11-21-88

Shaughnessy No: 128101

Date Out of EAB: NOV 21 1988

TO: John H. Lee
Product Manager #31
Registration Division (TS-767C)

FROM: Emil Regelman, Supervisory Chemist
Environmental Chemistry Review Section #2
Environmental Fate and Ground Water Branch, EFED (TS-769C)

THRU: Henry M. Jacoby, Acting Chief
Environmental Fate and Ground Water Branch/EFED (TS-769C)

Attached, please find the EFGWB review of:

Reg./File #: 707-RTL

Common Name: "RH-5287" (active ingredient)

Chemical Name: 4,5-Dichloro-2-octyl-isothiazole

Type product: Marine antifoulant

Product Name: Kathon 287; (C-9211M)

Company Name: Rohm & Haas

Purpose: Review of data/submissions

Date Received: 7/15/88; 8/11/88 Action Code: 116

Date Completed: 11/17/88 EAB #(s): 80918; 80959

Total Reviewing Time (decimal days): 2.5 days

Deferrals to: _____ Ecological Effects Branch, EFED

_____ Science Integration & Policy Staff, EFED

_____ Non-Dietary Exposure Branch, HED

_____ Dietary Exposure Branch, HED

_____ Toxicology Branch, HED

(1)

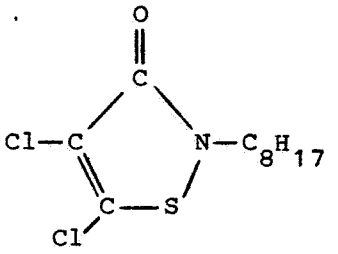
1. CHEMICAL:

Common name: None (identified by the company as RH-5287)
Chemical name: 4,5-dichloro-2-n-octyl-3(2H)-isothiazolone
"4,5-dichloro-2-octyl-isothiazole"

Chemical Abstracts Registry #: 64359-81-5

Trade name(s): Anti-Foulant C-9211M; Kathon-287

Structure:



Formulation: 30-31% active ingredient (RH-5287)
70% inert solvent

Physical/Chemical properties (technical product):

Appearance:	tan brown waxy solid
Melting point:	40-41°C
pH:	Not applicable
Specific gravity:	1.28 (at 25°C)
Solubility:	14 ppm (in water, 25°C)
	Miscible in most organic solvents
Vapor pressure:	4.5×10^{-6} Torr
Octanol/Water Partition coefficient:	logP= 6.4

2. STUDY/ACTION TYPE:

Review of studies submitted to support registration for use in antifouling marine coatings (aquatic nonfood use).

3. STUDY IDENTIFICATION:

- Carpenter, M. 1986. Determination of photodegradation of ^{14}C-RH-5287 in aqueous solutions. Performed by Analytical Bio-Chemistry Laboratories, Inc., Columbia, MO, ABC Final Supplementary Report #321171, Volume 1, completed July, 31, 1986. Submitted by Rohm and Haas Company, Spring House, PA.
MRID No. 40741301.

- Carpenter, M. 1986. Determination of photodegradation of ^{14}-C-RH-5287 in seawater. Performed by Analytical Bio-Chemistry Laboratories, Inc.

Columbia, MO, ABC Final Supplementary Report #342321, Volume 2, completed July 14, 1986. Submitted by Rohm and Haas Company, Spring House, PA.
MRID No. 40741302.

- Leak, T. 1987. Metabolite characterization of RH-5287 in bluegill sunfish (Lepomis macrochirus). A Supplemental Report to ABC Final Report 32971. Performed by ABC Laboratories, Inc. Columbia, MO. Submitted by Rohm and Haas Company, Spring House, PA.
MRID No. 40741304.

- Weeks, J.A. and Drendel, G.H. 1986. Environmental dissipation modeling of the marine antifoulant RH-5287. Performed by Labat-Anderson, Inc., Resource Analysis Division, Arlington, VA, Technical Report No. 310-86-35, completed June 16, 1986. Submitted by Rohm and Haas Company, Philadelphia, PA.
MRID No. 40741303.

- Letter of registrant (dated July 11, 1988) containing the response of the environmental fate review of 12/3/87 and a summary of the actions agreed upon at a meeting held on April 11, 1988. A copy of the letter is attached to the review.

4. REVIEWED BY:

Silvia C. Termes
Chemist, Review Section #2
OPP/EFED/EFGWB

Signature: [signature]
Date: November 18 1988

5. APPROVED BY:

Emil Regelman
Supervisory Chemist
Review Section #2
OPP/EFED/EFGWB

Signature: [signature]
Date: NOV 21 1988

6. CONCLUSIONS:

a. Photodegradation studies:

The submitted Final Reports (40741301, aqueous solutions; 40744102, seawater) were not reviewed. At the meeting held on April 11, 1988 (and confirmed in the registrant's letter of July 11, 1988), Rohm and Haas agreed to submit a new study to the Agency.

This study will be run in buffered aqueous solution (pH 7 to reduce hydrolysis) and without a sensitizer. Natural sunlight will be used.

b. Aquatic field dissipation study:

The Agency agreed at the April 11, 1988 meeting to review a modeling study which had been submitted earlier (see review 12/3/87), but to which more recent refinements were added. The model includes worse-

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case situations (New York, Norkfolk, and San Diego harbors). This study is being reviewed by Robert Hitch. The completion date for this study has been scheduled for 2/1/89.

At the meeting, a discussion (M.Firestone, R.Doyle, EPA/OPP) of experimental methods used to define release rates was included. The registrant was given a copy of a draft (Draft #6, 4/1/86) of the ASTM Standard Test Method for Organotin Release Rates of Anti-foulant Coating Systems in Sea Water.

c. Metabolite characterization in bluegill sunfish:

Even though considerable efforts were made to separate, extract, and classify the metabolites by several methods, no clear identification of the metabolites was made. Studies were conducted with fish viscera only (1.4 and 1.3 ppm of RH-5287 equivalents at 21- and 28-days exposure, respectively), but not with the edible parts (0.20 and 0.23 ppm at 21- and 28-days exposure, respectively).

