FEB 3, 1993

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EEB Out :

To: Dennis Edwards
Product Manager 19
Registration Division (H7505C)

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

Attached, please find the EEB review of...

Reg./File # : 000707-00203
Chemical Name : Dicofol
Type Product : Miticide
Product Name : Kelthane
Company Name : Rohm and Haas
Purpose : Submission of second supplemental report on rainbow trout early life-stage study

Action Code : 406 Date Due : 11/30/92
Reviewer : R. Felthousen Date In : 11/05/92

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)	42468204		123-2		
71-5(B)			72-4(A)	42000601	S	124-1		
72-1(A)			72-4(B)		RWD	124-2		
72-1(B)			72-5		11/15/92	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

ECOLOGICAL EFFECTS BRANCH

Chemical: Dicofol; Kelthane

100.0 Purpose of Submission

The Registrant (Rohm and Haas) has submitted supplemental information (MRID# 424682-02) to a report entitled, "Early Life Stage Toxicity of Dicofol to Rainbow Trout in a Flow-Through System (MRID 42000601). The purpose of the supplement is to provide additional comment to rebut the EEB conclusions made in the original submission of data.

101.0 Background

The study was contracted to KBN for evaluation. KBN found the study to be scientifically sound and to satisfy the guideline requirement for a fish early life-stage test. The MATC of Dicofol for the rainbow trout was found to be >4.4 and <7.9 ug/l a.i. mean measured concentrations (geometric mean MATC = 5.9 ug/l.). The concentrations tested were 1.1, 2.0, 4.4, 7.9, and 17.0 ug/l. Although there were deviations from recommended test procedures, KBN did not find them to be sufficient to invalidate the study and concurred with the reported results presented by the testing facility. The EEB concluded that the study was scientifically sound but did not concur with the NOEC value that was reported.

Statistical analysis indicated that, at test day 70, mean standard larval length was significantly reduced at 1.1, 7.9 and 17.0 ug a.i./l. In addition, analysis of length and weight data showed a statistically significant reduction in length at the 1.1 and 17.0 ug a.i./l levels at test termination. However, the KBN report stated that the effect on length "was not considered biologically significant since the data did not follow a typical dose-response relationship" (i.e., no statistically significant difference in length occurred at the 2.0 or 4.4 ug a.i./l concentrations). KBN concluded that the effect on length at the 1.1 ug a.i./l concentration was "spurious", indicating that it was a result of some unknown testing artifact?

The EEB questions this rationale. First of all, because an effect did not follow a "typical" dose-response relationship (i.e., linear- with effects increasing with increasing dose) does not mean the effect is spurious. The EEB is aware of numerous toxicological studies where, because of a chemical's pharmacodynamic properties or the metabolic/physiological characteristics of the test organism, the results have exhibited U-shaped, double-

humped or negative (i.e., decreasing effect with increasing dosage) dose responses, rather than a linear response. In fact, R. K. Tucker, a former EEB Section Head and noted ecotoxicologist, use to conduct seminars on the different types of response curves that he had encountered during his career as a toxicologist with the USFWS at the Denver Wildlife Research Center. Admittedly, these observations were based upon avian studies, where birds could regurgitate and/or otherwise shunt a xenobiotic from their system. Still, these events are real and do occur.

Secondly, taken to the extreme, given the variation that may be introduced into the testing scheme from any number of different sources or variables (biotic and abiotic) under any given set of conditions at any given time, one could argue that any observed effect may be "spurious" given the artificial nature under which most testing is conducted. Obviously, this approach is not practical or acceptable. Therefore, the presumption must be that, if, treatment effects are found that are statistically different from the control that the data represent real effects on the living organism and are not an artifact of the system, methodology and/or procedure employed to conduct the test (i.e., if the test is conducted according to good laboratory practice and guidelines). Only through repeated testing can it be determined whether or not the results of for any given study are spurious. Such replication has not been done in this case.

101.0 Discussion

The Registrant argues that the statistically significant effect on growth length observed at the lowest concentration tested was "spurious" in that it did not occur at the two next higher (2.0, 4.4 ug ai./L) concentrations tested (It is important to note that the effect was significant at both the 7.9 and 17.0 ug ai./L concentrations). Using this same logic it could also be argued that the data for the 2.0 and 4.4 concentrations may be "spurious" since statistically significant effects (at test day 70) were observed at concentrations both below and above these, concentrations (i.e. 3 of the 5 concentrations were statistically different from control). However, since there is only one data set, it is impossible to scientifically conclude that these data are any more "spurious" than the data for the lowest concentration.

The EEB telephoned Dr. William McAllister, Manager for Aquatic Toxicology at ABC Laboratories to discuss this issue. Dr. McAllister agreed that data analysis shows there was a statistically significant difference in

growth (length) between the 1.1 ug a.i./l concentration and control group but argued that the effect was temporal in that there were no statistical differences observed at the end of the study for this concentration. However, a statistical analysis done by KBN, on the data collected at test termination, demonstrated a significant reduction at 1.1 ug a.i./l and 17.0 ug a.i./l for both length and weight. The EEB telephoned Rosemary Graham Mora, the Associate Scientist with KBN Engineering that completed the DER, to confirm the analysis. Ms. Mora confirmed that the statistically significant differences for the 1.1 ug a.i./l concentration were found at both time intervals.

Rohm and Haas maintains, especially where growth is the measured endpoint, that typical dose-response curves usually occur when conducting aquatic studies. Although there are data to support this viewpoint, the EEB is also aware that there are certain classes of chemical compounds that do not "fit" the typical dose-response scenario. In fact, Dr. Tom Bailey, of EEB, has had experience with such chemicals while conducting aquatic studies on heavy metals and halogenated compounds, at the USFWS aquatic testing laboratory at Lacrosse, Wisconsin. This could explain why a typical dose-response curve was not observed for dicofol, which is a chlorinated hydrocarbon.

102.0 Conclusions

The EEB has reviewed the rebuttal and concludes that the Registrant has failed to provide adequate scientific rationale for changing the NOEC for the study. The EEB believes that the only scientific way to determine whether or not the statistically significant effects, observed at the lowest test concentration, are "spurious" is to replicate the study.

Therefore, the EEB must conclude, for this study, that dicofol caused a statistically significant reduction in larval fish length at 1.1 ug a.i./l . However, because an MATC value for growth cannot be determined (i.e., the lowest dosage resulted in an effect), the study can only be classified as "Supplemental" data.

2/3/93
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