

Shaughnessy No.: 128857

JUN 11 1988

Date Out of EAB: _____

To: Lois Rossi/Larry Schnaubelt
Product Manager (21)
Registration Division (TS)767C)

From: Frank Davido, Chief *Frank Davido*
Field Studies and Special Projects Section #5
Exposure Assessment Branch
Hazard Evaluation Division (TS)769C)

THRU: Paul F. Schuda, Chief
Exposure Assessment Branch/HEB (TS)769C)

Attached, please find the EAB review of....

Reg./File # : 707-ERL

Chemical Name : Myclobutanil

Type Product : Fungicide

Product Name : Systhane, Rally, RH-3866

Company Name : Rohm and Haas

Purpose : Review Dislodgeable Residue Data on Grapes

Submitted In Support of New Chemical Registration

Action code : 300 Date Received: 2/29/88

Date Completed: 6/1/88 EAB # (s) : 80473

TAIS Code : 42

Monitoring Study Requested: _____ Reviewing Time: 15 days

Monitoring Study Voluntarily: _____

Deferrals to:

_____ Ecological Effects Branch

_____ Residue Chemistry Branch

_____ Toxicology Branch

1. CHEMICAL:

Common/Chemical Name: Myclobutanil

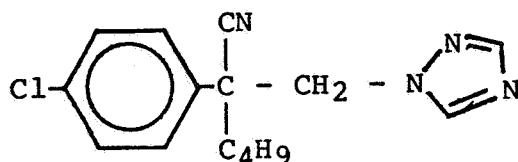
Product Name: alpha-Butyl-alpha-(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile

Other Names: Systhane, Rally, RH-3866

Company: Rohm & Haas Company

Shaughnessy No.: 128857

Structure:



2. TEST MATERIAL:

Dislodgeable residues on grape foliage after the application of Rally (myclobutanil) 60DF, a 60% dry-flowable formulation.

3. STUDY/ACTION TYPE:

Data submitted for foliar dislodgeable residues on grapes in support of registration of myclobutanil.

4. STUDY IDENTIFICATION:

Reg. File Nos.: 707-ERL

Accession Nos.: 404893-02

Record Nos.: 214087

MRID #s: Not Available

"Determination of Dislodgeable Residues of Myclobutanil on Grape Foliage," W. J. Zogorski, III, completed on November 9, 1987 by Rohm and Haas Company, Technical Report No. 31S-87-10.

5. REVIEWED BY:

Linda L. Kutney, Chemist
Monitoring Section 6
EAB/HED/OPP

Linda L. Kutney
Date: 6/1/88

6. APPROVED BY:

James D. Adams, Chemist
Field Studies and Special Projects Section 5
EAB/HED/OPP

James D. Adams
Date: 6/1/1988

7. CONCLUSIONS:

The petitioner used different methods than EAB to estimate whole body dose. The petitioners calculations resulted in much lower exposure estimates. For this reason, we will use our own methods of calculation for whole body dose and allowable exposure limit.

The most sensitive toxicological effect of Myclobutanil (i.e. the effect that occurs at a lower dosage than any other effect) is testicular atrophy, so reentry exposure to male workers was examined. The average whole body dose for a 70 kg male reentering a field just after the last application of myclobutanil at the maximum label rate is about 0.6 mg/kg/day. Using the No Effect Level (NOEL) of 2.5 mg/kg/day and a safety factor of 100, we estimate that 0.025 mg/kg/day is an appropriate Allowable Exposure Limit (AEL) for myclobutanil.

Analysis of the submitted data for males, compensating for the fact that the maximum allowable label rate of application was not used in the testing, we estimate that it will take 33 days for the exposure level for workers entering vineyards treated with Myclobutanil to decline to the allowable exposure limit.

8. RECOMMENDATIONS:

We recommend that the Registration Division require the petitioner to place a reentry interval of 33 days on the labels for the proposed use of Myclobutanil on grapes.

The petitioner may wish to submit evidence that Myclobutanil does not readily absorb through the skin. As an alternative to this, the petitioners may wish to reduce the maximum rate allowed on the label.

9. BACKGROUND:

Introduction:

The data were submitted by Rohm and Haas Co. to support the registration of myclobutanil. The study was submitted to fulfill Guidelines Requirement 132-1 (dislodgeable residue dissipation).

Directions For Use:

Myclobutanil is a fungicide used for the control of powdery mildew and rust disease in perennial grasses grown for seed, turf grass, apples, and grapes. It is applied as a ground or aerial spray at 6 to 12 oz ai/A in the spring or early summer; applications are repeated at 14- to 21-day intervals until two weeks before harvest.

