

Not
acceptable

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72-1

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SHAUGHNESSY NO

REVIEW NO.

EEB REVIEW

DATE IN: 09-05-91 OUT: 9/17/91

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SRRD/RD ACTION CODE/TYPE OF REVIEW 406 - Resubmission

MRID #(S) 419857-01

DP TYPE 001 - Submission Related Data Package

PRODUCT MANAGER, NO. D. Edwards (19)

PRODUCT NAME(S) Kelthane

TYPE PRODUCT F R I N H D Miticide

COMPANY NAME Rohm and Haas

SUBMISSION PURPOSE Review rebuttal to EEB review of

INCLUDE USE(S) rainbow trout acute study

COMMON CHEMICAL NAME Dicofol

MRID

41698401

41985701. SUPP.

RW Allen
This should be
blue-ink
dated

ECOLOGICAL EFFECTS BRANCH

Chemical Name: Dicofol (Kelthane Technical Miticide)

100.0 Purpose of Submission

The Registrant (Rohm and Haas) has submitted a rebuttal to an EEB review of a rainbow trout flow-through acute toxicity study (MRID 41695401), submitted to the Agency in November, 1990, to satisfy a Data Call-In Notice issued September 29, 1987.

101.0 Discussion

In a review completed on March 28, 1991, KBN Engineering and Applied Sciences, Inc. concluded that a rainbow trout flow-through acute toxicity study, conducted by Analytical Bio-Chemistry Laboratories, Inc. Columbia, Mo., was not scientifically sound because the measured concentrations at 0 and 96 hours were so greatly different that the actual concentrations the fish were exposed to were unknown. In a follow-up review of this study (See DER conducted by D. Rieder dated 4/10/91) the EEB concurred with KBN's conclusion and classified the study as "invalid" and not repairable to either "Supplemental" or "Core" classification.

On August 15, 1991 the Agency received a submission, prepared by aquatic toxicologists from Rohm and Haas as well as from Analytical Bio-Chemistry Laboratories, rebutting EEB's conclusions. Basically the rebuttal claimed the study was scientifically sound for the following reasons: (1) the variability of the concentrations at 0 and 96 hours is not significant through application of ASTM standards, (2) LC50 values calculated using three sets of measured concentrations fall within the most stringent C.I. (using the highest lower limit and the lowest higher limit); and (3) the LC50 is determined from the slope of the dose-response curve and the one dose level with the greatest variability has little impact on the LC50 since it is on the upper end of the dose-response curve.

In the following discussion the EEB will address each claim made by Registrant:

(1) the variability of the concentrations at 0 and 96 hours is not significant through the application of ASTM standards

In addressing this claim the EEB referred to the 1990 ASTM Standard Guide for Conducting Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians. Specifically, Section 11.9.3.4 (2) states:

"In each treatment the highest measured concentration obtained during the test divided by the lowest should be less than 1.5. The variability of the sampling should be determined before the beginning of the test to determine how many samples should be taken and analyses performed at each sampling point to ensure that the limit of 1.5 is not violated just because of sampling variability."

The Registrant states, for the study in question, that "...four of the five test levels meet this criterion", and the test level that is outside the range only slightly exceeds the criterion. Examination of the raw data show that the ratios for the highest and lowest measured concentrations are: 1.36, 1.23, 1.27, 1.61, and 1.46 (Note: In their rebuttal the Registrant rounded the values to the nearest decimal and reported 1.4, 1.2, 1.3, 1.6 and 1.5, respectively). What is crucial to the analysis is that the test level that violates the standard was one of the two levels where mortality occurred. The EEB believes that this is important because this test level is critical for calculating the LC50 value. Therefore, the EEB must conclude that the 1.5 standard established by ASTM has, in fact, been violated in this study.

- (2) LC50 values calculated using three sets of measured concentration (0 hour, 96 hour and mean measured value) show all values fall within the most stringent 95% C.I. (using the highest lower limit and the lowest upper limit):

LC50 calculations for 0-hour, 96-hour and mean measured and lowest measured concentrations are as follows:

Concentration	Probit LC50 Value (ppb)	95% CI
96-Hour	110	91-143
Mean Measured	124	95-180
0-Hour	137	97-221
Lowest measured	100	77-147

Depending upon the concentration analyzed, the difference between the lowest measured and the other concentrations ranged from 10 to 37%. The EEB agrees that all values fall within the most stringent 95% C.I. (i.e. between 97-143), however, depending on what data set are used, the LC50 value can vary as much as 37%. The EEB notes that the registrant reported the mean measured concentration LC50 value (124) as per ASTM standards. The point is that there is no way of knowing which is the correct

concentration to use for the analysis. For regulatory purposes, the EEB simply cannot accept LC50 data that has so much variation.

(3) the LC50 is determined from the slope of the dose-response curve and the one dose level with the greatest variability has little impact on the LC50 since it is on the upper end of the dose response curve.

In this case the dose level with the greatest variability just happened to be one of two dose levels where mortality occurred. Specifically, only 2 of 20 animals (10 percent mortality) died at this level. Given that the highest level tested only resulted in (65%) mortality, it is not known whether the 10% mortality level is at the "upper" end of the dose response or not. In fact, the data tend to support the argument that this level may be at the lower end of the dose response curve.

In addition to the previous discussion, the EEB analyzed the difference between the nominal concentrations and the 96-hour measured concentrations for each test level. Measured concentrations ranged from 26 to 44 percent of the nominal. ASTM standard Section 11.9.3.4 (3) states:

"If the measured concentration of the test material in any chamber is more than 30% higher or lower than the concentration calculated from the composition of stock solution and the calibration of the metering system, the cause should be identified."

