inspection of information provided from the chronic/oncogenicity study is sufficient to establish the correctness of the registrant's claim as to the stability of the test material. Repeated analyses over the period March 30, 1988 through November 8, 1989 showed the percent active ingredient to range 75.6-81.5%. (See appended excerpt from DER of MRID 41947501).

The registrant also claims that the additional two studies submitted on ADBAC establish that test solutions of ADBAC are hydrolytically and photolytically stable for 30 days. An independent inspection of these two studies is convincing that solutions of ADBAC prepared for use in the eye irritation study would have been stable. In the hydrolysis study, there was no evidence of significant degradation in the pH range 5-9 for the 30-day study period. In the photolysis study, ADBAC did not degrade in sterile aqueous pH 7 buffered solutions continuously irradiated using a Xenon arc lamp. The duration of the photolysis study was not indicated. (See appended review from E. Regelman, 8/2/89).

Conclusion:

Toxicology Branch considers the information provided by the registrant to be adequate to address the deficiency identified in the case of rabbit eye irritation study, and recommends that the study be upgraded to Core Guideline.

Cover Letter out of Period Dated Aug 16, 1989

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07437

81-4 - Rabbit - Eye Irritation

Reviewed by: John H.S. Chen, D.V.M. John H.S. Chen 8/8/89
Section I, Toxicology Branch - HFAS (H7509C)
Secondary reviewer: Yiannakis M. Ioannou, Ph.D. Stephen C. Dapson for 8/8/89
Section I, Toxicology Branch - HFAS (H7509C)

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DATA EVALUATION REPORT

Study Type: Primary Rabbit Eye Irritation

Tox. Chem. No.: 16E (not 16I)

MRID Number: 409197-01

Accession No.:

EPA File Symbol: 069105

Test Material: Alkyl dimethyl benzyl ammonium chloride (ADBAC)
(Lot No. 7293K; 80% Purity)

Synonyms/CAS No.:

Study Number(s): 88-3336-21

Sponsor: Chemical Specialties Manufacturers Association
Washington, DC 20036

Testing Facility: Hill Top Biolabs, Inc.
Miamiville, OH 45147

Title of Report: Repeated Eye instillation Study in Rabbits

Author(s): James J. Kreuzmann

Report Issued: October 10, 1988

Conclusions:

Conjunctial irritations were observed in one animal on day 5 and two animals on day 8 in the nominal 2.5 ppm dose group. Two animals in the 5.00 ppm dose group exhibited conjunctival irritation, one on day 8 and the other on day 15. All signs of eye irritation were absent 19 days post-treatment.

Toxicity Category: III

Classification of Data: Core Minimum
(Deficiency: lack of the information of chemical analysis concerning the test material characteristics and stability testing)

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I. Materials and Methods:

1. " Three groups of six young adult New Zealand white rabbits were used in this study." " The animals in Group 1 received a nominal concentration equivalent to that present in swimming pools under the maximum label recommended use rate (2.5 ppm) while the animals in Group 2 received a nominal concentration equivalent to twice that of Group 1 (5.0 ppm). The animals in Group 3 received 0.1 ml of sterilized water for irrigation, USP, into the right eye."

2. " The test material solutions or water (0.1 ml) were instilled into the right eye of each of these animals, once a day, five days per week, for three consecutive weeks. " " The treated eye of each rabbit was examined just prior to dosing on study days 1, 2, 5, 8, 12, 15, 19, and 22. The eyes were scored according to the standard Draize scoring system outlined in Appendix 1. "

II. Reported Results:

1. Low grade conjunctival irritation was evident in one animal on day 5 and 2 animals on day 8 in the nominal 2.5 ppm dose group. Two animals in the 5.0 ppm dose group exhibited comparable conjunctival irritation, one on day 8 and the other on day 15.

