

APPENDIX B

California Department of Food and Agriculture  
Worker Health and Safety Branch

Human Exposure Assessment

Myclobutanil  
(RALLY 40W)

**HS-1847** (HS # added 12/02)  
March 21, 1988

GENERAL CHEMISTRY

Myclobutanil is the common chemical name for alpha-butyl-alpha-(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile, a systemic fungicide to be marketed under the trade name RALLY 40W. The chemical formula is  $C_{15}H_{17}ClN_4$ , with a molecular weight of 288.8 d. Technical myclobutanil is a light yellow solid with a melting point range of 63° to 68°C and a boiling point range of 202° to 208°C. The vapor pressure is  $1.6 \times 10^{-6}$  torr. The material is soluble in common organic solvents (ketones, esters, alcohols, etc.) but insoluble in aliphatic hydrocarbon solvents. Its solubility in water is 142 ppm at 25°C. It is stable up to 300°C. The mode of action for myclobutanil's fungicide activity is the inhibition of ergosterol biosynthesis.

FORMULATIONS

There is currently one proposed registration for myclobutanil in California. It is a wettable powder formulation packaged in water-soluble bags called RALLY 40W. It is 40 percent active ingredient.

PROPOSED USE

The label provided for Rally 40W gives instructions for application to non-specified grape types for prevention and cure of Black Rot and Powdery Mildew. No other commodities are included. Three to five ounces of product per acre (0.075 to 0.125 pounds ai) are recommended, with the higher rate for use with susceptible varieties or high disease pressure. The product is to be applied in no less than 50 gallons of water per acre. Applications may begin at pre-bloom and continue on a 14 to 21 day schedule until a maximum of 1.5 pounds of product have been applied or until reaching 14 days before harvest.

LABEL PRECAUTIONS

The proposed label carries the Toxicity Category II signal word WARNING. Precautionary Statements and Statements of Practical Treatment appear appropriate. As presently listed, protective clothing and equipment required include goggles, mid-forearm to elbow-length chemical resistant gloves, a hat, long-sleeved shirt and long pants when mixing/loading or

applying Rally<sup>R</sup>. The user is advised to wash thoroughly after handling and before eating or smoking. The user is advised to launder contaminated clothing separately in hot water before reuse. The proposed label also gives specific directions concerning reentry; the proposed reentry interval being until spray has dried. Label instructions specifically require written or oral warnings be given to workers who may be expected to be in a treated area. Oral warnings must include the same information that written (posted) warnings would include such as date of treatment, protective equipment requirements and emergency procedures. There are also instructions in the safe handling of water soluble pouches.

#### BEHAVIOR ON SKIN

Studies on technical<sup>(1,2)</sup> and formulated<sup>(3)</sup> myclobutanil found it to be no more than slightly irritating to skin, but moderately<sup>(4,5)</sup> to severely<sup>(6,7)</sup> irritating to eyes. No mortality and only mild toxicity resulted from application of 5000 mg/kg dermally<sup>(8,9,10)</sup>. A subacute dermal toxicity study<sup>(11)</sup> also was done, using doses of 1, 10 and 100 mg/kg. Rats were treated 5 days a week for 4 weeks. No systemic toxicity resulted, only local skin irritation. Delayed hypersensitivity tests were performed for the technical material<sup>(12)</sup> and both liquid<sup>(13)</sup> and dry<sup>(14)</sup> formulations; the technical material was found to be slightly or equivocally allergenic. A dermal absorption study was performed on rats<sup>(15)</sup>. Myclobutanil labeled in the benzene ring with <sup>14</sup>C was dissolved in formulation blank to represent the emulsifiable concentrate, and an emulsion was prepared in water at 1/400 of the concentration to represent tank mix. Four rats were exposed to each of these preparations. Sixty microliters were applied to 4 cm<sup>2</sup> of shaved skin on the back of each rat. The dose site was swabbed after six hours, and the radioactivity in the swabs was counted, but only the range of recoveries in the swabs was reported. Another group of four rats was dosed with labeled myclobutanil intravenously. Excreta were collected for 7 days and assayed for radioactivity by liquid scintillation counting.

