Data Evaluation Report on the Acute Oral Toxicity of AE 0172747 Technical to Mallard Duck

PMRA Submission Number {.....} EPA MRID Number 466954-45

Data Requirement:	PMRA Data Code	{.....}
	EPA DP Barcode	D325337
	OECD Data Point	{.....}
	EPA MRID	466954-45
	EPA Guideline	850.2100

Test material: AE 0172747 **Purity:** 97.4% (w:w)
Common name AE 0172747
Chemical name: IUPAC 2-[2-Chloro-4-mesyl-3-((2,2,2-trifluoroethoxy)methyl)benzoyl]cyclohexane-1,3-dione
CAS name 2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]-benzoyl]-1,3-cyclohexanedione
CAS No. 335-104-84-2
Synonyms Bayer AE 0172747

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Date: 7/25/06

Reference/Submission No.: {.....}

Company Code	{.....}	[For PMRA]
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Date Evaluation Completed: dd-mm-yyyy

CITATION: Gallagher, S.P., J. Grimes, and J.B. Beavers. 2002. An Acute Oral Toxicity Study with the Mallard – AE 0172747; Substance, Technical; Product Code: AE 0172747 00 1C97 0001. Unpublished study performed by Wildlife International, Ltd., Easton, MD. Laboratory Project No. 512-120. Study submitted by Aventis CropScience, Frankfurt am Main, Germany. Study initiated February 20, 2002 and completed October 1, 2002.

DISCLAIMER: This document provides guidance for EPA and PMRA reviewers on how to complete a data evaluation record after reviewing a scientific study concerning the acute oral toxicity of a pesticide to avian species. It is not intended to prescribe conditions to any external party for conducting this study nor to establish absolute criteria regarding the assessment of whether the study is scientifically sound and whether the study satisfies any applicable data requirements. Reviewers are expected to review and to determine for each study, on a case-by-case basis, whether it is scientifically sound and provides sufficient information to satisfy applicable data requirements. Studies that fail to meet any of the conditions may be accepted, if appropriate; similarly, studies that meet all of the conditions may be rejected, if appropriate. In sum, the reviewer is to take into account the totality of factors related to the test methodology and results in determining the acceptability of the study.

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EXECUTIVE SUMMARY:

The acute oral toxicity of AE 0172747 Technical to 18-week old mallard duck (*Anas platyrhnchos*) was assessed over 21 days. AE 0172747 Technical was administered to the birds by gavage at nominal levels of 0 (vehicle control), 105, 175, 292, 486, and 810 mg ai/kg bw. The 21-day acute oral LD_{50} was >292 mg ai/kg bw, the dosage at which no more than 20% of the birds were observed to regurgitate following dosing. Based upon regurgitation noted by three birds at the 175 mg ai/kg bw level, the NOAEC was 105 mg ai/kg bw. Due to the significant regurgitation observed in this study, this study is classified as INVALID.

Regurgitation was noted in 0, 30, 20, 50, and 60% of the birds dosed at 105, 175, 292, 486, and 810 mg ai/kg bw, respectively. In addition, treatment-related clinical signs of toxicity (head shaking, frequent swallowing, reduced reaction to external stimuli, lethargy, wing droop, loss of coordination, lower limb weakness, and/or ruffled appearance) were observed to some degree in birds from all treatment levels, increasing in duration and severity with increasing treatment level. An apparent treatment-related effect on body weight gain was observed from days 0 to 3 in females from the 810 mg ai/kg level, and in males from the 486 and 810 mg ai/kg levels. From days 0 to 3, body weight changes in males averaged 52, 52, 46, 30, 18, and 5 g for the control, 105, 175, 292, 486, and 810 mg ai/kg bw levels, respectively. From days 0 to 3, body weight changes in females averaged 39, 47, 28, 65, 40, and -2 g for the control, 105, 175, 292, 486, and 810 mg ai/kg bw levels, respectively.

This toxicity study is classified as scientifically unsound and thus INVALID. This study does not satisfy the guideline requirement for an acute oral toxicity study with mallard duck.