The reported results indicate that the metabolites are highly polar (some may be anionic or cationic), as they were more readily extracted by aqueous systems (particularly by buffered water, pH 7.2, phosphate buffer) than by dichloromethane. The metabolites were not RH-5287 glucuronides. There was also evidence that some of the metabolites may be volatile (but this was not actually demonstrated).

Considering the intended use pattern of products containing RH-5287, the identity of the metabolites (which is still rather unclear and considered to be incompletely characterized because no attempts were made to identify the residues in the edible parts) is an important issue in the accumulation in fish studies. Therefore, the data requirements for accumulation in fish studies cannot be considered fulfilled.

d. Response to deficiencies in the Anaerobic Aquatic Metabolism of RH-5287 (EPA Accession No. 265904), 12/3/87 review:

The EFGWB has reviewed the response to the deficiencies (unspecified radiopurity, methodology for degradate identification, etc.). However, as noted in the Data Evaluation Record, Study 4, DISCUSSION Section (pp. 30-31), the EFGWB still has serious doubts about the quality of the study, particularly about the treatment of data. Therefore, the study cannot be considered acceptable to fulfill data requirements. A new study is required.

e. Other studies agreed to be repeated:

Aerobic aquatic metabolism (162-4)

Leaching and adsorption/desorption (163-1): This study is to be repeated using the batch equilibrium method. Four soils and an aquatic sediment

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will be utilized. The active ingredient will be tested in a pH 7 buffer along with 0.01 M $CaCl_2$.

The mobility of the aged residue will be analyzed by a column leaching experiment (half-life in spiking soil will be determined first), in which the aged soil will be added to four columns (each containing an agricultural soil). Leachates and soils will be radioassayed and the radioactivity characterized.

7. RECOMMENDATIONS:

The registrant should be informed of the following:

1. The data requirement for accumulation in fish studies has not been considered fulfilled because of unclear and incomplete characterization of metabolites (no edible parts were analyzed).

2. A new anaerobic aquatic metabolism study must be submitted.

3. The environmental dissipation modeling study is currently being reviewed by Robert Hitch (EPA/OPP). The scheduled data for completion of this review is 2/1/89.

4. The other studies (photodegradation in water, aerobic aquatic metabolism, batch-equilibrium adsorption/desorption and column leaching) are to be conducted as agreed.

The registrant is advised to improve the presentation of the study reports In the past, the submitted studies have shown poorly organized data/results, which have made the review process difficult.

8. BACKGROUND:

a. Introduction

The only submitted study that has fulfilled data requirements is the hydrolysis study (Manning's review, 8/11/83). Photodegradation in water, anaerobic and aerobic aquatic metabolism, leaching and adsorption/desorption studies, and pesticide accumulation in fish studies were reviewed at a later date (Termes review, 12/3/87). These studies did not fulfill data requirements.

A meeting was held with the registrant on April 11, 1988 to discuss the the deficiencies noted in the studies and the feasibility of using a modeling study to fulfill data requirements for aquatic field dissipation studies. A letter from the registrant dated July 11, 1988 contains a summary of the actions taken at the meeting.

The present review contains the EFGWB response to the registrant's letter (which also contains their response to the deficiencies noted in the 12/3/87 review) and the review of the supplementary studies submitted after the 12/3/87 review.

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b. Directions for use

Kathon (active ingredient RH-5287) is an algicide/barnicide developed for use in antifouling marine coatings (aquatic nonfood use). It is intended for distribution to the largest industrial formulator/painters involved in the painting of large military and commercial ships; it should not be available to private boat owners or small commercial establishments. The active ingredient RH-5287 (4,5,-dichloro-2-octyl-isothiazole) is formulated (30-31% active ingredient) in an organic solvent, which will be then formulated into paint by the purcharser.

10. DISCUSSION OF INDIVIDUAL STUDIES:

Please see attached review of the metabolite characterization study.

11. COMPLETION OF ONE-LINER: No one-liner has been completed.

12. CBI APPENDIX:

All data reviewed here are considered CBI by the registrant and must be treated as such.

KATHON 287 T

Page 7 is not included in this copy.

Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product 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.

X FIFRA registration data.

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

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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.

DATA EVALUATION RECORD

CASE GS --RH-5287 STUDY 1 PM 31

CHEM 128101 RH-5287: 4,5-Dichloro-2-octyl-isothiazole 165-4

BRANCH Environmental Fate and Ground Water

FORMULATION 00- Pure Radiolabeled Active Ingredient

Leak, T. 1987. Metabolite characterization of RH-5287 in bluegill sunfish (Lepomis macrochirus). A Supplemental report to ABC Final Report 32971. Performed by ABC Laboratories, Inc. Columbia, MO.
MRID No. 40741304

SUBST. CLASS: Marine Antifoulant

REVIEWED BY: S.C. Termes
TITLE: Chemist
ORG: EAB/HED/OPP
TEL: (703)557-2243

SIGNATURE: November 18, 1988

CONCLUSIONS:

This study was undertaken in order to identify the metabolites present in [^{14}C]-residues accumulated in bluegill sunfish. The first part of the study was reviewed by EFGWB on 12/3/88 and covered the studies with EPA Accession Nos. 265911, 265912, and 265913.

Even though considerable efforts were made to separate, extract, and classify the metabolites by several methods, no clear identification of the metabolites was made. Studies were conducted with fish viscera only (1.4 and 1.3 ppm of RH-5287 equivalents at 21- and 28-days exposure, respectively), but did not include studies with the edible parts (0.20 and 0.23 ppm at 21- and 28-days exposure, respectively).

The reported results indicate that the metabolites are highly polar (some may be anionic or cationic), as they were more readily extracted by aqueous systems (particularly by buffered water, pH 7.2, phosphate buffer) than by dichloromethane. The metabolites were not RH-5287 glucuronides. There was also evidence that some of the metabolites may be volatile (but this was not actually demonstrated).