This study was interpreted by dividing the percentage of the applied dermal dose recovered from the urine by the percentage of the intravenous dose recovered from the urine and multiplying the quotient by 100. This resulted in the figure of 30% absorption of tank mix in 6 hours, which corresponds to 76% in 24 hours. This procedure is questionable for two reasons. One is that the percentages used to calculate the ratio were percentages of the nominal dose, and recovery in each case was over 100%. The other is that although excretion of the intravenous dose apparently was complete after 7 days, appreciable amounts of labeled material were still being found in the urine of dermally dosed animals on day 7, and most probably would still have been present on day 8. The animals were sacrificed after 7 days, and their carcasses and the skin from the dose site were frozen, but no report of labeled material in skin or carcass is provided.

We conclude that the estimate of dermal absorption is too low, but data are not available to recalculate it. Consequently, we must assume 100% dermal penetration.

## BIOLOGICAL DISPOSITION

Feeding studies of cows<sup>(16,17,18,19)</sup>, hens<sup>(20,21)</sup>, rats<sup>(22,23)</sup> and mice<sup>(24)</sup> indicated rapid and complete absorption of myclobutanil from the gut. Excretion is also rapid, generally biphasic with alpha phase half life of 2 to 5 hours and beta phase half life of 25 hours or more. Excretion is almost entirely in the urine and feces, with less than 1% recovered from eggs or milk. Residues of myclobutanil are concentrated in the liver and excreted in bile, resulting in roughly equal distribution between urine and feces.

Analysis of samples by TLC resulted in the separation of 15 metabolites. Reports of the identity of seven of them have been submitted; all of the identified metabolites are oxidation products of the butyl side chain and/or of the nitrile and conjugates of these products. The 3-hydroxy butyl metabolite has been assigned the code RH-9090; it was found to constitute 23% of the labeled material recovered from the urine of cows fed labeled myclobutanil and 36% of the label recovered from eggs of dosed hens, but only 5 to 6% of the residues in rat urine. The identified metabolites account for about 80% of the recovered residues. The large number of metabolites and varying ratios make biological monitoring difficult to interpret; but since the compound is excreted largely intact, it would seem reasonable to suppose that a procedure could be developed that would convert the various partially oxidized forms to a single identifiable species.

## WORKER EXPOSURE STUDY

There is one worker exposure study available for mixer/loaders and applicators<sup>(25)</sup>. Six exposure trials were conducted, three grape vineyard sites with two trials per location. Airblast application equipment was used, drawn by an open-cab tractor. The application rate was specified as 0.125 lb. ai/acre, with an actual average rate of 0.117 lb. ai/acre (by tank analysis). Application and mixing/loading were done by separate personnel. The material was formulated as a wettable powder (RALLY 40W) contained in 4 oz. water soluble packets. The mixer/loaders job was primarily filling the tank with water and dropping in the required number of packets. From experience with this packaging method as an exposure mitigation procedure, the mixer/loader exposure should be extremely low, if none of the packets rupture prematurely.

Exposure monitoring was done using the following devices/procedures:

- Passive dermal dosimeters (effective area 64 cm<sup>2</sup>)
- Cotton gloves under work-gloves
- Outer glove washing with 1:1 water/isopropanol
- Face swabbing with alcohol solution
- Durham & Wolfe respirator exposure pads
- Urine collection (48 hours)

The workers wore long pants, long-sleeved shirts, hats, butyl rubber gloves and boots (not necessarily rubber). This constituted their protective clothing. The dermal dosimeters were located both above the protective clothing (outside the coveralls) and below all outer clothing (on either bare skin or over underwear). The dosimeters were situated such that

overlap of dosimeters was as minimal as possible. The dosimeters were 4 ply construction: gauze pad + alpha cellulose pad + aluminum foil + filter paper backing sheet. The dosimeters were located on the following body sites:

- On or under hat
- On top of both shoulders
- At nape of neck
- On "V" of chest
- Forearms
- Thighs
- Calves/Lower legs

Light cotton gloves were worn under the rubber work-gloves. The cotton gloves were used to measure potential penetrating exposure through the rubber gloves. Isopropanol: water washes were used to dislodge residue on the rubber glove exterior to estimate bare hand exposure. Face swabbing with the same alcohol solution collected removable residues on the unprotected face. Modified respirators (Durham & Wolfe) had cones fitted over respirator dust pads to estimate maximum potential inhalation exposure.