10. DISCUSSION OF INDIVIDUAL TESTS AND STUDIES:

A: MATERIALS AND METHODS

Pesticide Application:

Myclobutanil (Rally, 60% D, Rohm and Haas Co.) was applied using ground equipment (airblast sprayers) to a field plot (5 to 10 acres) in each of three different grape vineyards located in McFarland, CA (Ruby Seedless grapes), Earlimart, CA (Thompson Seedless grapes), and Madera, CA (Ruby Seedless grapes). The pesticide was applied four times, at 0.075-0.1125 lb ai/A, and a fifth time, at 0.125 lb ai/A, at intervals of about 2 weeks during April, May, and June, 1987. Each vineyard plot was treated with a total of 0.5 lb ai/A myclobutanil, the maximum label rate is 0.6 lb ai/A/year.

Analytical Methods:

For all samples except those intended for extractable residue analysis, leaf-disc samples were washed three times (20 minutes each time) on a reciprocating shaker with a detergent solution of 4 drops of Sur-Ten (1:50 dilution) in water. The three washes were combined, stored frozen in dry ice, and shipped to the lab. Samples were spiked in the field with 15 mg of myclobutanil; recoveries ranged from 70 to 106%. Recovery from wash samples spiked in the lab with 5-20 mg myclobutanil ranged from 87 to 114%.

Leaf wash samples were thawed at room temperature, extracted with methylene chloride, and the organic phase filtered through anhydrous sodium sulfate. The methylene chloride extracts were evaporated to dryness, redissolved in acetone:toluene (1:50), and analyzed for myclobutanil dislodgeable residues using GC with thermionic detection.

Unwashed leaf-disc samples were extracted in a blender with methanol, and the macerated sample filtered. The filtrate was mixed with sodium chloride and partitioned with hexane. The aqueous phase was extracted with methylene chloride, and the organic extracts were filtered through anhydrous sodium sulfate, evaporated to dryness, and redissolved in acetone:toluene (1:50). The extracts were cleaned up using Bio-Sil A column chromatography, and the eluant was mixed with methanol:toluene (3:100) and analyzed for myclobutanil residues using GC with electron capture detection.

Foliar Dislodgeable Residues (FDRs):

Three replicate samples of 60 leaf-discs each were collected from nonadjacent rows of grapevines in the center of each vineyard plot, using a leaf punch (2.54 cm in diameter), one day prior to the fifth application, and on days 0 (at 2 and 8 hours post treatment), 1, 3, 5, 7, 14, 21, 28, and 35 after the fifth

application. Leaf-disc samples were kept on ice prior to removal of dislodgeable residues. In addition, three replicate samples of 90 leaf-discs each were collected from the McFarland, CA vineyard test plot at each sampling interval; these samples were immediately frozen in dry ice, and were later shipped to the lab for use in determining the amount of extractable residues of myclobutanil in grape leaves. An additional, untreated plot in each vineyard served as a control.

B: REPORTED RESULTS

Dislodgeable Residues:

The foliar dislodgeable residue data appear to be of very good quality, in general.

A summary of the FDR's reported by Rohm and Haas along with whole body dose rates estimated from FDRs using the EAB exposure data base are included in the table below. Note that averages of dislodgeable foliar residue, based on one side of the leaf, are included in Table 1 below.

Analysis was submitted only for the parent myclobutanil compound, no data were submitted for any of its metabolites. Although the residue of concern in grapes consists of parent and RH-9090 free and conjugated metabolite, only 14% of the residue is expected to be metabolite (Memo by Pamela Hurley, Toxicology Branch, PP#7F3476/FAP#7H5524, 4/5/88, "Response to RCB Request for a List of the Regulable Residues in the Tolerance Expression").

Based on other published data, at least 99% of this whole body dose exposure is expected to be via the dermal route. In his 4/22/88 exposure assessment review of myclobutanil, Curt Lunchick concluded that "the factor that had the greatest influence on reducing the exposure to mixer/loaders was the use of protective gloves." The same conclusion could be made of workers reentering treated fields.

The petitioner claims that a 90% reduction to exposure exists due to a clothing protection factor supported by Popendorf et al., 1982, "Regulating OP Pesticide Residues for Farmworker Protection." When EAB read this article, this reference was not found. Popendorf did say that dermal contact to the hands of citrus workers in California was reduced 90% or more by the use of nylon, knit gloves. EAB agrees that clothing uncontaminated by pesticide residues affords some measure of protection to those parts of the body that are covered. However, that level of protection is expected to be a function of the type of cloth. Use of a reduction factor for clothing further assumes that the clothing is worn and is not itself a source of exposure to the residues; i.e. that the clothing is washed each day. For these reasons, the following tables (using EAB calculations) should be used to estimate the worker exposure rather than the petitioner's exposure estimations.