Taking into account the intended use pattern of products containing RH-5287 (aquatic, nonfood; marine environments), the identity of the metabolites (which is still rather unclear and considered to be incompletely characterized because no attempts were made to identify the residues in the edible parts) is an important issue in the accumulation in fish studies. Therefore, the data requirements for accumulation in fish studies cannot be considered fulfilled.

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MATERIALS AND METHODS

Test material: Tissue from viscera obtained by dissection from bluegill sunfish exposed to RH-5287 in water for 21- and 28-days. The exposure part of this study was previously reviewed by EFGWB (12/3/88 review) under EPA's Accession Nos. 265911, 265912, and 265913. The tissues contained 1.3 ppm of RH-5287 equivalent residues prior to initiation of the metabolite characterization (1.4 ppm and 1.3 ppm at 21- and 28-day exposure, respectively; data taken from the earlier phase of the study). The tissues had remained frozen at -20°C after completion of the exposure period.

Experimental procedures:

Study I- Extractability with base (blending of tissue sample with 100 mL of 0.05 M NaOH for one minute); filtered extract was analysed by LSC. Solids were then blended with 0.05 M HCl (100 mL; one minute), filtered (extracts analysed for radioactivity). Combined solids were mixed with 5-g Na_2SO_4 and then extracted with dichloromethane (extracts analysed for radioactivity; solids discarded). Tissue used was a 28-day viscera sample (1.53 g).

Radioactivity extracted:
Base.....71%
Acid.....Additional 25%
CH_2Cl_2.....less than 1%

Study II- Extractability with unbuffered water followed by base (0.05 N NaOH) and followed by partition by CH_2Cl_2 (at different pH). This study used 21-day viscera sample, of which 6.12 g was blended (1 min) with unbuffered water. The filtered extract was adjusted to pH 10, then extracted three times with 50 mL CH_2Cl_2. The aqueous phase was then acified to pH 2 with HCl and then extracted three times with CH_2Cl_2. The CH_2Cl_2 fractions were concentrated with vaccum (at less than 40°C) to a final volume of 5 mL. The organic extracts and the extracted water were analysed for radioactivity.

The soilds from the first aqueous extraction were again blended with 0.05 N NaOH. The filtered extract was partitioned three times with CH_2Cl_2. After concentration (to 5-mL), the CH_2Cl_2 extracts were radioassayed; postextracted water was also radioassayed.

Radioactivity extracted: Single extraction,
neutral water.....68%
Additional extraction
with NaOH.....31%
Partitioning at different
pH, with CH_2Cl_2.....11%*

*Overall, but no clear chemical separation

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Study III: Timed extraction with buffered water (100-mL of 0.05 M Na_2HPO_4, buffer, pH 7.2). Sample used was 1.12 g of day 28 viscera tissue.
Radioactivity extracted.....97% in 1-h of stirring

Study IV: Qualitative test for the presence of [^{14}C]-RH-5287 glucuronides. A 21-day exposure viscera sample (1.933 g) was stirred with buffered water (same conditions as in Study III) for 2-hours. Then, duplicate samples were radioassayed. Each of two equal portions of the extract was diluted to 1000 mL with water and then adjusted to pH 2 with HCl. One sample was boiled for 30-min while the other was kept at room temperature. When the boiled sample had cooled to room temperature, each of the samples was extracted three times with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated to 5 mL. Concentrates and remaining waters were radioassayed.
Radioactivity extracted:

Buffered water	75%
CH_2Cl_2, boiled	57%
CH_2Cl_2, nonboiled	52%

Study V: Determination of polarity classes by separating water-extracted fish residues on C-18 SepPak™ cartridges. For this experiment, a 28-day exposure viscera sample (1.303 g) was extracted three times 125-mL of phosphate buffer (see Study 3) for one hour each time. The filtered extracts were pooled, the volume brought to 357 mL, and radioassayed. One third of the pooled extract was gravity percolated through a cartridge; aliquots of the collected effluent was radioassayed. The effluent was again percolated through a second cartridge and aliquots of its effluent were radioassayed. The cartridge was eluted with 10 mL of methanol (eluate was radioassayed)
Radioactivity retained:

First cartridge	34%
Effluent from first cartridge	56%
Second cartridge	Additional 6.1%
Effluent from second cartridge	42%

Study VI: Separation into ionic characteristics using ion-exchange resins. A 21-day viscera sample (0.7521 g) was extracted with phosphate buffer (see Study III). Half of the extract was percolated through a 10 mL column of a cation exchange resin (Dowex 50, H^+ form); the effluent was percolated through a 10 mL anion exchange resin (Amberlite IRN-78, OH^- form). The "neutral" fraction was radioassayed. The cation exchange column was eluted with 25 mL of 1 N NH_4OH; the anion exchange column with 3 N HCOOH. Effluents were radioassayed.
Radioactivity extracted:

Extraction with buffered water	97%
Cation exhange fraction	28%
Anion exchange fraction	39%
"Neutral" fraction	30%

SUMMARY OF REPORTED RESULTS

Radiolabeled material was more readily extracted with aqueous systems than with dichloromethane, as shown in Studies I, II, and III. The most effective aqueous extractant was pH 7.2 phosphate buffer and then, in order of decreasing effectiveness, 0.05 N NaOH, unbuffered water, and 0.05 N HCl. The results of studies I-III are shown in Tables 1 to 3. That the radiolabeled material was more readily extracted by aqueous systems was taken as an indication that the metabolites were highly polar.

Study IV qualitatively indicated that the metabolites were not RH-5287 glucuronides because the radioactivity in dichloromethane extracts of boiled samples was comparable to those from nonboiled samples (in the presence of glucoronides, the radioactivity should have increased in the boiled samples as a consequence of the hydrolysis of the glucuronides). Results are shown in Table 4.