For biological monitoring, workers were instructed to collect all urines for 48 hours after the end of the workday. Laboratory and field spike recoveries for all media other than urine were greater than 90 percent.

Work tasks were separated and timed. Application took six hours, mixing/loading took two hours. These values were used for calculation of the milligrams of exposure to RALLY per hour of work-task. Table One shows the results calculated for exposure using the the data provided by the registrant. The registrant had also calculated exposure values per work-task but their method is in slight variance from CDFA standard practice. The results from both methods are comparable.

TABLE I: Calculated dermal exposure values (ug/hour) of workers mixing/loading and applying RALLY 40W (myclobutanil) fungicide to grapes.

	CLOTHING	
	w/ gloves-hat-long sleeve	w/o gloves-hat-short sleeve
Mixer/Loader	2.51	13.05
Applicator	1.37	45.35
Mixer/Loader/Applicator	3.88	58.40

CDFA, WH&S, H. Fong, 1988

One mixer/loader had much higher glove wash results than all the other workers. In fact, all of that worker's exterior residue results were the highest recorded for mixer/loaders. However, that worker still had non-detectable levels of residue on the interior dosimeters. Most of the calculated interior dosimeter results for both mixer/loaders and applicators are from non-detectable level (0.0002 ug/cm<sup>2</sup>) extrapolations.

Gloves provided a very high degree of protection to the workers' hands. Even with exterior glove-wash samples ranging from 7.45 to 306 ug, the cotton gloves only had from non-detected to 0.9 ug on them. The butyl rubber gloves provided at minimum an eight fold mitigation factor, with an average mitigation factor of greater than 1,000.

The difference in total dermal protective clothing (gloves, hat and long-sleeves versus none) accounted for a 5-fold decrease in exposure for mixer/loaders, a 33-fold decrease for applicators and a 15-fold decrease for mixer/loader/applicators. The mitigation measures used in this study are not unusual or unreasonable.

Inhalation exposure was very low for all workers. The highest detected inhalation exposure was for an applicator; 1.090 ug total. The average applicator inhalation exposure was 0.3648 ug/day (0.061 ug/hr) and the average mixer/loader inhalation exposure was 0.0677 ug/day (0.034 ug/hr).

Biological monitoring was conducted using urine. Both myclobutanil and its metabolite (identified as RH-9090) were measured. None of the urine samples taken over the 48 hour collection period had any detectable levels of myclobutanil or RH-9090. The limit of detection was 0.01 ppm. The registrant believes this data confirms the passive dosimetry results of low levels of exposure experienced by the workers in this study. However, according to previously cited studies, there are fifteen metabolic products of which RH-9090 is only a minor constituent in rat urine. Furthermore, parent compound (unchanged myclobutanil) is not excreted in large amounts in any of the test animals. The absence of both parent and RH-9090 does not necessarily support the registrants position and further research on metabolic fate of myclobutanil in support of biological monitoring procedures is suggested.

The Lifetime Average Daily Dosage (LADD) was calculated using the previous exposure data.

TABLE II: Lifetime Average Daily Dosage (LADD) for job tasks involved in the use of RALLY 40W (myclobutanil) in grape vineyards.

Job Task	Daily Exposure Absorbed Dose <sup>a</sup> (mg/12 hr)	Daily Dosage <sup>b</sup> (ug/kg/day)	LADD <sup>c</sup> (ug/kg/d)
Applicator (no gloves/hat, short sleeves)	0.36	6.6	0.41
Applicator (gloves, hat, long sleeves)	0.01	0.2	0.01
Mixer/Loader (no gloves/hat, short sleeves)	0.10	1.9	0.12
Mixer/Loader (gloves, hat, long sleeves)	0.02	0.4	0.02
Mixer/Loader/Applicator (no gloves/hat, short sleeves)	0.47	8.5	0.53
Mixer/Loader/Applicator (gloves, hat, long sleeves)	0.03	0.6	0.04

