1-9-91

066942
MRID No.

112701
Shaughnessy No.

Data Evaluation Record

# BRODIFACOUM

Avian Single Dose Oral $LD_{50}$

**GUIDELINE NUMBER:** 71-1 (a)

**CITATION:** Ross, D.B. 1978. The acute oral toxicity ($LD_{50}$) of Brodifacoum to the Mallard duck. Submitted by ICI Americas, Inc., Agricultural Products, Wilmington, Delaware 19897. Report No. ICI122WL/78507. Study No. ICI122WL. MRID 66942.

**REASON FOR SUBMISSION:**

FIFRA '88 Reregistration.

| | | | |
|---|---|---|---|
| RESULTS- | Valid _____ | Invalid X | Supplemental _____ |
| GUIDELINE- | Satisfied _____ | Partially Satisfied _____ | Not Satisfied X |

**DISCUSSION:**

The original DER (Turner, 1979) classified this study "Supplemental" because Vitamin K, an antidote for anticoagulants was used as a feed supplement. Later, Turner (1979) reclassified the study as "Core" because it was established that not enough Vitamin K was put into feed to make a difference and that the supplement was a different kind on Vitamin K. The study was then raised to "Core."

Examination of the data reveals that two (perhaps three) tests were run and the data combined in order to give a proper range of concentrations. This procedure is not statistically acceptable. EEB used Stephen's computer program to recalculate the $LD_{50}$ from ICI's data. The $LD_{50}$ was 1.42 mg/kg (CI 0.6 - 141.8 mg/kg).

The dosage column in the tables says, "Dose Volume" and "Mean dose level (mg/kg). A constant dose volume that produces a group mean dose concentration of Brodifacoum leads EEB to infer that the birds were dosed based upon the group's mean weight not their individual body weight. Therefore, each birds received a different dose of toxicant.

The observation period was extended to 5 weeks because of the time if takes anticoagulants to act. The mortality data is present in a table that lists deaths by the week of the study. It can not be determined when during the fourth week the last death occurred. The observation period after the last death should be longer than that for most anticoagulants.

**CONCLUSIONS:**

The study must be reclassified as "Invalid." The requirement must be met, therefore, another study should be submitted.

**REVIEWED BY:**

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Signature: James Goodyear
Date: Jan 7, 1991

**APPROVED BY:**

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Signature: L W T
Date: 1-9-91

VALIDATION SHEET CRF #_____PAGE_____OF_____

| FORMULATION: | | | IA | IB | T | FW | EC | R | | |
|---|---|---|---|---|---|---|---|---|---|---|
| % a.i. | SC # | CHEMICAL NAME | Validator: Larry Turner | | | | | Date: 4/14/79 | | |
| technical | | brodifacoum | Test Type: Avian acute oral $LD_{50}$ mallard duck | | | | | | | |
| | | | Test ID.# ES-C1 | | | | | | | |

CITATION: Ross, David B., Nicholas L. Roberts, and David M. Cameron. 1978. The acute oral toxicity ($LD_{50}$) of PP581 to the mallard duck. 10p. Study conducted by Huntingdon Research Centre. Submitted by ICI Americas, 10182-26; Acc. #234655, report 6I; 8/15/78.

RESULTS: Mallard duck acute oral $LD_{50}$ = 2.0 mg/kg (95% c.i. 0.8-4.8 mg/kg). Mortality was 10% at the two lowest levels of 0.3 and 0.6 mg/kg; 100% mortality occurred at doses of 18.4 mg/kg, except that only 70% mortality occurred at 70.7 mg/kg. Toxic symptoms included weakness, lethargy, lack of coordination, and hemorrhage. Weight loss occurred in some birds dosed at 18.4 mg/kg and up, but did not become apparent until 14 days after treatment. One of ten control birds died, apparently (from symptoms and autopsy) from lead shot poisoning. Most experimental mortalities occurred 7-14 days after treatment.

