

D162865
DPBARCODE (RECORD)
128997
SHAUGHNESSY NO

2-6-92
REVIEW NO.

EEB REVIEW

DATE IN: 03/28/91 OUT: 2/6/92

CASE # : 192680 REREG CASE # :
SUBMISSION # : S393378 LIST A, B, C, D
ID # : 003125-GIG

DATE OF SUBMISSION 03/19/91

DATE RECEIVED BY EFED 03/27/91

SRRD/RD REQUESTED COMPLETION DATE 07/24/91

EEB ESTIMATED COMPLETION DATE 02/06/92

SRRD/RD ACTION CODE/TYPE OF REVIEW 101 RESUBMISSION

MRID #(S) 418183-01

DP TYPE 001 SUBMISSION RELATED DATA PACKAGE

PRODUCT MANAGER, NO. SUSAN LEWIS, 21

PRODUCT NAME(S) FOLICUR TECHNICAL

TYPE PRODUCT F R I N H D FUNGICIDE

COMPANY NAME MOBAY CORPORATION

SUBMISSION PURPOSE

INCLUDE USE(S)

COMMON CHEMICAL NAME TEBUCONAZOLE

DP BARCODE: D162865

CASE: 192680
SUBMISSION: S393378

DATA PACKAGE RECORD
BEAN SHEET

DATE: 03/26/91
Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 101 RESUBMISSION
CHEMICAL: 128997 alpha-c2, (4-Chlorophenyl)ethyl-alpha-(1,1-dimethylethyl)-1H
ID#: 003125-GIG Folicur Technical
COMPANY: 003125 MOBAY CORPORATION
PRODUCT MANAGER: 21 SUSAN LEWIS 703-557-1900 ROOM: CM-2 227
PM TEAM REVIEWER: BENJAMIN CHAMBLISS 703-557-7382 ROOM: CM-2 221
RECEIVED DATE: 03/19/91 DUE OUT DATE: 09/25/91

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 162865 EXPEDITE: N DATE SENT: 03/26/91 DATE RET.: / /
DP TYPE: 001 Submission Related Data Package
ADMIN DUE DATE: 07/24/91 CSF: N LABEL: N
ASSIGNED TO DATE IN DATE OUT
DIV : EFED 03/27/91 / /
BRAN: EEB / / / /
SECT: / / / /
REVR : / / / /
CONTR: / / / /

* * * DATA PACKAGE REVIEW INSTRUCTIONS * * *

PLEASE REVIEW THIS AVIAN REPRODUCTION STUDY IN FULFILLMENT
OF GUIDELINE # 71-4: TOXICITY AND REPRODUCTION STUDY IN
MALLARD DUCKS.

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

DP BC	BRANCH/SECTION	DATE OUT	DUE BACK	INS	CSF	LABEL
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

FEB 6 1992

MEMORANDUM

SUBJECT: Review of avian reproduction study for the new chemical Tebuconazole (Folicur Technical).

FROM: Douglas Urban, Acting Branch Chief
Ecological Effects Branch
Environmental Fate and Effects Division (H7507C) *Douglas Urban* 2/4/92

TO: Susan Lewis, PM 21
Fungicide-Herbicide Branch
Registration Division

The registrant, Mobay Corporation, has resubmitted the following avian reproduction study to support the proposed application rates greater than 0.3 lb/A/season:

Flethcer, D.W. and C.A. Pederson (1990). Folicur Technical: Toxicity and Reproduction study in Mallard Ducks, Bio-Life Associates, Ltd., Neillsville, Wisconsin. Submitted by Mobay Corporation, Kansas City, Missouri. MRID No. 418183-01.

This study has been reviewed by EEB and found to be supplemental as complete statistical verification of the data was not possible. The study may be upgraded to core if the individual data cited in Section 14B of the attached DER are submitted and the discrepancies listed in Section 14C are adequately addressed.

Although the above mentioned study is supplemental, the guideline requirement for avian reproduction testing with technical tebuconazole has been fulfilled. In EEB's review, dated 12/24/90, it was determined that a new bobwhite quail reproductive study (MRID No. 41624201) was core and that along with the NOEC of 73.5 ppm in another bobwhite quail study (MRID 40700910), the data requirement for avian reproduction was fulfilled.

If you have any questions concerning this matter, please contact Tracy Perry at 305-6451 or Henry Craven at 305-5320.



