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

APR 5 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

SUBJECT: Myclobutanil Avian Reproduction Studies

FROM: Anthony F. Maciorowski, Chief
Ecological Effects Branch
Registration Division (H7507C)

TO: Julie Fairfax, PM Team-21
Fungicide-Herbicide Branch
Registration Division (H7505C)

We are writing this memo as a follow-up to the numerous FAXes, meetings, phone calls, and requests for assistance from Rohm and Haas concerning their chemical myclobutanil. Most recently, Mr. Norm Cook of my staff talked at length with Dr. Kevin Reinert of Rohm and Haas concerning avian reproduction dose levels (copy of conversation attached). It became obvious from the conversation that Rohm and Haas has elected to use test concentrations geared towards EECs and refinement of the NOEL. This decision by Rohm and Haas is contrary to recommendations provided by EEB over the past three years and most recent protocol review (24 March 1993).

We ask that this memo, along with our numerous previous reviews, serve as documentation on this matter. Further, we request that the Registration Division notify Rohm and Haas voicing our concern so there is no future misunderstanding over EEB's position should the study prove inadequate.

Attachment

EEB FILE
128857

April 5, 1993

NOTE TO: EEB File

SUBJECT: Myclobutanil Avian Reproduction Studies: Phone Conversation with Dr. Kevin Reinert of Rohm and Haas

FROM: Norm Cook, EEB
EFED (H7507C)

On April 5, 1993, I returned a call to Dr. Kevin Reinert of Rohm and Haas concerning myclobutanil and the avian reproduction studies. Dr. Reinert requested clarification concerning EEB's recent review of avian reproduction protocols and dose levels (copy attached). Particularly, we discussed the following:

*** Our discussion initially concerned EECs for turf, and Dr. Reinert indicated that Rohm and Haas is repeating turf residue/decline studies as "per the guidelines" for EFGWB. (As the discussion progressed, he stated this is a season-long turf study being done using uncut grass.) He also indicated that for the PRISM model EFGWB had utilized a turf 1/2-life of 9.4 days and he gave me the MRID No. (426988-01).

*** We then discussed the avian reproduction dose levels, and he stated the levels they are using are: 75, 130, 180, and 260 ppm. He indicated that they used their EEC calculations to develop the levels and are trying to refine the NOEL, but may get an LOEL at the 260 ppm level. They made this decision based on available structure activity data for similar compounds (but, apparently, they were looking more at NOELs rather than LOELs).

*** I told Dr. Reinert that EEB's main concern with the dose levels chosen was whether they would capture both a NOEL and a LOEL. Ideally, the study should obtain both levels and would prove to be applicable to all use situations. I told him how we had looked at the mammalian chronic data where dose levels were as high as 1000 ppm in the rat 2-generation study and 10,000 ppm in a 3-month mouse feeding study. Assuming similar sensitivity, birds should be able to tolerate a level of 1250 ppm without a problem.

*** As we discussed the dose levels further, Dr. Reinert indicated that they understood EEB's eco-risk assessment to focus on NOELs rather than LOELs, but with the new paradigm EEB now focused on LOELs. I stated that we utilized both levels, but our "triggers" for concern are

when EECs exceed LOELs. I indicated that I believed this was presented in EEB's 1986 Eco-Risk SEP. Dr. Reinert also stated that he had received other EEB reviews that discussed only NOELs, rather than LOELs, but as our discussion continued, it appeared this might have been due to situations where only NOELs were available in the studies.

*** Our discussion continued on dose levels and EECs and the following major points came out:

1. I stated that EEB preferred avian reproduction studies that produced both a NOEL and LOEL. Although the Subdivision E guidelines don't spell this out, but give registrants an option to run such studies either based on EECs or with levels designed to produce a NOEL and LOEL, I indicated EEB prefers the latter and new guidelines would most likely make it mandatory.

2. Relative to EECs, I asked if Rohm and Haas had other foliar residue data (e.g, that developed for tolerances), and Dr. Reinert presented me with more grass residue values which he said generally run in the 100 -125 ppm range on day zero. I pointed out that EECs are but one component of what determines when avian reproduction studies are required. The components are: EECs, breeding birds are exposed, the pesticide is applied repeatedly, and the pesticide is persistent.

3. Dr. Reinert reiterated that the present study is geared more towards EECs, as they've determined them, and generating a NOEL rather than a LOEL.

4. Dr. Reinert asked if there was anything they could do now to improve the study, and I said that I doubted it now that they were already running the study. I pointed out, though, that if only one level (a NOEL or LOEL) was obtained, then EECs, 1/2-life, persistence, and the results of the new turf study would prove critical in determining the usefulness of the study. Further, EFGWB would have the lead on the fate issues. The worst-case would be that Rohm and Haas would have to repeat the study.

In closing, I indicated I was surprised that they were not trying to do a study that would develop a NOEL and LOEL. He indicated that they had made their decision to take their approach, and we agreed that we would have to wait and see how everything played out.