The EEB believes that the submitted study may violate this standard. The EEB mentions this because ABC Labs have conducted other studies where they were able to keep variation within the standard. This seems to suggest that there was some a problem (i.e., diluter or calibration problem, hydrolysis, microbial, etc.) with the conduct of this particular study, the cause of which was not reported.

104.0

Conclusions

The EEB has conducted a review of the Registrant's submission and has specifically addressed each claim made in the rebuttal. The EEB believes that the original Data Evaluation Report, conducted by KBN and further reviewed by EEB, was correct in finding the study not to be scientifically sound and "Invalid".

As such, the data requirement (72-1) for a Freshwater Fish Acute Flow-through Toxicity Test is still required to support reregistration of Dicofol.

Richard W. Felthousen, Wildlife Biologist
EFED/EEB

Allen W. Vaughan 9.16.91
Al Vaughan, Acting Head-Section 2
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8
.9895295

.226556

1

SLOPE = 5.555162
95 PERCENT CONFIDENCE LIMITS = 2.911022 AND 8.199303

LC50 = 110.1062
95 PERCENT CONFIDENCE LIMITS = 91.22656 AND 142.9639

LC10 = 65.04226
95 PERCENT CONFIDENCE LIMITS = 41.7741 AND 80.03446

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS
1	.2787264	108.4506	89.56773 151.0263

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H	GOODNESS OF FIT PROBABILITY
8	.226556	1	.9895295

SLOPE = 5.555162
95 PERCENT CONFIDENCE LIMITS = 2.911022 AND 8.199303

LC50 = 110.1062
5 PERCENT CONFIDENCE LIMITS = 91.22656 AND 142.9639

LC10 = 65.04226
95 PERCENT CONFIDENCE LIMITS = 41.7741 AND 80.03446

DO YOU WISH TO RUN ANOTHER DATA SET?

ENTER Y OR N.

?

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

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1	.2787264	108.4506	89.56773 151.0263

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96 Hour

6

Felthousen Dicofol fish acute

CONC.	NUMBER EXPOSED	NUMBER DEAD	PERCENT DEAD	BINOMIAL PROB. (PERCENT)
160	20	13	65	13.1588
51	20	2	10	2.012253E-02
33	20	0	0	9.536742E-05
19	20	0	0	9.536742E-05
8.100001		20	0	0

9.536742E-05

THE BINOMIAL TEST SHOWS THAT 51 AND +INFINITY CAN BE USED AS STATISTICALLY SOUND CONSERVATIVE 95 PERCENT CONFIDENCE LIMITS, BECAUSE THE ACTUAL CONFIDENCE LEVEL ASSOCIATED WITH THESE LIMITS IS GREATER THAN 95 PERCENT.

AN APPROXIMATE LC50 FOR THIS SET OF DATA IS 120.1952

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS
1	.2787264	120.1952	88.87062 202.7145

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H
5	.1745651	1

GOODNESS OF FIT PROBABILITY
.9029854

Mean Measure

SLOPE = 3.78258
95 PERCENT CONFIDENCE LIMITS = 2.202181 AND 5.36298

LC50 = 124.3496
95 PERCENT CONFIDENCE LIMITS = 95.03869 AND 180.9571

LC10 = 57.39772
95 PERCENT CONFIDENCE LIMITS = 34.57748 AND 76.41394

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS
1	.2787264	120.1952	88.87062 202.7145

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H	GOODNESS OF FIT PROBABILITY
5	.1745651	1	.9029854

SLOPE = 3.78258
95 PERCENT CONFIDENCE LIMITS = 2.202181 AND 5.36298

LC50 = 124.3496
95 PERCENT CONFIDENCE LIMITS = 95.03869 AND 180.9571

Felthousen Dicifol fish acute

CONC.	NUMBER EXPOSED	NUMBER DEAD	PERCENT DEAD	BINOMIAL PROB. (PERCENT)
190	20	13	65	13.1588
39	20	2	10	2.012253E-02
29	20	0	0	9.536742E-05
21	20	0	0	9.536742E-05
9.3	20	0	0	9.536742E-05

THE BINOMIAL TEST SHOWS THAT 39 AND +INFINITY CAN BE USED AS STATISTICALLY SOUND CONSERVATIVE 95 PERCENT CONFIDENCE LIMITS, BECAUSE THE ACTUAL CONFIDENCE LEVEL ASSOCIATED WITH THESE LIMITS IS GREATER THAN 95 PERCENT.

AN APPROXIMATE LC50 FOR THIS SET OF DATA IS 127.8497

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS
1	.2787264	127.8496	84.15778 263.6793

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H
4	.1430332	1
GOODNESS OF FIT PROBABILITY		
.6802258		

O-Hair

SLOPE = 2.952209
95 PERCENT CONFIDENCE LIMITS = 1.835691 AND 4.068726

LC50 = 137.0437
95 PERCENT CONFIDENCE LIMITS = 97.70885 AND 221.0272

LC10 = 50.89471
95 PERCENT CONFIDENCE LIMITS = 29.7043 AND 72.042

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS
1	.2787264	127.8496	84.15778 263.6793

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H	GOODNESS OF FIT PROBABILITY
4	.1430332	1	.6802258

SLOPE = 2.952209
95 PERCENT CONFIDENCE LIMITS = 1.835691 AND 4.068726

C50 = 137.0437
95 PERCENT CONFIDENCE LIMITS = 97.70885 AND 221.0272

LC10 = 50.89471