2. No signs of corneal opacity were observed at any time during the study.

3. All signs of eye irritation were absent 19 days post-treatment.

Toxicity Category III

III. Classification of Data: Core Minimum

Deficiency: lack of the information of chemical analysis concerning the test material characteristics and stability testing)

Signed and dated GLP and QAU statement were included.

D18 [illegible]

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ADBAC Quat Steering Committee Response to Agency Data Evaluation Report (DER)

Data Requirement:	Repeated Eye Irritation in Rabbits
Active Ingredient:	Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC)
MRID No.:	409197-01
Laboratory:	Hill Top Biolabs, Inc., Miamiville OH
Lab Project No.:	88-3336-21
Title:	Repeated Eye Instillation Study in Rabbits

Agency Conclusion:

Classification of data: Core minimum

(Deficiency: Lack of the information of chemical analysis concerning the test material characteristics and stability testing).

Response to Agency DER:

It is unclear if the Agency conclusion regarding chemical analysis of test material characteristics and stability testing refers to the ADBAC 80% MUP (Lot No. 7293K) test substance or to the aqueous solutions prepared in this study.

The stability of the ADBAC test substance has been demonstrated in the course of the ADBAC data development program. During the period of time that this eye irritation study was being conducted, stability analyses were conducted on the same lot of this test substance which was being used in a chronic toxicity/oncogenicity study in rats at another laboratory. Periodic analyses showed that ADBAC was stable under storage during the course of this two-year study

(MRID No. 419475-01). A copy of the summary results from these analyses is attached.

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If the Agency reviewer's concern is with the stability of the test substance in the prepared test solution, ADBAC has been shown to be hydrolytically and photolytically stable in 30-day hydrolysis and aqueous photolysis studies (MRID Nos. 408356-02 and 408356-03). In addition, aqueous test solutions were made fresh for each application in this eye irritation study.

Page ___ is not included in this copy.

Pages 2 through 8 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Guideline Series 83-5: Combined Chronic Toxicity/Oncogenicity in Rats

010476

EPA Reviewer: Brian Dementi, Ph.D.
Review Section III, Toxicology Branch I
Health Effects Division

Signature: Brian Dementi
Date: 8/20/92

EPA Acting Section Head:
Karen Hamernik, Ph.D., Review Section III
Toxicology Branch I, Health Effects Division

Signature: [illegible]
Date: 8/7/93

DATA EVALUATION REPORT

STUDY TYPE: Combined chronic toxicity/oncogenicity in rats

TEST MATERIAL: Alkyl dimethyl benzyl ammonium chloride (ADBAC)

TOX. CHEM. NUMBER: 016E

P.C. NUMBER: 069105

SYNONYMS: Benzalkonium chloride

CAS Number: 68391-01-5

STUDY NUMBER: 53-543

MRID NUMBER: 419475-01

SPONSOR: ADBAC QUAT Joint Venture/
Chemical Specialties Manufacturers Association
1913 Eye Street, N.W.
Washington, D.C. 20006

TESTING FACILITY: Bushy Run Research Center
6702 Mellon Road
Export, PA 15632

TITLE OF REPORT: Chronic Dietary Toxicity/Oncogenicity Study with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Rats

AUTHORS: M.W. Gill, S.J. Hermansky, and C.L. Wagner

REPORT ISSUED: Completion date, July 8, 1991

CONCLUSIONS: ADBAC was administered via the diet to Sprague-Dawley rats for 104 weeks at doses of 0, 300, 1,000, and 2,000 ppm. The average daily intake values of ADBAC at these dietary levels were 13, 44, and 88 mg/kg/day for males and 17, 57, and 116 mg/kg/day for females. ADBAC was not oncogenic under the conditions of this study. Systemic toxicity, as indicated by decreased body weight, body weight gain, and food consumption, occurred with a LOEL of 2,000 ppm and a NOEL of 1,000 ppm. The following treatment related effects were observed:

300 ppm -- Equivalent to 13 mg/kg/day in males and 17 mg/kg/day in females. No treatment-related effects were observed.