VALIDATION CATEGORY: Supplemental

CATEGORY RATIONALE: The reported results appear to give an accurate estimation of the $LD_{50}$. However, different birds apparently were tested at different times, and 2 of 10 test groups were reported as being from a different batch of birds. The report identifies the test material as technical, but no % a.i. was given. In addition, it is unclear which birds and which time frames were used in the statistical computation of the $LD_{50}$ value.

CATEGORY REPAIRABILITY: It is possible that this test could be upgraded to core if additional information is received. Specifically, Ecological Effects requires that the exact dates that various groups were dosed be reported, the % a.i. be idenfied, and complete information on the statistical analysis - including log-probit graphs - be furnished. Registrant should also justify why the test should not be considered unacceptable on the basis of a high chi square value indicating heterogeneous data.

ABSTRACT: Young adult mallards were given single oral doses of brodifacoum to determine the $LD_{50}$ values. An initial range-finding study used two birds per concentration at levels from 2-179 mg/kg. For the main study, 6 groups of 10 birds/concentration were tested at mean dose levels of 0 (control), 9.2, 18.4, 35.5, 70.7, and 141.8 mg/kg. Because mortality was higher than expected, four additional groups were tested at mean dose levels of 2.1, 3.4, 0.3, and 0.6 mg/kg. It is unclear if these four groups were tested concurrently, but the report did state that the 0.3 and 0.6 mg/kg groups were from a different batch of birds. Because mortality occurred mostly towards the end of 14 days, observations were continued to a total of 35 days.

Other than as noted above, procedures generally followed the proposed guidelines with respect to housing conditions, food and consumption, weights, necropsies, etc. However, dosing of birds was based on mean dose levels for each group, rather than dosing each individual bird at a precise level according to its individual weight. Also the percent a.i. was not given, although the test material was specified as technical.

Statistical analysis was reported to have followed Litchfield and Wilcoxon, but it is unclear how the different treatment times related to the analysis, ie. which test groups were analyzed. This reviewer, using Finney probit analysis, calculated an $LD_{50}$ of 1.6 mg/kg (1.0-2.7) for the four lowest dose levels that were reported as being tested subsequent to the initial six groups. A second $LD_{50}$ of 2.4 mg/kg (1.2-4.8) was calculated for all ten test groups. However, the chi square value for the latter analysis was 20.035 for 9 degrees of freedom, whereas a maximum value of 16.919 is allowable at the .05 level of probability.

Mallard acute oral $LD_{50}$
Talon tech (brodifacoum)
L. Turner 4/14/79

all doses considered (see validation)

| | |
|---|---|
| 0.3 | |
| 1. | |
| 10. | |
| 0.6 | |
| 1. | |
| 10. | |
| 2.1 | |
| 7. | |
| 10. | |
| 3.4 | |
| 7. | |
| 10. | |
| 9.2 | |
| 6. | |
| 10. | |
| 18.4 | |
| 10. | |
| 10. | |
| 35.5 | |
| 10. | |
| 10. | |
| 70.7 | |
| 7. | |
| 10. | |
| 141.8 | |
| 10. | |
| 10. | |
| 1.078 | M |
| 4.594 | YINT |
| 8.460 | LW M |
| 20.035 | $CHI^2$ |
| 2.378 | LD50 |
| 1.178 | LOCL |
| 4.802 | UPCL |
| 0.154 | LD10 |
| 0.037 | LOCL |
| 0.647 | UPCL |
| 36.737 | LD90 |
| 13.015 | LOCL |
| 103.697 | UPCL |

only "follow-up" doses used (See validation)

| | |
|---|---|
| 0.3 | |
| 1. | |
| 10. | |
| 0.6 | |
| 1. | |
| 10. | |
| 2.1 | |
| 7. | |
| 10. | |
| 3.4 | |
| 7. | |
| 10. | |
| 2.093 | M |
| 4.571 | YINT |
| 3.005 | LW M |
| 1.297 | $CHI^2$ |
| 1.603 | LD50 |
| 0.967 | LOCL |
| 2.657 | UPCL |
| 0.391 | LD10 |
| 0.167 | LOCL |
| 0.916 | UPCL |
| 6.570 | LD90 |
| 2.376 | LOCL |
| 18.172 | UPCL |