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TABLE 1:

FOLIAR DISLODGEABLE RESIDUE AND HUMAN REENTRY EXPOSURE LEVELS
Myclobutanil on California Grapes

Days After Last Application	FDRs †		Avg Whole Body Dose,	
	Reported (ng/cm ²)	Average (ng/cm ²)	mg/hour	mg/8-hr day
0	16 38 158	71	0.70	5.6
0 (2 Hours)	316 360 376	351	4.50	36.0
0 (8 Hours)	290 328 346	321	4.00	32.0
1	248 300 334	294	3.50	28.0
3	232 250 310	264	3.20	25.6
5	198 226 134	186	2.20	17.6
7	140 208 88	145	1.55	12.4
14	56 88 66	70	0.68	5.4
21	30 58 26	38	0.34	2.72
28	16 50 22	29	0.25	2.00
35	14 26 14	18	0.14	1.12

† These Foliar Dislodgeable Residues were calculated by EAB from the submitted data but are based on one side of the leaf in order to be useful with EAB's surrogate exposure data base for fieldworkers.

TABLE 2: DERMAL EXPOSURE RATES CALCULATED BY EAB
Myclobutanil on California Grapes

Days After Last Application	Average FDRs ng/cm ²	Average Whole Body Dose	
		mg/8-hr day	mg/kg/day
0 (Previous to last spray)	70	5.6	0.080
0 (2 Hours)	350	36.0	0.514
0 (8 Hours)	322	32.0	0.457
1	294	28.0	0.400
3	264	25.6	0.366
5	186	17.6	0.251
7	146	12.4	0.177
14	70	5.4	0.077
21	38	2.72	0.039
28	30	2.00	0.029
35	18	1.12	0.016

C: STUDY AUTHORS CONCLUSIONS/QUALITY ASSURANCE MEASURES

Control punches were fortified in the field with myclobutanil. Reported recoveries ranged from 90 to 122%. Fortifications were also done in the lab, at the 10 and 20 mg level; recoveries ranged from 101 to 114%. As expected, these recoveries are higher than those performed in the field. Although these fortifications were done at a much higher concentration than that of the samples, the recoveries were acceptable.

No field-fortifications or sample results of any metabolites were submitted. Assuming that the concentration of parent is an adequate estimation of total foliar dislodgeable residues, the recoveries and quality control are acceptable.

D: REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS

EAB expects that nearly 100% of the human reentry exposure for the proposed use of myclobutanil on grapes will be via the dermal route. The submitted data (although not worse case because the maximum 0.6 lb. a.i./A rate was not applied) suggests that at the 0.83 X rate of application (0.5 lb. a.i./A), about 350 ng/cm² FDR could be expected initially. After 3 days, this amount dropped to 264 ng/cm²; after 7 days, less than 186 ng/cm² was available as FDR. By 35 days, only 18 ng/cm² of myclobutanil was available as foliar dislodgeable residue. The dissipation of the foliar residues is not rapid -- it took about 6 days for a decrease of 50% to occur.

In terms of whole body dose to a worker exposed for 8 hours, EAB calculates that an initial dose due to dislodgeable residues of 36 mg/day is expected to decrease to 25.6 mg/day after 3 days, 12.4 mg/day after 7 days and 1.1 mg/day after 35 days.

The petitioner apparently used Popendorf's transfer equation to estimate the following dermal exposure rates:

TABLE 3, Exposure estimated by the petitioner:

Days after application	Whole Body Dose (mg/day)
1	1.221
3	0.997
5	0.782
7	0.625
14	0.287

These results reported by Rohm and Haas are an average of 22% of the EAB estimated value for whole body dose. This is equivalent to almost 80% lower whole body doses rates. The major cause for this difference is the clothing protection factor which was used by the petitioner to reduce the dose to 10% of the amount which would otherwise be predicted. In addition, the petitioner used a two-sided calculation for the area of the leaf, and EAB assumes that the leaf collects residue predominantly on one-side. These and other possible differences in calculation technique lead to large differences in the final whole body dose. EAB does not agree with the conclusion that only 10% of the exposure should be considered due to a clothing protection factor. Additional evidence will be needed to show that such an exposure reduction is appropriate. The Popendorf reference cited earlier in this review does not appear to support the petitioner's conclusion about the 90% clothing protection factor.