From the unexplainable losses in ^{14}C-label (Studies II and IV) the author indicated that some of the metabolites may be volatile (or that otherwise the loss in ^{14}C-label was a result of adsorption onto the glassware surface). The author cited a reference on the degradation of isothiazolones to CO_2 through malonamic, malonic, acetic, and formic acids "under certain conditions".

From Study V, it was concluded that the metabolites may be of two separate polarity classes (Table 5). The author concluded from Study VI that some metabolites may be cationic or anionic and that metabolic products of various ionic speciation may form.

No further work directed at purification of these metabolites was performed.

REVIEWER'S COMMENTS

Although the author indicated in the PROJECT STRATEGY AND OBJECTIVES that metabolites were to be isolated and identified, no further steps were taken beyond classification of the possible nature of the metabolites. Therefore, the identity of the metabolites present in viscera tissues is still unclear. No reasons were given for not identifying the metabolites.

Also, the studies were conducted with the viscera tissues only. Therefore, identification of metabolites in edible parts is missing. [^{14}C]-residues in edible parts after 28-days exposure was 0.23 ppm.

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KATHON 287 T

Page _____ is not included in this copy.

Pages 12 through 17 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product 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.

X 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.

INDEPENDENCE MALL WEST PHILADELPHIA PA 19105 U.S.A. TELEPHONE (215) 592-3000
CABLE ADDRESS ROHMHAAS TELEX 845-247 TWX 710-670-5335 TELECOPIER (215) 592-3377

ROHM AND HAAS COMPANY

July 11, 1988

Mr. John Lee
Product Manager (31)
Disinfectants Branch
Registration Division (TS-767C)
U.S. Environmental Protection Agency
401 "M" Street, SW
Washington, DC 20460

Dear Mr. Lee:

Attached is the Rohm and Haas Company's response to EPA's review of our environmental fate package for Anti-foulant C-9211M (EPA File Symbol 707-RTL).

REF:

1) Letter from John H. Lee to John Walker, December 11, 1987. (Attachment I)
2) Meeting of April 11, 1988 between Rohm and Haas Company and EPA.
   Attendees from EPA - Mr. John Lee - Product Manager, Registration Division
   Mr. Valdis Goncorous - Registration Division
   Ms. Sylvia Termes - Chemist, EAB/HED
   Mr. Emil Regelman - Supervisor Chemist, EAB/HED
   Mr. Michael Firestone - EAB/HED
   Mr. Rich Doyle - EAB/HED
   Attendees from Rohm and Haas - D. Streelman, J. Barrett, A. Jacobson, J. Harrington, John Walker, along with John Weeks of Labat-Anderson.

The following ten (10) studies were submitted on October 29, 1986 in support of the use of the active ingredient RH-5287 as a marine antifoulant, and are part of the EPA review in Attachment I.

	Guideline Number	Study
1)	161-2	Determination of Photodegradation of ^{14}C-RH-5287 in Aqueous Solution (TR 310-86-27) (Accession # 265902)
2)	161-2	Determination of Photodegradation of ^{14}C-RH-5287 in Seawater (TR 310-86-29) (Accession # 265903)
3)	162-3	Anaerobic Aquatic Metabolism of ^{14}C-RH-5287 (TR 310-86-28) (Accession # 265904)
4)	162-4	Aerobic Aquatic Metabolism of C-9211/RH-5287 in Seawater (TR 310-86-26) (Accession # 265906)

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	Guideline Number	Study
5)	162-4	Aerobic Aquatic Metabolism of C-9211/RH-5287 in Pond Water (TR 310-86-30) (Accession #)
6)	163-1	Determination of Adsorption/Desorption Constants of C-9211/^{14}C-RH-5287 (TR 310-86-31) (Accession # 265904)
7)	164-2	Environmental Dissipation Modeling of the Marine Antifoulant RH-5287 (TR 310-86-35) (Accession #)
8)	165-4	Time-Independent Flow-Through Toxicity of RH-5287 to Bluegill Sunfish (Lepromis macrochirus) (TR-310-86-34) (Accession # 265911)
9)	165-4	Uptake, Depuration and Bioconcentration of ^{14}C-RH-5287 by Bluegill Sunfish (Lepromis macrochirus) (TR 310-86-33) (Accession # 265912)
10)	165-4	Characterization of RH-5287 in Fish Tissues and Water From a Bioconcentration Study (TR 310-86-32) (Accession # 265913)

The status of each of the above studies is summarized in Attachment II, with an appropriate cross reference to the EPA response of December 11, 1987. We are presently submitting three supplemental studies which address specific deficiencies noted by the Agency. These include:

1)	161-2	Carpenter, M. (1986) Determination of Photodegradation of ^{14}C-RH-5287 in Aqueous Solution: ABC Final Supplementary Report # 321171 (Volume 1)
2)	161-2	Carpenter, M. (1986) Determination of Photodegradation of ^{14}C-RH-5287 in Seawater: ABC Final Supplementary Report # 342321 (Volume 2)
3)	165-4	Leak, T. (1987) Metabolite Characterization of RH-5287 in Bluegill Sunfish (Lepromis macrochirus): A Supplemental Report to ABC Final Report # 32971: (Volume 4)

We are also resubmitting the Environmental Dissipation Modeling of the Marine Antifoulant RH-5287 Study with some additional refinements (TR-310-86-35) (Volume 3). After our meeting with the Exposure Assessment Branch on April 11, 1988, it is our understanding that the Agency has agreed to evaluate this modeling study as a possible alternative to an actual field study on environmental dissipation. We feel that this study contains significant exposure data which can be utilized to assess the environmental risks associated with the use of C-9211M as a marine antifoulant. Recent refinements to the above model (found in Appendix B) assess the extent of dissipation of RH-5287 in a saltwater pond, as well as the size of the pond required to yield detectable levels of RH-5287 in the water. We are formally submitting three copies of the above four (4) studies through the Office of Pesticide Programs.

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In addition, it is our understanding that the following actions were agreed upon at the meeting on April 11, 1988:

1) Photodegradation - in water (161-2)
An aqueous photolysis study will be repeated in aqueous buffer (pH 7, to reduce hydrolysis) and without a sensitizer. Natural sunlight will be used.