a - dermal absorptions is estimated as 100 percent; therefore, daily exposure and absorbed dose are equal

b - daily dosage is for a 54.8 kg. worker

c - work period is 40 days/year in a 40 year career of a 70 year lifetime

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#### EXPOSURE AT REENTRY

The registrant has submitted a foliar dislodgeable residue degradation study for the evaluation of potential exposure to field workers who reenter treated vineyards for cultural activities (26). Three seedless table grape vineyards near Porterville in the San Joaquin Valley were monitored beginning in mid-June, 1987, at predetermined intervals for a period of 35 days after a fifth and final application of Rally<sup>R</sup> 60 DF. In each case the final application rate was 0.125 pounds of active ingredient per acre for a final total of 0.5 pounds ai to each vineyard for the season. Dilution rates and earlier application rates varied, but the season total was consistent for all three vinyards. Methods used for sample collection were modified from those of Gunther, et al.(27) and Iwata, et al. (28) and the protocol was reviewed prior to the onset of the study and found to closely follow a standardized sampling plan developed by CDFA. WH&S also observed the layout of the sample areas and collection of the presamples. After collection, the leaf samples were chilled on ice until field extraction could occur. The extracts were then frozen on dry ice and shipped. Average recovery of field fortified leaf disk samples was 104 percent.

The registrant has chosen to estimate potential dermal exposure of workers

at reentry using a transfer coefficient of 10000 cm<sup>2</sup>/hour which equals the highest reported transfer coefficient in the literature. This figure was arrived at by doubling the 5000 cm<sup>2</sup>/hour transfer coefficient of Zweig-Popendorf (29) due to the two leaf surfaces involved. By multiplying the transfer coefficient by the quantity of residue present at the expected time of reentry and by the number of hours of expected work per day the estimated exposure is achieved. Table III presents the exposures predicted by the registrant (at 10000 cm<sup>2</sup>/hour) and calculated exposures based on the original Zweig-Popendorf factor (at 5000 cm<sup>2</sup>/hour). At present, there is no known transfer coefficient that applies strictly to grapes, however, estimates range between 5000 and 30,000 cm<sup>2</sup>/hour. Should the transfer factor ultimately be determined experimentally to be 30,000 cm<sup>2</sup>/hour, the Annual Average Daily Dosage would be 5 and 6 ug/kg/day for males and females, respectively, reentering at 24 hours post-application.

Table III - Potential Exposure of Male and Female Fieldworkers at Reentry 2, 24 and 72 Hours Post-Application Calculated using both 5000 and 10000 cm<sup>2</sup> per hour transfer coefficients<sup>1</sup>

REENTRY TIME	Daily Exposure <sup>2</sup> mg/day		Daily Abs. Dosage <sup>3</sup> ug/kg/day		Days/ Season <sup>4</sup>	AADD ug/kg/day <sup>5</sup>		LADD ug/kg/day <sup>6</sup>	
	5000	10000	5000	10000		5000	10000	5000	10000
Male									
2 hours	0.7	1.4	10	20	60	2	3	1.1	1.7
24 hours	0.6	1.2	9	17	60	2	3	1.1	1.7
72 hours	0.5	1.1	7	16	60	1	3	0.6	1.7
Female									
2 hours	0.7	1.4	13	26	60	2	4	1.1	2.3
24 hours	0.6	1.2	11	22	60	2	4	1.1	2.3
72 hours	0.5	1.1	9	21	60	2	3	1.1	1.7

1. The application monitored was the final of 5 serial applications occurring over a 2 month period. The season total of myclobutanil applied to each of the treated vineyards was 0.5 lbs. ai.
2. Calculated daily exposure with 90 percent clothing protection factor
3. Daily exposure/body weight (70 kg male, 54.8 kg female) x 100 percent dermal absorption x 1000
4. Days of exposure per year based on four months fieldwork at 15 days per month during the period when myclobutanil is likely to be present (in this study the applications took place over a two month period; myclobutanil levels were almost non-detectable 35 days past the last application)
5. Annual Average Daily Dosage = daily absorbed dosage x 60 days/ 365 days
6. Lifetime Average Daily Dosage = AADD x 40 working years/ 70 year lifetime

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