1,000 ppm -- Equivalent to 44 mg/kg/day in males and 57 mg/kg/day in females. No treatment-related toxicity was observed.

2,000 ppm -- Equivalent to 88 mg/kg/day in males and 116 mg/kg/day in females. Male and female body weights were decreased by approximately 5% and 6%, respectively. Male and female body weight gains were decreased by approximately 11% and 14%, respectively. Food consumption was significantly decreased in both males and females. In general, the effects on body weight and body weight gain paralleled the effects on food consumption. No treatment-related toxicity was observed based on clinical pathology parameters, and gross and microscopic pathology did not reveal any evidence of toxicity in the treated animals.

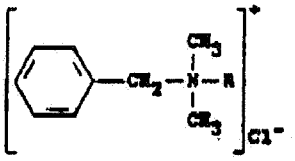
CORE CLASSIFICATION: This study is classified as Core Minimum for combined chronic toxicity/oncogenicity studies because although adequate toxicity as shown by at least a 10% decrease in body weight gain was demonstrated in both males and females, a palatability problem may have contributed to the effects observed on body weight and body weight gain.

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Alkyl dimethyl benzyl ammonium chloride (ADBAC)

Formula: A mixture of alkyl dimethyl benzyl ammonium chlorides of the general formula in which R represents a mixture of the alkyls from $C_{12}H_{25}$ to $C_{16}H_{33}$. The distribution analogs with alkyl chain lengths of 12, 14, and 16 were 40%, 50%, and 10%, respectively.



Lot number: 7293K

Purity: 81.09% active ingredient; the sponsor indicated that the substance also contained ethanol (10-15%)

Physical property: Pale-yellow, viscous liquid

Stability: Stable for at least 14 days when stored at room temperature

2. Rationale for Dose Selection

Dietary levels of ADBAC for the current study were selected based upon the results of 14-day and 90-day dietary range-finding studies (BRRC report numbers 51-513 and 51-503, respectively). The doses selected for the current study were intended to produce toxicity at the high dose and no toxicity at the low dose. The specific toxic end points used to set the doses for the current study were not

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Pages 11 through 14 are not included in this copy.

The material not included contains the following type of information:

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_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

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Shaughnessy No.: 069105
Date Out of EFGWB: AUG 2 1989

To: John Lee
Product Manager PM #31
Registration Division (H7505C)

From: Emil Regelman, Supervisory Chemist
Environmental Chemistry Review Section #2
Environmental Fate & Ground Water Branch/EFED (H7507C)

AUG 2 1989

Thru: Henry Jacoby, Acting Chief
Environmental Fate & Ground Water Branch/EFED (H7507C)

Attached, please find the EFGWB review of...

Reg./File # : 069105

Chemical Name: ADBAC

Type Product : biocide

Product Name : n.a.

Company Name : ADBAC Quat Joint Venture

Purpose : Review studies submitted in response to the 1985 Registration Standard.

Action Code: 400 EFGWB #(s): 90363

Date Received: 10/3/88 Total Reviewing Time: 8 days

Date Completed: 8/2/89

Deferrals to: ___ Ecological Effects Branch

___ Dietary Exposure Branch

___ Non-Dietary Exposure Branch

___ Toxicology Branch I

___ Toxicology Branch II

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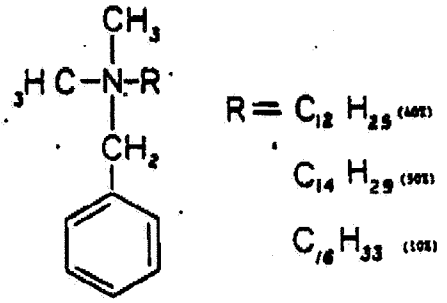
1. **CHEMICAL:** **Common name:**

ADBAC.

Chemical name:

Alkyl dimethyl benzyl ammonium chloride.