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CONCURRENCES							
If you have any questions concerning this matter, please							
SYMBOL	H7507C	H7507C	H7507C				
SURNAME	T. Perry	Cramer	[Signature]				
DATE	2/4/92	2/4/92	2/4/92				



DATA EVALUATION RECORD

1. CHEMICAL: Terbuconazole (Folicur). Shaughnessey No. 128997.
2. TEST MATERIAL: a-[2-(4-Chlorophenyl)ethyl]-a-(1-1-dimethyl-ethyl)-1 H-1,2,4-triazole-1-ethanol; CAS # 107534-96-3; 96.9% purity; white solid with a weak characteristic odor.
3. STUDY TYPE: Avian Reproduction Study.
Species studied: Mallard (Anas platyrhynchos).
4. CITATION: Fletcher, D.W. and C.A. Pedersen (1990). Folicur Technical: Toxicity and Reproduction Study in Mallard Ducks, Bio-life Associates, Ltd., Neillsville, Wisconsin. Submitted by Mobay Corporation, Kansas City, Missouri. MRID NO. 418183-01.
5. REVIEWED BY:
Tracy Perry
Wildlife Biologist
EEB/EFED (H7507C)
Signature: Tracy D. Perry
Date: 5/16/91
6. APPROVED BY:
Henry T. Craven
Head, Section IV
EEB/EFED (H7507C)
Signature: Henry T. Craven
Date: 2/4/92
7. CONCLUSIONS: This study is scientifically sound, but does not fulfill the guidelines for an avian reproduction test with the mallard. Complete statistical verification of the study was not possible due to lack of individual data. The NOEL was found to be 320 ppm a.i. (mean measured concentration) and the LOEL was 611 ppm a.i. (mean measured concentration).
8. RECOMMENDATIONS: Study may be upgraded to core if the data cited in Section 14B are submitted and the discrepancies in this review are adequately addressed.

9. BACKGROUND: Resubmission of data for registration.

10. DISCUSSION OF INDIVIDUAL TESTS: N/A

11. MATERIALS AND METHODS:

A. Test Animals: Birds used in the study were 25 week old mallard ducks (Anas platyrhynchos) who were approaching their first breeding season. All birds originated from Whistling Wings, Inc. in Hanover, Illinois and were phenotypically indistinguishable from wild birds.

B. Dosage: Dietary levels chosen for this study were based upon results from a previous mallard duck reproduction study. Test levels used are as follows: 0 ppm a.i. (vehicle control), 170 ppm a.i. (T-I), 340 ppm a.i. (T-II), 680 ppm a.i. (T-III).

Ducks received their respective test diets for 133 days. Test diets were prepared 24 hours prior to administration and fresh batches were made weekly. Feed was offered at the beginning of each test week and supplemented, as needed, throughout the week. Corn oil and acetone vehicles (< 2 parts of vehicle per 98 parts of feed) were used to incorporate Folicur Technical into the feed (Purina Game Breeder Layena). During test weeks 11-19, the quantity of test diet prepared was increased due to an increased food demand during egg production.

All diets were prepared using an upright Hobart H-600-DT mixer. Folicur Technical was dissolved first in acetone and then the appropriate amount of corn oil was added. This mixture was added to the basal feed and mixed for 10-15 minutes. The vehicle control was prepared using the same method. Pesticide concentrations in the feed were measured during test weeks 1, 5, 10, 15, and 19. Well water was checked for contaminants every three months.

C. Study Design: One hundred and twenty-eight mallards (64 males and 64 females) were randomly distributed into 4 groups as follows:

Group	Dosage Levels (ppm a.i.)	No. of Pens	<u>Birds per Pen</u>	
			Males	Females
V. Control	0	16	1	1
T-I	170	16	1	1
T-II	340	16	1	1
T-III	680	16	1	1

Upon arrival at testing facility, birds were placed on a 77 day quarantine period to determine their suitability for test and to acclimate them to laboratory conditions. During this time, they were fed a test free diet (Purina Duck Grower W/O) and were given well water ad libitum. Pens and pans were rinsed daily. Fluorescent lights provided 8 hours of light per day. Room temperature ranged from 48° F - 76° F with relative humidity between 37% and 100%. Birds were identified using uniquely numbered metal leg bands.

