


Shaughnessy No.:068103

Date Out of EAB: JUN 19 1985

To: Henry Jacoby
Product Manager 21
Registration Division (TS-767)

From: Samuel Creeger, Chief 
Review Section #1
Exposure Assessment Branch
Hazard Evaluation Division (TS-769)

Attached, please find the EAB review of...

Reg./File # : 45639-OE
Chemical Name: Methyl Isothiocyanate
Type Product : Fungicide (Wood Preservative)
Product Name : SN-584
Company Name : Nor-AM
Purpose : Hydrolysis study to support use as a wood preservative

| | | | |
|-----------------|----------------|-----------------------|-----------------|
| Action Code(s): | <u>171</u> | EAB #(s) : | <u>5579</u> |
| Date Received: | <u>5/2/85</u> | TAIS Code: | <u>61</u> |
| Date Completed: | <u>6/18/85</u> | Total Reviewing Time: | <u>1.5 days</u> |

Deferrals to: Ecological Effects Branch
 Residue Chemistry Branch
 Toxicology Branch

1. CHEMICAL:

Methyl Isothiocyanate, MITC, SN-584
 $\text{CH}_3 - \text{N} = \text{C} = \text{S}$

2. TEST MATERIAL:

$^{14}\text{CH}_3\text{NCS}$

3. STUDY/ACTION TYPE:

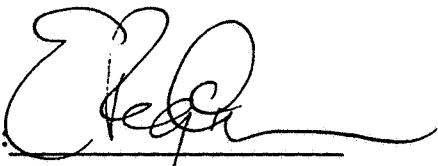
Hydrolysis

4. STUDY IDENTIFICATION:

Repenthin, W. and J. Frkinge. 1985. Determination of the Rate of Hydrolysis of Methylisothiocyanate (MITC) in Buffered Water Solutions at pH Values of 5, 7 and 9 at 25°C. Schering Report W/101 (Company Confidential). Department Allgemeine Physikochemie, Fachbereich Physikochemie und Informatik, Schering AG. February 1, 1985. Accession 257305

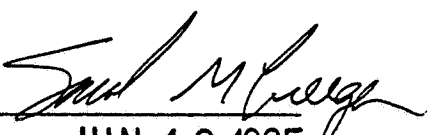
5. REVIEWED BY:

Emil Regelman
Chemist
EAB/HED/OPP

Signature: 
Date: 6/18/85

6. APPROVED BY:

Samuel Creeger
Chief
Review Section #1, EAB/HED/OPP

Signature: 
Date: JUN 19 1985

7. CONCLUSIONS:

This hydrolysis study is not acceptable in support of the hydrolysis data requirement due to numerous cited deficiencies.

8. RECOMMENDATIONS:

The registrant should respond to the deficiencies noted in section 10 of this review.

In addition, an effort must be made to enhance the structure of the text to conform to that of conventional American scientific papers, to include the correct (English) labelling of all tables and figures.

9. BACKGROUND:

A. Introduction

Nor-Am has submitted a study to support the hydrolysis data requirement. The registrant proposes to use the ai methylisothiocyanate as a fungicide (wood preservative) in utility poles.

Previously submitted hydrolysis studies (review of 7/30/84), were found inadequate in support of the hydrolysis data requirement.

B. Directions for Use

No new directions for use were submitted with this action. A copy of the proposed label is appended to the previous review.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES:

A. Study Identification

Repenthin, W. and J. Erking. 1985. Determination of the Rate of Hydrolysis of Methylisothiocyanate (MITC) in Buffered Water Solutions at pH Values of 5, 7 and 9 at 25°C. Schering Report W/101 (Company Confidential). Department Allgemeine Physikochemie, Fachbereich Physikochemie und Informatik, Schering AG. February 1, 1985. Accession No. 257305

B. Materials and Methods

Radio MITC was prepared, and found to be 99.4% pure with a specific activity of 0.261 mCi/mg (method for determination of purity was not specified). A working standard was then prepared by dilution of the radiolabelled MITC with unlabeled MITC (97.5% pure); the resultant specific activity was reported to be approximately 0.5 uCi/mg.