Structure:



2. **TEST MATERIAL:**

Ring-labeled [^{14}C]alkyl dimethyl benzyl ammonium chloride.

3. **STUDY/ACTION TYPE:**

Review studies submitted in response to the September 1985 Registration Standard.

4. **STUDY IDENTIFICATION:**

Carpenter, M. and M. Fennessey. 1988a. Determination of the photolysis rate of ADBAC in pH 7 buffered solution at 25°C. ABC Final Report #35713. Unpublished study prepared by Analytical Bio-Chemistry Laboratories, Inc., Columbia, MO, and submitted by Chemical Specialties Manufacturing Association, Washington, DC. (40835603)

Carpenter, M. and M. Fennessey. 1988b. Hydrolysis of ADBAC as a function of pH at 25°. ABC Amended Final Report #35712. Unpublished study performed by Analytical Bio-Chemistry Laboratories, Inc., Columbia, MO, and submitted by Chemical Specialties Manufacturers Association, Washington, DC. (40835602)

Daly, D. and W. Cranor. 1988. Soil/sediment adsorption-desorption of alkyl dimethyl benzyl ammonium chloride. ABC Final Report 35716. Unpublished study prepared by Analytical Bio-Chemistry Laboratories, Inc., Columbia, MO, and submitted by Chemical Specialties Manufacturers Association, Washington, DC.

Daly, D. and W. Cranor. 1988. Aerobic aquatic metabolism of alkyl dimethyl benzyl ammonium chloride. ABC Final Report #35715. Unpublished study performed by Analytical Bio-Chemistry Laboratories, Inc., Columbia, MO, and submitted by Chemical Specialties Manufacturers Association, Washington, DC. (40835604)

Fackler, P. 1989. Bioconcentration and elimination of ^{14}C-residues by bluegill (Lepomis macrochirus) exposed to alkyl dimethyl benzyl ammonium chloride (ADBAC). Study No. 11572-0287-6103-140B, Report No. 89-1-2921. Unpublished study performed by Springborn Life Sciences, Inc., Wareham, MA, and submitted by ADBAC Quat Joint Venture/Chemical Specialties Manufacturers Assoc., Washington, DC. (41026801)

5. **REVIEWED BY:**

Dana Spatz
Chemist, ECRS #2
EFGWB/EFED/OPP

Date: AUG 2 1989

6. **APPROVED BY:**

Emil Regelman
Supervisory Chemist, ECRS #2
EFGWB/EFED/OPP

Date: AUG 2 1989

7. **CONCLUSIONS:**

A. HYDROLYSIS

This study is acceptable and fulfills EPA Data Requirements for Registering Pesticides by providing information on the hydrolysis of ring-labeled [^{14}C]ADBAC at pH 5, 7, and 9. ADBAC did not hydrolyze in pH 9 sterile aqueous buffer solutions incubated at 25 ± 1°C; ADBAC was relatively stable to hydrolysis in pH 5 and 7 solutions, decreasing by ≤2.3% of the recovered during 30 days.

B. PHOTODEGRADATION IN WATER

This study is scientifically sound, but does not meet Subdivision N guidelines for the following reason:

- the intensity and wavelength distribution of the light source were not reported, nor were they compared to natural sunlight.

ADBAC did not degrade in sterile aqueous pH 7 buffered solutions that were continuously irradiated using a xenon arc lamp; ADBAC degraded with a half-life of 7.1 days in similar solutions that were sensitized with 1% acetone. ADBAC did not degrade in the respective dark controls.

One [^{14}C]compound, isolated 30 days posttreatment from the sensitized irradiated solution at 74.5% (6.97 ppm) of the applied, was not identified. Because there are many organic photosensitizers present in the environment, it is important to identify the major photoproduct that was detected in the photosensitized system. Therefore, the identification of this photoproduct is also required in order to satisfy the Photodegradation in Water data requirement.