D. Pen Facilities: All birds were housed indoors in 2' x 4' x 2' wire pens maintained over concrete. A thermostatically controlled, heated environment was provided for the birds. The average daily maximum and minimum temperatures were 62° F and 55° F respectively (range 46° F to 78° F). Average daily humidity was 89% (range 60% to 100%). During weeks 1-7 of the test period, incandescent lighting was provided 7 hours a day. At the beginning of week 8, incandescent lighting was increased to 17 hours a day and was maintained throughout the remainder of the study. The lighting intensity reported was between 9 and 20 footcandles at bird's eye level.

E. Adult Observations/Gross Pathology: Adult birds were observed daily for clinical signs of toxicity indicative of test material effect. Gross necropsies were performed on the one bird that died during the study and on 25% of all surviving adults from each group at study termination.

F. Body Weight & Food Consumption: Birds were weighed at initiation, prior to egg laying (test week 7), and at termination of the test period. Food consumption was measured on a biweekly basis by subtracting the estimated food wasted and the remaining feed by the amount of feed offered. This number was then divided by the number of days to get grams/bird/day.

G. Eggs/Eggshell Thickness: " Eggs were collected and candled daily during the production period. The total number of eggs collected, the total number of nondefective eggs, and the total number of defective (broken, cracked, or soft-shelled) eggs were recorded for each group. Eggs collected during test weeks 4 through 9 and during test week 20 (1 day only) were recorded but were not incubated. "

Nondefective eggs were collected after birds had received the test diet for nine consecutive weeks. These eggs were placed in an egg storage room (average daily maximum and minimum temperature of 66° F and 60° F, respectively, and 74% average relative humidity) and were turned once daily during a 7 day

collection period.

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Once a week, eggs were placed in an incubator maintained at 99.4° F to 100° F with a wet bulb reading of 81° F to 88° F. Relative humidity ranged from 44% to 62%. Eggs were turned automatically every 4 hours while in the incubator. On incubation day 23, the eggs were transferred to hatching trays.

This procedure was followed for each of the 10 collection periods. The following data were recorded for each egg collection period:

- a. # hatched
- b. # unhatched
- c. # of infertile eggs
- d. embryo life at 14 and 21 days (based on candling)
- e. examination of unhatched eggs for stage of development

Eggs were collected on the first day of alternate weeks to determine eggshell thickness. Since the week egg collection began was not specified in the methods section, one can only assume that the submitted protocol was followed (weeks 1, 3, 5, 7, etc.). Eggshell thickness was determined by taking 3 measurements at the equatorial circumference.

H. Hatchlings: F₁ generation birds were housed in 45.7-cm x 61-cm x 45.7-cm cages which were located in a separate building from their parents. Ducklings were divided by group and pen number and, whenever possible, ducklings from more than one parental pen within the same treatment group were housed together; wing bands were used in these cases to identify individual birds. Ducklings were observed daily and received untreated diet during the 14-day observation period.

The following data were recorded for each hatch:

- a. weight of ducklings on days 1 and 14
- b. viability of ducklings over a 14-day period
- c. gross necropsies of selected ducklings on day 14

I. Statistical Analyses: Analysis of Variance was used to statistically analyze each of the following parameters:

- Adult body weight (male and female weights separately).
- Food consumption of adult birds.
- Overall eggshell thickness.
- Eggshell thickness from separate intervals of egg laying period.
- Hatchling body weights on days 1 and 14.

Contingency Table Analysis was used to statistically analyze the following set of parameters:

- Viable embryos vs. 1 week eggs (nonviable 1 week embryos).
- Eggs set vs. midterm eggs (nonliving 3 week embryos).
- Eggs set vs. full term eggs.
- Eggs set vs. nonviable embryos.
- Eggs set vs. unhatched eggs.
- Eggs set vs. live 3 week embryos.
- Eggs laid vs. normal eggs (uncracked, unbroken).
- Eggs laid vs. defective eggs.
- Eggs laid vs. eggs set.
- Females tested vs. eggs laid.
- Hatchlings on day 1 vs. hatchlings on day 14.

12. REPORTED RESULTS:

A. Diet Analysis: Mobay Corporation's analyses show that the test material was homogeneously distributed in the diet with a coefficient of variance of less than 10 percent. The mean of the measured dietary concentrations were 157, 320, and 611 ppm a.i. (92, 94, and 90%) for the 170, 340, and 680 nominal concentrations respectively (Table 3, attached).

B. Mortalities: One mortality was recorded during this study. A female in the T-III (680 ppm a.i.) test group died during test week 15 after appearing listless and anorexic the previous day. No clinical signs were noted in any of the survivors during the study.