Attachment

cc: A. Maciorowski, EEB
H. Mansfield, EEB
B. Chambliss, RD
J. Fairfax, RD
A. Abramovitch, EFGWB
B. Conerly-Perks, EFGWB
D. Jones, EFGWB

DP Barcode : D189066
PC Code No : 128857
EEB Out :
MAR 25 1993

To: Susan Lewis
Product Manager 21
Registration Division (H7505C)

From: Anthony F. Maciorowski, Chief
Ecological Effects Branch/EFED (H7507C)

Attached, please find the EEB review of...

Reg./File # : 000707-00215
Chemical Name : Myclobutanil
Type Product : Fungicide
Product Name : Rally 40W
Company Name : Rohm and Haas Company
Purpose : Registrant submission avian reproduction protocols and dose selection information. studies.
Action Code : 352 Date Due : 05/20/93
Reviewer : H. Mansfield Date In : 03/16/93

EEB Guideline/MRID Summary Table: The review in this package contains an evaluation of the following:

GDLN NO	MRID NO	CAT	GDLN NO	MRID NO	CAT	GDLN NO	MRID NO	CAT
71-1(A)			72-2(A)			72-7(A)		
71-1(B)			72-2(B)			72-7(B)		
71-2(A)			72-3(A)			122-1(A)		
71-2(B)			72-3(B)			122-1(B)		
71-3			72-3(C)			122-2		
71-4(A)			72-3(D)			123-1(A)		
71-4(B)			72-3(E)			123-1(B)		
71-5(A)			72-3(F)			123-2		
71-5(B)			72-4(A)			124-1		
72-1(A)			72-4(B)			124-2		
72-1(B)			72-5			141-1		
72-1(C)			72-6			141-2		
72-1(D)						141-5		

Y=Acceptable (Study satisfied Guideline)/Concur
P=Partial (Study partially fulfilled Guideline but additional information is needed
S=Supplemental (Study provided useful information but Guideline was not satisfied)
N=Unacceptable (Study was rejected)/Nonconcur

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

MAR 24 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Myclobutanil-- Evaluation of Dose Levels and Avian Reproduction Study Protocols
DP Barcodes: D189066, D189061, & D189071
ID Nos: 000707 -00251, -00221, -EGE

FROM: Anthony F. Maciorowski, Chief
Ecological Effects Branch
Environmental Fate and Effects Division (H7507C)

TO: Julie Fairfax, PM Team 21
Fungicide\Herbicide Branch
Registration Division (H7505C)

BACKGROUND

Rohm and Haas submitted protocols for two avian reproduction studies, one with the bobwhite quail and the other with the mallard duck, for evaluation by EEB. The company also submitted a rationale for the selection of dosage levels. These studies were submitted to support a turf registration, but the studies were also triggered by many other registration petitions.

DISCUSSION

An avian reproduction study should determine both a LOEL and NOEL. The original avian reproduction studies produced no statistically significant reproductive effects, and indicated only that the NOEL was $\geq$ 60 ppm.

For the new avian reproduction studies, Rohm and Haas selected dose levels of 75, 130, 180, and 260 ppm. The company indicated that they expect that these dose levels will allow for the determination of a NOEL and LOEL. The submitted protocols report dose levels of 75, 125, 175, and 250 ppm. Regardless of whether the values cited in the dose selection document or the values cited in the protocols are used, these values do not approximate the EECs that EEB has calculated.

The methods that Rohm and Haas used to select the dose levels involved many of the same rationales that EEB found nonpersuasive in a rebuttal response dated August 18, 1992.

Although EEB does not concur with Rohm and Haas' line of reasoning in their selection of the dose levels, if a LOEL and NOEL are determined, EEB will have enough information to evaluate the risk that birds may incur from the use of myclobutanil on turf. The risk from other uses may be evaluated as well as turf has the highest application rate of any proposed use. If the current avian reproduction studies do not determine a LOEL, EEB can not complete the risk characterization of myclobutanil.

EEB is concerned that the numbers Rohm and Haas has selected

(1) will not be high enough for the LOEC to be found
(2) are spaced so closely that they may be statistically similar
(3) do not approximate the EEC.
Further, the lowest test level that the company selected for the current avian reproduction study does not overlap the highest test level of the previous study. This leaves no room for error or variation.

EEB offers the following dose selection rationale:

The guidelines require that a minimum of three concentrations be tested. The lowest concentration should be less than the NOEL of the last test (60 ppm) to allow for any errors in testing. The guidelines recommend factors of five for choosing subsequent dose levels. If 50 ppm is selected as the lowest concentration and increments of factors of five are employed, the other two concentrations tested should be 250 and 1250 ppm.

Rohm and Haas selected 4 dose levels for the avian reproduction test. Although this is not required, it is preferred. If the registrant wishes to employ a fourth test level, 50, 250, 800, and 1250 ppm could be used.

It is desirable to test as high as necessary to observe reproductive effects without killing the birds. Often a 4 week range finding test is employed to ascertain that prolonged exposure to a high level of pesticide will not kill the test birds.

CONCLUSIONS

The submitted protocols appear to follow the guidelines. There is, however, a slight variation between the test levels selected in the dose selection document and those in the protocols.

EEB recommends dose levels of 50, 250, 800, and 1250 ppm. A range finding test may be necessary because EEB is not interested in avian mortality, but rather in chronic and reproductive effects.

If you have any questions, please call Heather Mansfield at 305-5064.