2) Aerobic Aquatic Metabolism (162-4)
The aerobic aquatic metabolism of C-9211/RH-5287 in seawater will be repeated. The EPA's recommendation and suggestions will be addressed.

3) Leaching and Adsorption/Desorption (163-1)
A soil sediment adsorption/desorption study will be repeated on the parent material using the batch equilibrium method. Four soils and an aquatic sediment will be utilized. Aqueous buffer (pH 7) will be used along with 0.01 M $CaCl_2$.

The mobility of the aged residue will be analyzed by a column leach experiment. In a preliminary study, the half-life of RH-5287 in spiking soil will be determined. The aged soil will be added to four columns, each containing a discrete Agricultural soil. The leachate and soil will be radioassayed and characterization of ^{14}C-activity determined.

We would appreciate a timely confirmation of the above actions, so that the above studies can be resumed as soon as possible. We have also completed a review of the ASTM protocol regarding leaching, and are currently developing a modified protocol on dynamic leach rates which we would like to discuss with the Agency before proceeding with the study. We will be in contact shortly to set up a mutually agreeable meeting date.

We look forward to an expeditious review of this response.

Sincerely,

Wendy W Bingaman

Wendy W. Bingaman
Regulatory Specialist
Industrial Chemicals North America

WWB:meb
Attachment
(2u/426u)

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Attachment I

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Rohm & Haas Company
Independence Mall West
Philadelphia, PA 19105

Attention: John Walker
Product Integrity Department

Gentlemen:

Subject: Anti-Foulant C-9211 M
EPA File Symbol 707-RTL
Your Submission Dated October 29, 1986

The Agency has completed a review of the Environmetnal Fate data you submitted. The conclusions and recommendations are as follows.

I. CONCLUSIONS

A. Determination of Photodegradation of ^{14}C-RH-5287 in Aqueous Solution Determination of Photodegradation of ^{14}C-RH-5287 in Seawater

These studies are unacceptable as presented. Up to 36 percent of the applied radioactivity could not be accounted for and, therefore, the material balance is incomplete.

In addition, EPA Data Requirements for registering pesticides are not fulfilled because degradates were inadequately characterized by thin-layer chromatography (TLC). In seawater experiments, approximately 73 percent of applied radioactivity in irradiated samples on day 30 were identified as "ring cleavage products" alone without any further attempts to characterize ... these materials. In experiments in deionized water, the species left at the origin (57 to 67% of applied radioactivity after 30 days in sensitized media) was identified as the ring-cleavage product 3,3'-dithiobis-n-octylpropionamide (RH-893-I) by comparison to a standard and by assuming that two immobile compounds were identical. This is not an acceptable procedure. It was also implied that 2-N-(n-octyl)-3-(2H)-isothiazolone (RH-893) and 2-N-(n-octyl)-4-chloro-1-isothiazolin-3-one (RH-085) were identified, but they were not quantified. The identity of major degradates requires confirmation by adequate methodology.

Also, the artificial light source was incompletely characterized and no comparison to natural sunlight was presented.

B. Anaerobic and Aerobic Aquatic Metabolism of ^{14}C-RH-5287

In both of these studies, the purity of the [^{14}C]-RH-5287 was not specified. The total radioactivity of the parent compound accounted for at time 0 was 33.4 percent (aerobic) and 31.4 percent (anaerobic). Degradate identification by TLC was inadequate and incomplete. No attempts to confirm the identity of degradates by adequate methodology other than TLC were made. Therefore, because of the poor recoveries and erratic data, no valid conclusions can be drawn.

1. Anaerobic Aquatic Metabolism of ^{14}C-RH-5287

Even though two-dimensional TLC was used in addition to one-dimensional TLC, degradate identification was not adequate. Two-dimensional TLC data were obtained from extracts that were kept frozen for unspecified periods of time after completing one-dimensional TLC experiments and, unless storage stability data are known, care should be exerted in interpreting two-dimensional TLC results.

2. Aerobic Aquatic Metabolism of ^{14}C-RH-5287 in Seawater

Although degradates were separted by one-dimensional TLC, only R_f values were given without any attempt to identify them. A region labeled as Remainder was not properly identified. After 28 days the total radioactivity recovered by TLC was 21.6 percent at Remainder and 40 percent at the origin.

C. Determination of Adsorption/Desorption of C-9211/^{14}C-RH-5287 (batch equilibrium, unaged soil/sediment)

This study may be acceptable if you can clarify which kind of material was used in the study.

From the title, it appears that the commercial material may have also been used. However, it is not clear if experiments with C-9211 were conducted. The purity of the ^{14}C-RH-5287 was not given, but the lot number and specific activity indicate that it was the same material used in aquatic metabolism studies (purity also not specified).

The calculated Freundich K_{ads} values ranged from 13.7 for the loamy sand soil to 905 for the sandy-clay aquatic sediment. For the first desorption phase, K_{des} for the loamy sand was 31.7 and 49.1 percent for sandy-clay aquatic sediment. The K_{des} values for these soils (second desorption phase) were 31.6 and 200, respectively.

No attempts to characterize degradates were made. It appears that an inadequate solvent system was used for the TLC procedure. In some instances, as high as 81.7 percent of the applied material remained at the origin.

D. Time-Independent Flow-Through Toxicity of RH-5287 to Bluegill Sunfish (Lepomis macrochirus) Uptake, Depuration, and Bioconcentration of ^{14}C-RH-5287 Characterization of RH-5287 in Bluegill Sunfish (Lepomis macrochirus)

These studies are unacceptable as presented. In the studies involving radiolabeled RH-5285, the purity of the test substance was not specified.

Only the parent compound was identified and no attempts to identify and confirm other detected metabolites (by other than TLC) were made. The amounts of radioactive material remaining at the origin were as high as 20 times that identified as the parent compound.