Standard buffer solutions were prepared to identical ionic strengths, at pH's of 5, 7 and 9.

Both water and volumetric-ware were reportedly sterilized prior to use (method unspecified). It was unclear whether other glassware (such as vials) or reagents were likewise sterilized.

The experiment consisted of injecting 250 μ l of a stock MITC solution (in methanol) (concentration 20.35 mg/ml, specific activity 0.474 μ Ci - method of preparation of this solution was not specified) into 100 ml of each buffer solution in unspecified containers, then transferring 1.85 ml aliquots to small vials (number of vials, and number of replicates, if any, not specified). Vials were presumably then sealed. Vials were transferred to a dark, thermostated water bath and maintained at 25°C (range of temperature control was not specified).

At intervals, 100 μ l aliquots were taken from (the same?) vial and injected into an HPLC equipped with a 254 nm UV detector (despite the reported absorption maximum for MITC of 235 nm). Fractions (0.4 ml) were collected, mixed with scintillation cocktail, and directly counted by LSC using the quench curve method.

The authors report that a second detection system was in use during the HPLC runs - a scintogram - although there are no additional details of this in the submitted report.

C. Reported Results

A copy of the reported data (% of parent remaining) are summarized in the appendix ("REGRESSION ANALYSIS OF RESIDUE DECLINE DATA") for each pH. Half-lives at 25°C were calculated by this reviewer to be 156, 496 and 136 hours (6.5, 21, 5.7 days), for pH 5, 7 and 9, respectively.

The only hydrolytic product which formed at pH 5 and 7 was $\text{CH}_3\text{NH}_3\text{OH}$. At pH 9, the additional products $\text{S}=\text{C}(\text{CH}_3\text{NH})_2$ (dimethylthiourea) and CH_3NH_2 also formed. It is unclear from the report what method of identification and quantification was used to confirm these findings. Limited HPLC tracings submitted with this study suggested very limited sensitivity for the reported degradates, and a concomitant high dependency on the "scintogram" results (which could not be confirmed). Likewise, reportedly excellent material balances could not be confirmed.

D. Study Author's Conclusions/Quality Assurance Measures

The limit of the determination, reported on page 21 of the study, was syntactically incoherent, and is therefore unknown and unconfirmed. In addition, the statistical table on that page had German headings and was incomprehensible.

E. Reviewer's Discussion and Interpretation of Study Results

This study was presented in an extremely superficial and grammatically awkward manner, precluding confirmation of the results. In addition to the deficiencies noted previously, neither raw counting data nor sample calculations were included with the report.

Finally, although the reported data at each pH appeared to be highly correlated, the inability to confirm a large number of significant deficiencies makes all reported data suspect.

Therefore, this study cannot be accepted in support of the hydrolysis data requirement.

11. COMPLETION OF ONE-LINER:

No additional data were added to the ongoing one-line data summary.

12. CBI APPENDIX:

There is no CBI appendix.

REGRESSION ANALYSIS OF RESIDUE DECLINE DATA

NAME: E. REGELMAN

DATE: 5/31/85

TITLE: Report Table 1. Hydrolytic decay of MITC

REMARKS: pH 5 data

FILE NAME: MITC RESIDUE LEVELS IN % INTERVALS IN Hours

DATA ENTRIES 1 TO 10

| | | | |
|--------------------|--------------------|---------------------|--------------------|
| 96.9 at .16 Hours | 59.3 at 49.4 Hours | 23.2 at 172.4 Hours | 4.2 at 747.9 Hours |
| 88.3 at 4.2 Hours | 45.7 at 76.2 Hours | 15.2 at 217 Hours | |
| 70.1 at 28.2 Hours | 39.4 at 112 Hours | 5.7 at 337.7 Hours | |

N= 10 SUM X= 1745.16 SUM X²= 771810 SUM Y= 33.9238 SUM Y²= 126.21 SUM X*Y= 3837.41
For the 95% confidence level, the appropriate 't' VALUE=1.8604 (For a one tailed test)