Results Synopsis

Test Organism Size/Age (Mean Weight): Approx. 18 weeks of age; 905-1259 g at test initiation

LD_{50}: >292 mg ai/kg bw 95% C.I.: N/A
Probit slope: N/A 95% C.I.: N/A
NOAEL: 105 mg ai/kg bw
Endpoint(s) Affected: Clinical signs of toxicity, body weight gains
Most sensitive endpoint: Clinical signs of toxicity

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I. MATERIALS AND METHODS

GUIDELINE FOLLOWED: The study protocol was based on procedures outlined in the U.S. EPA Ecological Effects Test Guidelines OPPTS No. 850.2100, and U.S. EPA Pesticide Assessment Guidelines §71-1. Deviations from OPPTS 850.2100 included:

1. The pre-test health of the population (including mortality) was not specified.

2. Significant regurgitation was observed at all but the lowest dosage level.

The significant regurgitation observed make this study INVALID.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

A. MATERIALS:

1. Test Material AE 0172747 Technical

Description: Beige crystalline solid

Lot No./Batch No. : LE 356

Purity: 97.4% (w:w)

Stability of compound under test conditions: Stability experiments were not conducted; however, the doses were administered directly after preparation.

Storage conditions of test chemicals: Ambient conditions

Physicochemical properties of AE 0172747 Technical.

Parameter	Values	Comments
Water solubility at 20EC	Not reported	
Vapor pressure	Not reported	
UV absorption	Not reported	
pKa	Not reported	
Kow	Not reported	

(OECD recommends water solubility, stability in water and light, pKa, Pow, and vapor pressure of test compound)

2. Test Organism:

Species (common and scientific names): Mallard duck (*Anas platyrhynchos*)

Age at study initiation: Approximately 18 weeks old

Weight at study initiation (mean and range): 905-1259 g (combined sexes)

Source: Whistling Wings, Inc., Hanover, IL

(EPA recommends using either bobwhite quail or mallard duck. Birds should be at least 16 weeks old at test initiation and should be uniform in size and weight as well as phenotypically indistinguishable from wild birds).

B. STUDY DESIGN:

1. Experimental Conditions

a. Range-finding study: It was reported that original dosages were established based upon toxicity data provided by the Sponsor. Original proposed test concentrations for the definitive study were 0, 292, 486, 810, 1350, and 2250 mg ai/kg bw; however, based upon the response of the mallard on the day of dosing, the 1350 and 2250 mg ai/kg bw dosages were replaced with dosages of 105 and 175 mg ai/kg bw.

b. Definitive study

Table 1: Experimental Parameters

Parameter	Details	Remarks *Criteria*
Acclimation		A detailed composition of the game bird ration was provided.
Period:	6 weeks	*The recommended acclimation period is a minimum of 15 days. OECD recommends a minimum of 7 days.*
Conditions: (same as test or not)	Same as test	
Feeding:	Laboratory-formulated game bird ration and tap water, *ad libitum*	
Health: (any mortality observed)	Not reported; it was reported that birds exhibiting abnormal behavior or physical injury were not used.	
Pen size and construction materials	75 x 90 cm floor space 45 cm height Cages were constructed from vinyl-coated wire grid.	*Pen size and construction should conform to good husbandry practices and should not create crowding stress.* *OECD recommends that pens be suitable for the captive rearing of that species.*
Test duration	21 days	*Recommended test duration is one day for dosing and at least 14 days observation.*