II. RECOMMENDATIONS

A. Determination of Photodegradation of ^{14}C-RH-5287 in Aqueous Solution (161-2) - Determination of Photodegradation of ^{14}C-RH-5287 in Seawater (161-2)

New studies are required. Particular attention should be addressed to the following aspects of the studies.

1. Light Source--Nature of source, intensity, wavelength distribution, and time of exposure as well as a comparison to natural sunlight should be included.

2. Glassware--Because earlier experiments indicated that silanized glass adsorbed less parent compound than unsilanized glass, the former should be used to minimize adsorption.

3. Solubility in Water--Reported as "relatively insoluble in water" the actual value should be included in report. In your letter to Analytical Bio-Chemistry Laboratories, Inc., the solubility in water is given at 2.3 to 14 ppm.

4. Identification of Degradates--Adequate methodology (other than TLC) to identify and confirm major degradates is required.

5. Temperature of dark controls and irradiated samples should be kept within comparable ranges.

6. Recoveries be expressed in terms of applied radioactivity rather than as percents of recovered from TLC plates.

It is recommended that, if possible, the pH and dissolved oxygen content at the time of sampling are recorded and reported. If teflonware is used (Teflon-covered stirring bar, for example) it is recommended that the teflonware also be rinsed with the extracting solvent (hydrophobic material tends to adhere to teflon).

B. Anaerobic Aquatic Metabolism of ^{14}C-RH-5287 (162-3) - Aerobic Aquatic Metabolism of ^{14}C-RH-5287 (162-4)

New studies are required. Particular attention should be addressed to the following aspects of the studies.

1. Purity of radiolabeled material and solubility in water should be specified.

2. Identification and confirmation of major degradates by adequate methodology other than TLC is necessary. Prolonged periods of time between extraction of residues and their identification should be avoided, unless adequate storage stability data are provided.

3. Use (and specify, if used) silanzied glassware to minimize adsorption of parent compound onto the vessels.

4. Analytical data on composition of seawater (pH dissolved oxygen content, metal ions, anions, dissolved solids, etc.) should be included.

5. Data must be reported in consistent units. Parent residues and degradates should be reported as percents of applied radioactivity rather than as percents of recovered from TLC plates.

It is recommended that pH and dissolved oxygen content be monitored throughout the testing period or at least measured, recorded, and reported at each sampling time. Data on pH can be useful in assessing if any hydrolytic reaction has taken place.

C. Determination of Adsorption/Desorption Constants of C-9211/ ^{14}C-RH-5287 (163-1)

Additional information must be submitted to clarify the type of test material used and the radiochemical purity of the labeled compound for reevaluation of the batch equilibrium, unaged soil/sediment studies.

New studies are required using aged soil/sediment to assess the mobility of major degradates formed under anaerobic aquatic conditions. Because the produt is intended for use in marine environments, it is recommended that experiments with seawater/representative soil (sand be included. If seawater is used, analysis of the seawater should be reported. Individual major degradates should be used if adsorption/desorption studies are conducted. Alternatively, an aged column leaching study may be conducted.

It is also recommended that the pH and dissolved oxygen content of the water/soil system is recorded (and reported) at least at each sampling time (including time zero and final time).

D. Time-Independent Flow Through Toxicity of RH-5287 to Bluegill Sunfish (Lepomis macrochirus) (165-4) - Uptake, Depuration, and Bioconcentration of ^{14}C-RH-5287 (165-4) - Characterization of RH-5287 in Bluegill Sunfish (Lepomis macrochirus) (165-4)

New studies are required. Particular attention should be addressed to the following aspects of the studies.

1. The purity of the radiolabeled material must be specified.

2. If silanized glassware was used, this should be specified.

3. Attempts should be made to characterize and confirm the identity of detected degradates by methodology other than TLC. When the percent of unextractable radioactivity is high, the use of another solvent(s) is recommended.

4. If unlabeled reference materials are used in TLC experiments, the report should indicate how they were located in the plate.

5. It is recommended that pH and dissolved oxygen content be measured at regular intervals during the test(s) period.

E. An Aquatic Field Dissipation Study (164-2) is required because at environmentally significant pH's (5 and 7) the half-life of the active ingredient in water is greater than 4 days.

III. NOTE TO YOUR FILES

A. The study "Aerobic Aquatic Metabolism of RH-5287 in Pond Water" was not reviewed because it is not pertinent to current data requirements.

B. The study "Environmental Dissipation Modeling of the Marine Antifoulant RH-5287" was not reviewed because it contains data generated by computer modeling only.

IV. An additional paragraph will be required in the directions for the section of the label to state that this product is "intended for distribution to the largest industrial formulator/painters involved in the painting of large military and commercial ships; it should not be available to private boat owners or small commercial establishments."

Due to deficiencies cited above, do not submit final labels at this time.

This letter does not constitute registration and the product may not be lawfully marketed until it is registered.

Sincerely yours,

John H. Lee
Product Manager (31)
Disinfectants Branch
Registration Division (TS-767C)

ATTACHMENT II

A. Determination of Photodegradation of ^{14}C-RH-5287 in Aqueous Solution (TR 310-86-27) (Accession #265902)

Determination of Photodegradation of ^{14}C-RH-5287 in Seawater (TR 310-86-29) (Accession #265903)

The Agency noted the following deficiencies: (REF: I.A. Conclusions and II.A. Recommendations)

1. The Agency indicated that up to 36% of the applied radioactivity could not be accounted for and therefore, the material balance is incomplete.
2. Degradates were inadequately characterized by thin-layer chromatography (TLC). Adequate methodology (other than TLC) is required to identify and confirm major degradates.
3. The light source was inadequately characterized.
4. The glassware should have been silanized.
5. The solubility of RH-5287 should have been presented in the reports.
6. The temperature of dark controls and irradiated samples should be kept within comparable ranges.
7. The recovery of ^{14}C-activity from TLC plates should be expressed in terms of applied radioactivity rather than as percents of recovered from TLC plates.
8. Measure pH and dissolved oxygen content at every sampling interval.