DF=8 CORRELATION COEFFICIENT=.913443 CORRELATION COEFFICIENT SQUARED=.834378
Y-INTERCEPT= 4.17031 RELATIVE % ERROR OF THE SLOPE= 15.8% % LOSS PER Hour= .44%

SLOPE= -.004, its UPPER 95% CL= -.003 and its LOWER 95% CL= -.006
HALF LIFE= 155.5 Hours, its UPPER 95% CL= 220 Hours and its LOWER 95% CL= 120.3 Hours

DAY ZERO LEVEL=64.735%, its UPPER 95% CL=169.724 % and its LOWER 95% CL=24.691 %

REGRESSION ANALYSIS OF RESIDUE DECLINE DATA

NAME: E. REGELMAN

DATE: 5/31/85

TITLE: Report Table 1. Hydrolytic decay of MITC

REMARKS: pH 7 data.

FILE NAME: MITC RESIDUE LEVELS IN % INTERVALS IN Hours

DATA ENTRIES 1 TO 10

| | | | |
|--------------------|---------------------|---------------------|-------------------|
| 94 at .75 Hours | 72.3 at 124.2 Hours | 61.4 at 268.4 Hours | 30 at 792.1 Hours |
| 88.4 at 28.6 Hours | 68.6 at 145.6 Hours | 55.2 at 360.4 Hours | |
| 77.8 at 96.3 Hours | 66.3 at 193.6 Hours | 41.7 at 530.6 Hours | |

10 SUM X= 2540.55 SUM X²= 1.19508E+06 SUM Y= 41.3427 SUM Y²= 172.008 SUM X*Y= 9734.36
For the 95% confidence level, the appropriate 't' VALUE=1.8604 (For a one tailed test)

DF=8 CORRELATION COEFFICIENT=.995156 CORRELATION COEFFICIENT SQUARED=.990335
Y-INTERCEPT= 4.48969 RELATIVE % ERROR OF THE SLOPE= 3.5% % LOSS PER Hour= .14%

SLOPE= -.001, its UPPER 95% CL= -.001 and its LOWER 95% CL= -.001
HALF LIFE= 495.5 Hours, its UPPER 95% CL= 529.9 Hours and its LOWER 95% CL= 465.2 Hours

DAY ZERO LEVEL=89.094 %, its UPPER 95% CL=95.972 % and its LOWER 95% CL=82.709 %

REGRESSION ANALYSIS OF RESIDUE DECLINE DATA

NAME: E. REGELMAN

DATE: 5/31/85

TITLE: Report Table 1. Hydrolytic decay of MITC

REMARKS: pH 9 data

FILE NAME: MITC

RESIDUE LEVELS IN %

INTERVALS IN Hours

DATA ENTRIES 1 TO 10

| | | | |
|--------------------|---------------------|----------------------|---------------------|
| 95.6 at .25 Hours | 36.7 at 124.6 Hours | 24.3 at 194 Hours | 11.7 at 432.5 Hours |
| 75.2 at 25 Hours | 31.7 at 146 Hours | 15.9 at 268.8 Hours | |
| 38.1 at 96.6 Hours | 27.7 at 172.2 Hours | 12.35 at 313.1 Hours | |

N= 10 SUM X= 1773.05 SUM X²= 471428 SUM Y= 33.8311 SUM Y²= 118.868 SUM X*Y= 5199.6
For the 95% confidence level, the appropriate 't' VALUE=1.8604 (For a one tailed test)

DF=8 CORRELATION COEFFICIENT=.959473 CORRELATION COEFFICIENT SQUARED=.920589
Y-INTERCEPT= 4.28492 RELATIVE % ERROR OF THE SLOPE= 10.4% % LOSS PER Hour= .51%

SLOPE= -.005, its UPPER 95% CL= -.004 and its LOWER 95% CL= -.006
HALF LIFE= 136.3 Hours, its UPPER 95% CL= 168.9 Hours and its LOWER 95% CL= 114.2 Hours

DAY ZERO LEVEL=72.596 %, its UPPER 95% CL=113.173 % and its LOWER 95% CL=46.568 %