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Parameter	Details	Remarks *Criteria*
Dose preparation [Indicate method of confirmation of dose]	Dispersed in corn oil	
Mode of dose administration	Gavage	*Gavage or gelatin capsule is recommended*
Dose levels nominal: measured:	0 (vehicle control), 105, 175, 292, 486, and 810 mg ai/kg bw Not verified	*Dose levels should be a minimum of 5 treatment levels unless LD_{50} is demonstrated to be greater than 2000 mg ai/kg*
Solvent/vehicle, if used type: amount/bw:	Corn oil 5 ml/kg bw (approx. 0.5% of bw)	*The test material should be administered without a vehicle if possible. Maximum vehicle should not exceed 0.1 to 1.0% of body weight.*
Number of birds per groups/treatment for negative control: for solvent/vehicle control: for treated:	N/A 10 (5 per sex) 10 (5 per sex)	*Recommended number of birds in a treatment group is 10 and 10 birds for each control and vehicle group.*
No. of feed withholding days before dosing	At least 16 hours	*Food should be withheld for at least 15 hours prior to dosing.*
Test conditions Temperature: Relative humidity: Photoperiod:	21.4 ± 0.7°C 35 ± 12% 8 hours light/16 hours dark	Humidity was lower than recommended (45-70%). Light intensity averaged 292 lux. *The recommended photoperiod is 10 hours of light and 14 hours of dark.*
Reference chemical, if used name: concentrations tested:	None tested	

2. Observations:

Table 2: Observations

Criteria	Details	Remarks *Criteria*
Parameters measured (mortality/individual body weight at test initiation and termination/ mean feed consumption/ others)	Mortality Clinical signs of toxicity Food consumption Body weight Necropsy	*Body weight should be measured at test initiation, on day 14 and at the end of the test if the test is extended beyond 14 days. Mortality should not be more than 10% in controls.* *Feed consumption should be measured as average daily food consumption.*
Indicate if the test material was regurgitated	Yes - 3/5 males from the 175 mg/kg level, 2/5 females from the 292 mg/kg level, 2/5 males and 3/5 females from the 486 mg/kg level, and 4/5 males and 2/5 females from the 810 mg/kg level regurgitated the test substance within 3 hours of dosing.	*Regurgitation is an indication that the dose was rejected. If this problem persists, the test should be repeated.*
Groups on which necropsies were performed	All birds (decedent and surviving) were subject to gross necropsy.	*Gross necropsies should be performed with inspections of the GI tract, liver, kidneys, heart, and spleen.*
Observation intervals	Birds were observed multiple times on day 0, and at least twice daily thereafter except on day 21, when they were observed once prior to study termination. Body weights were measured individually on days 0, 3, 7, 14, and 21. Average food consumption was determined by pen for days 0-3, 4-7, 8-14, and 15-21.	
Were raw data included?	Yes	

II. RESULTS AND DISCUSSION:

A. MORTALITY:

No mortalities were observed at any test level during the 21-day study. However, regurgitation was noted in 0, 30, 20, 50, and 60% of the birds dosed at 105, 175, 292, 486, and 810 mg ai/kg bw, respectively. Therefore, the 21-day LD_{50} was estimated to be >292 mg ai/kg bw, the dosage at which no more than 20% of the birds were observed to regurgitate following dosing, and the NOAEL for mortality was conservatively estimated to be >105 mg ai/kg bw, the only dosage where no regurgitation was observed.

Table 3: Effect of AE 0172747 Technical on Mortality of Mallard Duck.

Treatment (mg ai/kg bw)		No. of Birds	Cumulative Mortality					
			day 1	day 2	day 3	day 4	day 14	day 21
Vehicle control		10	0	0	0	0	0	0
105		10	0	0	0	0	0	0
175		10 [(a)]	0	0	0	0	0	0
292		10 [(b)]	0	0	0	0	0	0
486		10 [(c)]	0	0	0	0	0	0
810		10 [(d)]	0	0	0	0	0	0
NOAEL		>105 mg ai/kg bw						
LD_{50}		>292 mg ai/kg bw						
Reference chemical	mortality	N/A						
	LD_{50}	N/A						
	NOAEL	N/A						

[(a)] 30% regurgitation observed (all male)
[(b)] 20% regurgitation observed (all female)
[(c)] 50% regurgitation observed (2 male, 3 female)
[(d)] 60% regurgitation observed (4 male, 2 female)