C. Gross Necropsy: No abnormal pathological findings were found for the adult birds sacrificed. Gross pathological examination of the T-III test bird that died showed petechial hemorrhaging in the skin, a very hard liver, a dark-colored spleen, and an enlarged heart. The study author concluded these observations to be incidental findings.

D. Adult Body Weight and Food Consumption: No statistically significant differences in body weights were recorded at test initiation, prior to egg laying (test week 7), or at termination (Table 1, attached).

No statistically significant differences in food consumption were recorded throughout the investigation (Table 2, attached).

E. Reproductive Results: "Statistically significant increases were noted in the numbers of infertile eggs versus eggs set in the T-III Test group ($P < 0.05$), midterm eggs (embryos not

showing life at the day 14 candling) versus fertile eggs set in the T-II and T-III Test groups ($P < 0.05$), and full term eggs versus fertile eggs set in the T-III Test group ($P < 0.01$). A statistically significant decrease was noted in the number of eggs hatched versus fertile eggs set in the T-III Test group ($P < 0.01$). All of these differences were considered to be treatment-related."

No other statistical differences, with regard to other egg parameters, were noted throughout the study.

F. Offspring Body Weight: Although some statistically significant differences in mean body weights were recorded for certain groups within hatches, these intergroup differences were not considered to be consistent or dose related.

G. Viability: No statistically significant differences were noted.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

" Statistically significant increases were noted in the numbers of infertile eggs in the T-III Test group, midterm eggs in the T-II and T-III Test groups, and full term eggs in the T-III Test group. A statistically significant decrease was noted in the number of eggs hatched in the T-III Test group. These differences were all considered to be treatment-related. "

" The ingestion of Folicur Technical at 340 and 680 ppm a.i. by the parental generation appeared to adversely affect the reproductive success. However, only one death was recorded in the T-III Test group's F₀ generation during the investigation. The no-observed-effect level was determined to be 170 ppm a.i."

A good laboratory practice statement, complying with FIFRA (40 CFR, Part 160), was signed by the study director. A quality assurance statement was included and signed by Bio-Life Associates Ltd.'s Quality Assurance Officer. Audits were conducted on 1/9/90 (test day 1) and 4/3/90 (test week 13). The Quality Assurance Officer visually inspected the birds on 1/9/90, 4/3/90, and 5/21/90 (test week 19). A final data audit was conducted on 8/14/90.

14. REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Test Procedure: Test procedures include the following

discrepancies:

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* Although the study area was supposedly a heated, temperature-controlled environment, the temperature ranged from 46° F to 78° F with relative humidity between 60% and 100%. Guidelines recommend a temperature of 70° F with a 55% relative humidity.

* It was not clear whether cracked eggs were chosen randomly for eggshell thickness determination and whether cracked eggs were included in the selection. If cracked eggs were not included in the selection, this would bias the thickness measurement data. Since the thinness of the shell may result in cracking, excluding cracked eggs from the selection would mean that only eggs with normal or thick shells would be measured.

* The light intensity reported during the study was between 9 and 20 footcandles at bird's eye level. The recommended illumination intensity during the lighting phase of the reproductive study is six footcandles.

* Study birds were on the test diet for 9 weeks only, instead of the recommended 10, before eggs were selected for hatching.

* The relative humidity of the egg storage room was an average of 74% versus the recommended 65%.

* The temperature of the hatcher were maintained at 99.4° F to 100° F with a mean relative humidity ranging from 44% to 62%. The recommended temperature is 102° F with a relative humidity of 70%.

* There was no mention of a ventilation system in the study area, as required by the guidelines.

B. Statistical Analysis: A preliminary statistical analysis was performed using a shortened version of EPA's "SAS" program "Bigbird" followed by Duncan's Multiple Range Test (Table 1A, attached). The only significant difference ($p < 0.05$) between the control and treatment groups was found in the number of hatchlings per hen in the T-III (611 ppm) test group. Based on the mean measured concentration, the NOEL should be 320 ppm a.i. A thorough statistical analysis cannot be performed until the following data are submitted:

1. Individual body weights of adult birds at initiation and termination of the study.

2. Hatchling weights reported as pen means.

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3. 14-day survivor weight reported as pen means.

4. 14-day survivors reported as pen totals.

5. Food Consumption reported as pen totals.

C. Discussion/Results: Bio-Life Associates Ltd. noted statistically significant increases in the number of infertile eggs in the T-III Test group, midterm eggs in the T-II and T-III Test groups, and full term eggs in the T-III Test group. A statistically significant decrease was also noted in the number of eggs hatched in the T-III Test group. A no-effect-level (NOEL) of 170 ppm a.i. (nominal concentration tested) was reported.