A 2.5 mg/kg/day No Observed Effect Level (NOEL) was used by the Toxicology Branch for calculation of the Allowable Daily Intake of myclobutanil. The 2.5 mg/kg/day NOEL could be used to estimate the allowable exposure to foliar dislodgeable residues. Using a safety factor of 100, we estimate an allowable exposure level (AEL) of 0.025 mg/kg/day for myclobutanil. Because the chronic effect is testicular atrophy, we have considered the exposure to a 70 kg male.

The EAB-calculated whole body doses in Table 1 could then be compared with the 0.025 mg/kg/d AEL to estimate exposure. The highest dermal exposure estimated from submitted data was 36 mg/d at 2 hours after the last application of myclobutanil.

This is equivalent to 0.514 mg/kg/day myclobutanil for a 70 kg man reentering a vineyard 2 hours after the last treatment. Compensating for the fact that the maximum 0.6 lb. a.i./acre yearly treatment was not applied, (only 0.5 lb. a.i./acre was applied), up to 0.62 mg/kg/day myclobutanil would be expected as a whole body dose to the same man at 2 hours after application.

It would take an estimated 30 day period following the last dosage of myclobutanil for the whole body dose to decrease to the AEL of 0.025 mg/kg/day. This amount would increase to 33 days compensating for the fact that the maximum dose of 0.6 lb. a.i./acre was not used to generate the submitted data.

11. COMPLETION OF ONE-LINER:

Not Applicable

12. CBI APPENDIX:

Not Applicable

REGISTRATION DIVISION DATA REVIEW RECORD

Confidential Business Information - Does Not Contain National Security Information (E.O. 12065)

44866 Hic

1. CHEMICAL NAME

MYCLOBUTANIL

3/1/88

2. IDENTIFYING NUMBER	3. ACTION CODE	4. ACCESSION NUMBER	TO BE COMPLETED BY PM
<u>707-ERL</u>	<u>111</u>	<u>40489302</u>	5. RECORD NUMBER <u>214087</u>
			6. REFERENCE NUMBER <u>1</u>
			7. DATE RECEIVED (EPA) <u>01/27/88</u>
			8. STATUTORY DUE DATE
			9. PRODUCT MANAGER (PM) <u>ROSSI/SCHNAUBEL</u>
			10. PM TEAM NUMBER <u>21</u>

14. CHECK IF APPLICABLE

☐ Public Health/Quarantine

☐ Minor Use

☐ Substitute Chemical

☐ Part of IPM

☒ Seasonal Concern

☐ Review Requires Less Than 4 Hours

TO BE COMPLETED BY PCB

11. DATE SENT TO HED/TSS

12. PRIORITY NUMBER

13. PROJECTED RETURN DATE

15. INSTRUCTIONS TO REVIEWER

A. HED ☐ Total Assessment - 3(c)(5)
☐ Incremental Risk Assessment - 3(c)(7) and/or E.L. Johnson memo of May 12, 1977.

C. ☐ BFS
D. ☐ TSS/RD
E. ☐ Other

B. SPRD (Send Copy of Form to SPRD PM)
☐ Chemical Undergoing Active RPAR Review
☐ Chemical Undergoing Active Registration Standards Review

F. INSTRUCTIONS

REVIEW DISLODGEABLE RESIDUE

DATA (GRAPES) SUBMITTED IN

SUPPORT OF NEW CHEMICAL

REGISTRATION.

ATTN: JIM ADAMS

16. RELATED ACTIONS

NOTE: DATA PREVIOUSLY FORWARDED TO HED/EAB

17. 3(c)(1)(D)

☐ Use Any or All Available Information ☐ Use Only Attached Data
☐ Use Only the Attached Data for Formulation and Any or All
☐ Available Information on the Technical or Manufacturing Chemical.

18. REVIEWS SENT TO

☐ TB ☐ EEB ☐ EF ☐ PL
☐ RCB ☒ EFB ☐ CH ☐ BFS

19. To	TYPE OF REVIEW	NUMBER OF ACTIONS							
		Registration	Petition	EUP	SLN	Sec. 18	Inert	MNR. USE	Other
HED	TOXICOLOGY								
	ECOLOGICAL EFFECTS								
	RESIDUE CHEMISTRY								
	☒ ENVIRONMENTAL DATA								
RD/TSS	CHEMISTRY								
	EFFICACY								
	PRECAUTIONARY LABELING								
BFS	ECONOMIC ANALYSIS								

20. ☐ Label Submitted with Application Attached

21. ☐ Confidential Statement of Formula

22. ☐ Representative Labels Showing Accepted Uses Attached

23. Date Returned to RD (to be completed by HED)

24. Include an Original and 4 (four) Copies of This Completed Form for Each Branch Checked for Review.