C. LEACHING-ADSORPTION/DESORPTION

This study is unacceptable because the soils were autoclaved prior to testing. Autoclaving of soils prior to the initiation of an adsorption/desorption study renders the validity of the study as questionable, because autoclaving may affect the physical and chemical properties of the soils. Soil CEC, crystalline structure, and hydrophobicity may be affected by autoclaving.

D. AEROBIC AQUATIC METABOLISM

This study is scientifically sound, but does not meet Subdivision N guidelines for the following reason:

several [^{14}C]residues present at ≥0.01 ppm were not identified (one degradate, present at up to 0.12 ug/g was isolated but not identified; and "remainder", defined as a composite of all the scraped TLC material exclusive of the origin, the parent, and the unidentified degradate, accounted for up to 0.97 ug/g).

Alkyl dimethyl benzyl ammonium chloride (ADBAC) was fairly stable during 30 days of incubation in flooded sandy loam soil maintained at 24–27°C in the dark.

E. ACCUMULATION IN FISH

This study is scientifically sound, but does not meet Subdivision N guidelines for the following reason:

[^{14}C]residues in the water and fish were not characterized.

Total [^{14}C]ADBAC residues accumulated in bluegill sunfish with maximum bioconcentration factors of 33x in edible tissues, 160x in nonedible tissues, and 79x in whole fish during 35 days of exposure to [^{14}C]ADBAC residues at 0.036–0.13 ppm in a flow–through system. Maximum concentrations of residues (uncharacterized) occurred after 35 days of exposure and were 3.4, 13, and 6.6 ppm in edible tissues, nonedible tissues, and whole fish, respectively. After 21 days of depuration, [^{14}C]residues in edible tissues, nonedible tissues, and whole fish were 2.4, 5.3, and 3.7 ppm, respectively; [^{14}C]residues in the edible tissues did not decline significantly from the concentrations detected during the exposure period.

8. RECOMMENDATIONS:

HYDROLYSIS

The Hydrolyis data requirement has been fulfilled by this submission.

PHOTODEGRADATION IN WATER

The Photodegradation In Water data requirement remains a data gap. In order for this study to fulfill the photodegradation data requirement, the ADBAC degradate isolated at 30 days posttreatment must be identified, and the artificial light source must be characterized and compared to natural sunlight.

LEACHING–ADSORPTION/DESORPTION

The Leaching–Adsorption/Desorption data requirement remains a data gap.

AEROBIC AQUATIC METABOLISM

The Aerobic Aquatic Metabolism data requirement remains a data gap. In order for this study to fulfill the aerobic aquatic metabolism data requirement, [^{14}C]residues isolated at ≥0.01 ppm must be identified.

ACCUMULATION IN FISH

The Accumulation in Fish data requirement remains a data gap. In order for this study to fulfill the accumulation in fish data requirement, the registrant must characterize [^{14}C]residues in the treated water and fish tissues present at concentrations ≥0.05 ppm.

Status of Data Requirements as per the 1985 Registration Standard

Satisfied

Hydrolysis 161-1

Not Satisfied

notodegradation in Water 161-2
Anaerobic Aquatic Metabolism 162-3
Aerobic Aquatic Metabolism 162-4
Leaching-Adsorption/Desorption 163-1
Aquatic (sediment) Field Dissipation 164-2
Accumulation in Fish 165-4
Accumulation in Aquatic Non-Target Organisms 165-5

9. BACKGROUND:

ADBAC is effective against a broad spectrum of microorganisms. It is registered as a bactericidal, fungicidal, and algaecidal agent in a variety of indoor and aquatic sites such as cooling towers, oil field recovery systems, swimming pools, animal quarters, household premises, commercial and industrial premises, hospital premises, food processing equipment, etc.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES:

See individual DER's attached.

11. COMPLETION OF ONE-LINER:

One-liner is attached.

12. CBI APPENDIX:

Not applicable.