EEB's preliminary analysis showed a statistically significant decrease in the number of eggs hatched in the T-III test group only (611 ppm a.i.). The NOEL, in this case, should be 320 ppm a.i. (mean measured concentration).

There were several other discrepancies in the submitted study (other than those outlined in Section 14) which made interpretation of the study difficult:

1. The protocol and amendment section in Appendix C was never referenced in the study report. It is questionable whether the protocol was followed, as there are some discrepancies between the methods cited in the report and those outlined in the protocol and amendment section.

Example: The protocol states that: " During the quarantine and approximately the first five to eight weeks of the study, birds will be maintained in total darkness for 16 hours each day and 8 hours of fluorescent lighting. At approximately test week 6 to 9, incandescent lighting will be turned on for four hours each day. The incandescent lighting will be increased by four hours each week until a maximum of 16 hours has been reached."

However, the methods section of the report states:
" At the beginning of test week 1, incandescent lighting was turned on for seven hours per day. The incandescent lighting was increased to seventeen hours per day at the beginning of test week 8 (2/27/90) and was maintained throughout the remainder of the study. "

2. Other methods were not clearly explained, such as:
" Eggshell thickness determinations began after egg

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production reached 20% in the Vehicle Control group. At that point in time, egg production in the Test groups was as follows: T-I, 12%; T-II, 7%; and T-III, 5%. "

EEB questions what 20% egg production means? In addition, it appears from this data as though a treatment-related decrease in egg production exists. Why was this point not addressed in the report?

3. Two different definitions of "midterm eggs" were given: those embryos which are not showing life at the day 14 candling and the day 21 candling (see text on page 28 and table on page 46).

4. There is a discrepancy concerning data in Table 6 (Reproductive Data by Pen - Mallard Ducks) which is similar to ones cited in previous EEB reviews of Bio-Life Associates, Ltd.'s avian reproduction studies (see Mark Roberts' review of "Maneb Technical: Toxicity and Reproduction Study in Mallard Ducks," February, 1990). Seventy-two eggs of the total laid were not accounted for in the table. One can assume that these are eggs which were collected, but not incubated, during weeks 4 through 9 and during week 20. If this is the case, it should be footnoted in the table.

D. Adequacy of the Study:

(1) Classification: Supplemental.

(2) Rationale: Complete statistical verification was not possible due to lack of raw data.

(3) Repairability: Study may be upgraded to core if the data cited in Section 14 B are submitted and the discrepancies discussed in this review are adequately addressed.

15. COMPLETION OF ONE-LINER: Yes, May 16, 1991.

Table 1A Summary of Statistical Analyses of Various Reproductive Parameters tested with the Mallard.

Parameter	Measured Concentrations of Folicur Technical (ppm)			
	(0)	(157)	(320)	(611)
Total Food Consumption	data not available			
Female Body Weight Change	data not available			
Male Body Weight Change	data not available			
Hatchling Weight	data not available			
14-day Survivor Weight	data not available			
14-day old Survivors/hen	data not available			
Eggshell Thickness	0.385	0.399	0.389	0.398
Eggs laid/hen (EL)	51.0	51.9	45.5	40.6
Eggs cracked/hen (EC)	1.1	1.4	0.8	0.9
Eggs set/hen (ES)	44.7	45.5	39.9	35.9
Viable embryos/hen (VE)	42.1	43.9	38.0	32.8
Live 3-week embryos/hen (LE)	36.2	38.2	31.5	26.5
Number hatchlings/hen (NH)	29.6	30.2	25.6	17.1**
ES/EL [#]	69.2	69.7	69.9	70.4
VE/ES [#]	77.5	80.2	80.1	74.5
LE/VE [#]	69.6	69.7	68.1	64.7
NH/LE [#]	66.2	63.7	66.0	54.1
NH/EL [#]	48.4	49.8	48.4	39.8

** Significantly different from the control value ($p < 0.05$).

[#] Reported as arcsine transformed data.

14

Page _____ is not included in this copy.

Pages 15 through 23 are not included.

The material not included contains the following type of information:

- ☐ Identity of product inert ingredients.
 - ☐ Identity of product impurities.
 - ☐ Description of the product manufacturing process.
 - ☐ Description of quality control procedures.
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 - ☐ Sales or other commercial/financial information.
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