RESPONSE:

1. Recovery of ^{14}C-activity was in excess of 90% of the day 0 values. Because the photolysis vessels were silanized, the values at day 0 represent the initial amount of ^{14}C-activity in solution.

2. Supplemental studies (which are being submitted simultaneously with this response) were performed to further characterize the ^{14}C-activity that remained at the origin. These include:

   Carpenter, M. (1986) Determination of Photodegradation of ^{14}C-RH-5287 in Aqueous Solution: ABC Final Supplementary Report #321171.

   Carpenter, M. (1986) Determination of Photodegradation of ^{14}C-RH-5287 in Seawater: ABC Final Supplementary Report #342321.

   The ring cleavage products RH-893-I and RH-1680 were identified. Using a multi-elution TLC solvent almost all of the ^{14}C-activity was moved away from the origin. Though some of the ^{14}C-activity did not cochromatograph with any of the standards, all of this activity was more polar than RH-1680 and/or RH-893-I. This strongly suggests that these unknowns are ring cleavage degradates.

3. The absorbance spectrum of the filter (Figure 3) and RS lamp source (Figure 4) were presented (ABC Report 32117 and 34232, Accession #'s 265902 and 265903). The spectrum of natural sunlight appears in Federal Register, Volume 50, Number 188, Friday, September 27, 1985, pg. 39293. The lamp was characterized by a comparison of the intensity versus wavelength. The intensity of the RS lamp is not as high as sunlight, however, like sunlight, intensity generally increases

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with wavelength. With sunlight, one would expect similar chemical reactions but the reaction rate to be greater in sunlight due to increase photon energy impinging on the system.

4. A preliminary experiment showed that a 13% loss in soluble ^{14}C-activity occurred in nonsilanized glassware whereas a 3% loss was observed when silanized glassware was used. For this reason, silanized glassware (Silar) was used in the photolysis study.

5. In our product chemistry submittal for RH-5287, the water solubility was determined to be 14 ppm at 25 C. (Accession #262747).

6. Both the dark and irradiated samples were placed into the same environmental chamber. The chamber was set at 25 C. As a result of trying to obtain intensities approaching sunlight, significant heat is generated by the lamp. Thus, the average temperature in the environmental chamber was 32 C.

7. Though the results from TLC analysis were expressed as percent ^{14}C recovered from the TLC plate, the raw data also contains recoveries as a percent of applied radioactivity. On all TLC plates, the entire spotted channel is scraped and radioassayed. Thus, recoveries expressed as percent recovered essentially equals percent applied. Table 13 from the photolysis study done in aqueous buffer compares the radioactivity recovered from the TLC plate as a percent of the ^{14}C-activity applied. Rohm and Haas asked ABC Laboratories to present the data as percent ^{14}C-activity recovered because of the variability that occurs between applied and recovered. Additionally, if any loss were to occur because of volatilization, it would have been already lost during sample concentration.

8. The pH of the aqueous buffer and seawater was measured at every sample interval. The dissolved oxygen content was measured only on the bulk seawater.

ACTION:

As agreed upon at the April 11th 1988 meeting, an aqueous photolysis study will be run only in aqueous buffer (pH 7, to reduce hydrolysis) and without a sensitizer. Natural sunlight will be used.

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B. Anaerobic Aquatic Metabolism of ^{14}C-RH-5827 (TR 310-86-28) (Accession #265904)

The following deficiencies were noted: (Reference I.B.1. Conclusions and II.B. Recommendations)

1. The radiopurity of ^{14}C RH-5287 and the solubility in water were not specified.
2. Degradate identification by TLC was inadequate and incomplete. Two dimensional TLC data was obtained from extracts that were kept frozen for unspecified periods of time after completing one-dimensional TLC experiments.
3. Use (and specify, if used) silanized glassware during the study.
4. Analytical data on the composition of seawater should be included.
5. Parent residues and degradates should be reported as percents of applied radioactivity rather than as percents of radioactivity recovered from TLC plates.

RESPONSE:

1. The radiopurity of lot 298.04 was 99.67% immediately after synthesis. Additionally, in an aerobic soil metabolism study (initiated on October 22, 1984) and an aerobic aquatic metabolism study in pond water (initiated October 16, 1984) both of which used lot No. 298.04 of ^{14}C-RH-5287, the chromatographic analysis of day 0 samples showed 93.2% and 94.2% of the parent compound, respectively. Thus, we believe the radiopurity at the time of the initiation of the experiment was in excess of 93%.

   In our product chemistry submittal for RH-5287, the water solubility was determined to be 14 ppm at 25 C. (Accession #262747).

2. A number of articles in chromatographic journals have demonstrated that multidimensional TLC provides greater separation power than LC or GC alone. At the 194th ACS meeting, Professor Hartwick (Rutgers University) stated that one of his reasons for spending a great deal of time and money to develop a GC-LC interface was because multidimensional TLC still provided greater separation capacity than LC or GC alone. TLC is an extremely powerful chromatographic tool and the readily available manufactured plates provide reproducibility.

   The stability of the compound when stored frozen is supported by data from the Aerobic Soil Metabolism of RH-5287. A sample of sterile soil was dosed and frozen on October 22, 1984. It remained frozen until May 12, 1986 when it was extracted and analyzed. Two-dimensional TLC showed that 93.2% of the extracted radioactivity were parent compound. Even if the radiopurity was 100% at initiation, less than 7% of the parent compound degraded after approximately 19 months.

3. With hindsight, it would have been proper to silanize the glassware used in this experiment. However, since the experimental period was one year, the effects of adsorption to glassware would be minimized. At the conclusion of the experiment, the glass metabolism vessel was washed with methanol and contained only 2.6% of the recovered ^{14}C-activity.

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4. The dissolved oxygen content, ionic component concentration, etc. were not determined for seawater, only for the sediment used in this study.