B. SUBLETHAL TOXICITY ENDPOINTS:

All control birds appeared normal and healthy during the study. At the 105 mg ai/kg bw level, head shaking and frequent swallowing were observed in 4 birds (three male and 1 female) approximately 1-2 hours following dosing. At the 175 mg ai/kg bw level, aside from regurgitation as previously described, no additional effects were observed during the study. At the 292 mg ai/kg bw level, head shaking and frequent swallowing were observed in two males during the first 2.5 hours of dosing. All birds from the 105, 175, and 292 mg ai/kg bw levels recovered within 3 hours of dosing, and appeared normal and healthy for the remainder of the study. At the 486 mg ai/kg bw level, in addition to regurgitation, three additional female birds exhibited head shaking and/or frequent swallowing during the 3 hours following dosing. All birds appeared to be normal and healthy from 4 hours of dosing through the afternoon of day 3. On the morning of day 4, one male was observed with reduced reaction to external stimuli, wing droop, loss of coordination, and lower limb weakness, and clinical signs of toxicity continued to be displayed by this bird through the end of the study, although the animal appeared to be improving at termination. One female displayed similar signs of toxicity from the morning of

day 5 through the afternoon of day 6, but was normal and healthy throughout the remainder of the test. One male displayed lethargy and slight loss of coordination on the afternoon of day 8, but was normal and healthy throughout the remainder of the test. No other clinical signs were observed at this level. At the 810 mg ai/kg bw level, in addition to regurgitation previously described, head shaking and/or frequent swallowing were observed in six birds (3 per sex) within 1 hour and 45 minutes of dosing. All birds appeared normal by approximately 2 hours of dosing; however, signs of toxicity were observed in all birds from the afternoon of day 3 through the afternoon of day 9. Toxic signs included reduced reaction to external stimuli, ruffled appearance, lethargy, wing droop, loss of coordination, and lower limb weakness. Three birds continued to exhibit signs through the termination of the study, but appeared to be recovering by study termination. All other birds recovered by the morning of day 10, and appeared normal and healthy for the remainder of the study.

Visual inspection of the body weight data indicated a treatment-related reduction in body weight gain compared to the control group from days 0 to 3 in males at the 486 mg ai/kg bw level and males and females at the 810 mg ai/kg bw level. From days 0 to 3, body weight changes in males averaged 52, 52, 46, 30, 18, and 5 g for the control, 105, 175, 292, 486, and 810 mg ai/kg bw levels, respectively. From days 0 to 3, body weight changes in females averaged 39, 47, 28, 65, 40, and -2 g for the control, 105, 175, 292, 486, and 810 mg ai/kg bw levels, respectively. No apparent treatment-related effects on food consumption were observed at any treatment level compared to the controls, and no treatment-related findings were observed at necropsy. Incidental findings including developing gonads in all males from all levels (including controls); multiple yellow plaques in the right thoracic air sac in one male from the 175 mg ai/kg level; a small and/or pale spleen in one male from each of the 486 and 810 mg ai/kg levels; and a small polyp attached to the wall of the large intestines in one male from the 486 mg ai/kg level.

Table 4: Sublethal Effect of AE 0172747 Technical on Mallard Duck.

Mean Body Weight Change, g									
Treatment, (mg ai/kg bw)		**Males**				**Females**			
		Days 0-3	**Days 3-7**	**Days 7-14**	**Days 14-21**	**Days 0-3**	**Days 3-7**	**Days 7-14**	**Days 14-21**
Vehicle control		52	-21	-11	-13	39	-28	2	-40
105		52	-25	-4	-11	47	-7	20	-23
175		46	-32	12	-5	28	-23	-2	-38
292		30	-14	24	-40	65	-15	17	-34
486		18	-37	12	-42	40	-35	6	-34
810		5	-43	12	-11	-2	-48	41	-3
NOAEL		292 mg ai/kg bw				486 mg ai/kg bw			
EC_{50}		Not determined				Not determined			
Reference chemical	effect: NOAEL: LD_{50}:	N/A				N/A			