5. Although TLC analysis was presented in the tables only as a percent of ^{14}C-activity recovered, analysis as a percent of ^{14}C-activity applied appears in the raw data. On all TLC plates, the entire spotted channel was scraped and radioassayed. Thus, recoveries expressed as percent recovered essentially equals percent applied. The recovery from the TLC plates is presented in Tables 9, 10, 13, and 14. Because of the variability that occurs when percent ^{14}C-activity applied is determined, Rohm and Haas prefers to present data as percent recovered from the TLC plate. It would appear that after extensive manipulation and evaporation/concentration, volatilization would not be a factor.

Aerobic Aquatic Metabolism of C-9211/RH-5287 in Seawater (TR 310-86-26) (Accession #265906)

The above study has the same deficiencies noted in the Anaerobic Aquatic Metabolism study. (Reference I.B.1. Conclusions and II.B. Recommendations)

ACTION:

We agree with the EPA that this study should be repeated. Rohm and Haas is currently initiating a repeat study of the Aerobic Metabolism of RH-5287 in seawater and with aquatic sediment. The EPA's recommendations and suggestions will be addressed.

Aerobic Aquatic Metabolism of C-9211/RH-5287 in Pond Water (TR 310-86-30) (Accession #)

The study was not reviewed by EPA because it was not pertinent to current data requirements.

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C. Determination of Adsorption/Desorption Constants of C-9211/^{14}C-RH-5287
(TR 310-86-31)
(Accession #265904)

The following deficiencies were noted: (REF: I.C. Conclusions and IIC. Recommendations)

1. Clarification of the test material and radiochemical purity of the labeled compound are needed.

2. New studies are required using aged soil/sediment to assess the mobility of major degradates formed under anaerobic aquatic conditions.

ACTION:

A repeat study on the parent material will be performed using the batch equilibrium method. Four soils and an aquatic sediment will be utilized. Aqueous buffer (pH 7) will be used along with 0.01 M $CaCl_2$.

The mobility of aged residue will be analyzed by a column leach experiment. In a preliminary study, the half life of RH-5287 in spiking soil will be determined. The aged soil will be added to four columns, each containing a discrete agricultural soil. The leachate and soil will be radioassayed and the characterization of ^{14}C-activity determined.

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D. Time-Independent Flow-Through Toxicity of RH-5287 to Bluegill Sunfish (Lepromis macrochirus) (TR 310-86-34)
(Accession #265911)

Uptake, Depuration and Bioconcentration of ^{14}C-RH-5287 by Bluegill Sunfish (Lepromis macrochirus) (TR 310-86-33)
(Accession #265912)

Characterization of RH-5287 in Fish Tissues and Water From a Bioconcentration Study (TR 310-86-32)
(Accession #265913)

The following deficiencies were noted: (REF: I.D. Conclusions and II.D. Recommendations)

1. The radiopurity of ^{14}C-RH-5287 was not specified.
2. There was no attempt to identify and confirm other detected metabolites (by other than TLC).
3. The use of silanized glass should be specified.
4. State how ^{12}C reference standards were visualized on TLC plates.
5. Measure pH and dissolved oxygen content periodically during the experiment.

RESPONSE:

1. The radiopurity of lot 298.04 was 99.67% immediately after synthesis. Additionally, in an aerobic soil metabolism study (initiated on October 22, 1984) and an aerobic aquatic metabolism study in pond water (initiated October 16, 1984) both of which used lot no. 298.04 of ^{14}C-RH-5287, the chromatographic analysis of day 0 samples showed 93.2% and 94.2% of the parent compound, respectively. Thus, we believe the radiopurity at the time of initiation of the experiment was in excess of 93%.

2. A supplemental study (Metabolite Characterization of RH-5287 in Bluegill Sunfish (Lepromis macrochirus): A Supplemental Report to ABC Final Report #32971, ABC Final Report #32971-2) is being submitted at this time to further characterize the metabolites. Metabolites were characterized by their inability to interact with glucuronidase, their retention or lack of retention on C-18 packing, their retention (or lack of) on ion exchange packing, and their extractability with different solvents (water, base, acid).

3. The test system was not silanized prior to the initiation of the experiment. However, the test is preceded by a system equilibration period to assure that the desired nomimal exposure level is achieved before fish are exposed. The nominal exposure for this experiment was 1.2 ppb, and this level was obtained following a 24 hour glass equilibrium period. The nominal concentration was maintained throughout the study as demonstrated by the analytical results of the actual test solutions.

4. The TLC plates were over-spotted with cold reference materials and visualized under short UV light (Ref. Accession #265913).

5. Water quality was determined at every sampling. (Table 11, ABC Report No. 32970, Accession Number 265912).

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E. Aquatic Field Dissipation Study (164-2)

The following deficiencies were noted: (Reference II.E. Recommendations and III.B. Note to Files)

1. The Agency feels that an aquatic field dissipation study is required because at environmentally significant pH's (5 and 7) the half-life of the active ingredient in water is greater than 4 days.

2. The Environmental Dissipation Modeling of the Marine Antifoulant RH-5287 study was not reviewed because it contained data generated by computer modeling only.

RESPONSE:

An Aquatic Field Dissipation Study (164-2) was not submitted because of the unavailability of an EPA-accepted protocol for marine antifoulants. In lieu of this, a modeling study, Environmental Dissipation Modeling of the Marine Antifoulant RH-5287, Technical Report No. 310-86-35 is being resubmitted. This model was originally submitted as part of our environmental fate data package, but was not reviewed by the contract reviewers (DYNAMAC) because they perceived that it contained data generated by computer modeling only. After the April 11 meeting between members of EPA's Exposure Assessment Branch and Rohm and Haas, EPA has agreed to review the initial study along with some recent refinements (Appendix B). These refinements assess the extent of dissipation of RH-5287 in a saltwater pond, as well as the size of the pond required to yield detectable levels of RH-5287 in the water. Rohm and Haas wishes to emphasize that the document does not contain theoretical data alone, but also includes significant exposure data needed to assess the environmental risks associated with the use of RH-5287.

(3q/1q)

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