Mean Feed Consumption, g/bird/day									
Treatment, (mg ai/kg bw)		Males				Females			
		Days 0-3	Days 4-7	Days 8-14	Days 15-21	Days 0-3	Days 4-7	Days 8-14	Days 15-21
Vehicle control		68	71	65	81	60	54	65	62
105		119	85	98	97	113	84	97	86
175		98	84	100	94	89	75	85	83
292		102	90	125	114	109	87	95	88
486		94	66	84	77	136	73	102	87
810		105	62	95	101	88	33	91	99
NOAEL		810 mg ai/kg bw							
EC_{50}		Not determined							
Reference chemical	effect NOEL LD_{50}	N/A							

C. REPORTED STATISTICS:

As no mortalities were observed, the LD_{50} was visually determined to be greater than the level where no more than 20% of birds were observed to regurgitate the dosage. No statistical analyses were applied to separate mean responses among treatment groups for the endpoints of food consumption and body weight.

D. VERIFICATION OF STATISTICAL RESULTS:

Statistical Method: The reviewer statistically analyzed total body weight change for males and females using ANOVA, followed by Dunnett's test via Toxstat statistical software; data satisfied the assumptions of normality and homogeneity of variances. The NOAEL for mortality, food consumption, and clinical effects were determined visually.

LD_{50}: >292 mg ai/kg bw 95% C.I.: N/A
Probit slope: N/A 95% C.I.: N/A
NOAEL: 105 mg ai/kg bw
Endpoint(s) Affected: Clinical signs of toxicity

E. STUDY DEFICIENCIES:

This study may have been scientifically compromised due to the significant (≥20%) regurgitation observed at all except the lowest dosage level.

F. REVIEWER'S COMMENTS:

The reviewer's conclusions agreed with the study authors. The reviewer's analysis of total body weight change did not detect any significant differences for males or females; however, the reviewer agrees with the study author's assessment that body weight change was significantly reduced at various assessment intervals (i.e., days 0-3). Results reported for the mortality, clinical effects, and necropsy data appear useful; however, due to the regurgitation, potential effects on body weight and food consumption are not reliable in this study.

In-life dates were February 22 – March 15, 2002.

A detailed description of the laboratory-formulated avian diet was provided in Appendix III of the report.

G. CONCLUSIONS:

This study is scientifically unsound and is thus INVALID. Regurgitation at all but the lowest dose makes this study invalid. Treatment-related clinical signs of toxicity (regurgitation, head shaking, frequent swallowing, reduced reaction to external stimuli, lethargy, wing droop, loss of coordination, lower limb weakness, and/or ruffled appearance) were observed to some degree in birds for all but the lowest treatment levels. Averse effects were seen to increase in severity and duration in accordance with increasing administered dose. The NOAEL was determined to be 105 mg ai/kg bw based on the occurrence of these incidents. In addition, an apparent treatment-related effect on body weight gain was observed from days 0 to 3 in females from the 810 mg ai/kg level, and in males from the 486 and 810 mg ai/kg levels. No treatment-related mortality or apparent effects on food consumption were observed, and no treatment-related gross pathological findings were observed at necropsy. Study authors assigned the LD_{50} was assigned as the dosage at which no more than 20% of the birds were observed to regurgitate following dosing (>292 mg ai/kg bw).

LD_{50}: >292 mg ai/kg bw 95% C.I.: N/A
Probit slope: N/A 95% C.I.: N/A
NOAEL: 105 mg ai/kg bw
Endpoint(s) Affected: Clinical signs of toxicity, body weight gains
Most sensitive endpoint: Clinical signs of toxicity

III. REFERENCES:

U.S. Environmental Protection Agency. 1996. Series 850 - Ecological Effects Test Guidelines (draft), OPPTS Number 850.2100: Avian Acute Oral Toxicity Test.

U.S. Environmental Protection Agency. 1982. *Pesticide Assessment Guidelines, FIFRA Subdivision E, Hazard Evaluation: Wildlife and Aquatic Organisms,* subsection 71-1. Environmental Protection Agency. Office of Pesticide Programs. Washington, D.C.

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