07/25/2006

Data Evaluation Report on the Acute Oral Toxicity of AE 0172747 Technical to Northern Bobwhite Quail

PMRA Submission Number {.....} EPA MRID Number 466955-01

Data Requirement:	PMRA Data Code	{.....}
	EPA DP Barcode	D325337
	OECD Data Point	{.....}
	EPA MRID	466955-01
	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: 5/9/06

Secondary Reviewer: Teri S. Myers
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Date: {.....}

Secondary Reviewer(s): Jeannette Martinez
{EPA/OECD/PMRA}
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 Northern Bobwhite – AE 0172747; Substance, Technical; Product Code: AE 0172747 00 1C97 0001. Unpublished study performed by Wildlife International, Ltd., Easton, MD. Laboratory Project No. 512-119. 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 34-week old northern bobwhite quail (*Colinus virginianus*) was assessed over 17 days. AE 0172747 Technical was administered to the birds by gavage at nominal levels of 0 (vehicle control), 292, 486, 810, 1350, and 2250 mg ai kg bw. The 17-day acute oral LD_{50} was >2250 mg ai/kg bw. Based upon treatment-related ruffled appearance and lethargy observed in birds from the 810, 1350, and 2250 mg ai/kg bw dose groups, the 17-day NOAEL was 486 mg ai kg bw. According to the US EPA classification, AE 0172747 Technical would be classified as practically non-toxic to northern bobwhite quail on an acute oral basis.

No treatment-related mortality or effects on body weight or food consumption were observed, and no treatment-related gross pathological findings were observed at necropsy. Clinical signs of toxicity (ruffled appearance and/or lethargy), however, were observed in birds from the ≥810 mg ai/kg bw levels.

This toxicity study is classified as scientifically sound, is thus acceptable and does satisfy the guideline requirement for an acute oral toxicity study with northern bobwhite quail.

Results Synopsis

Test Organism Size/Age (Mean Weight): 34 weeks of age; 181-225 g at test initiation

LD_{50}: >2250 mg ai/kg bw 95% C.I.: N.A
Probit slope: N.A 95% C.I.: N.A
NOAEL: 486 mg ai/kg bw
Endpoint(s) Affected: 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:

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

This deviation does not affect the scientific soundness of the study.

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 20°C	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): Northern bobwhite quail (*Colinus virginianus*)

Age at study initiation: Approximately 34 weeks old

Weight at study initiation (mean and range): 181-225 g (combined sexes)

Source: Waverly Game Birds on Chester, Centreville, MD

(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 dosages were established based upon toxicity data provided by the Sponsor and the results of a range-finding test which indicated relatively low toxicity at a dosage of 1000 mg/kg (no further details provided).

b. Definitive study

Table 1: Experimental Parameters

Parameter	Details	Remarks *Criteria*
Acclimation Period: Conditions: (same as test or not) Feeding: Health: (any mortality observed)	 Approximately 20 weeks Same as test Laboratory-formulated game bird ration and tap water, *ad libitum* Not reported; it was reported that birds exhibiting abnormal behavior or physical injury were not used.	Starting 2 days after arrival in the laboratory (at 14 weeks of age), the birds were given water soluble antibiotics in their drinking water for 7 days. A detailed composition of the game bird ration was provided. *The recommended acclimation period is a minimum of 15 days. OECD recommends a minimum of 7 days.*
Pen size and construction materials	78 x 51 cm floor space 20 to 25 cm height (sloping) Floors, ceilings, and external walls were constructed of wire mesh and side walls were constructed from galvanized sheeting.	 *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	17 days	*Recommended test duration is one day for dosing and at least 14 days observation.*
Dose preparation [Indicate method of confirmation of dose]	Dispersed in corn oil	

Parameter	Details	Remarks *Criteria*
Mode of dose administration	Gavage	*Gavage or gelatin capsule is recommended*
Dose levels nominal: measured:	0 (vehicle control), 292, 486, 810, 1350, and 2250 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	Approximately 19 hours	*Food should be withheld for at least 15 hours prior to dosing.*
Test conditions Temperature: Relative humidity: Photoperiod:	22.6 ± 0.84°C 24 ± 11% 8 hours light/16 hours dark	Humidity was lower than recommended (45-70%). Light intensity averaged 129 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	None reported	*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 at least twice daily on days 0 through 16, and once on day 17. Body weights were measured individually on days 0, 3, 7, 14, and 17. Average food consumption was determined by pen for days 0-3, 4-7, 8-14, and 15-17.	
Were raw data included?	Yes	

II. RESULTS AND DISCUSSION:

A. MORTALITY:

One incidental mortality occurred in the 810 mg ai/kg bw treatment group; this hen displayed a ruffled appearance on days 4-5, was normal in appearance from the afternoon of day 5 through day 12, but was noted to be lethargic with a ruffled appearance on day 13. The hen also displayed wing droop on day 14, and was euthanized following body weight procedures due to her emaciated condition. Necropsy confirmed emaciation, with a loss of muscle mass and a prominent keel. In addition, the gizzard contents were bile-stained, and ulcers

wee scattered throughout the intestinal wall. Due to the isolated nature and timing of the clinical signs and body weight loss, this mortality was not considered treatment related. No other mortality was observed during the study. The 17-day acute LD_{50} was >2250 mg ai/kg bw, and the NOAEL for mortality was 2250 mg ai/kg bw.

Table 3: Effect of AE 0172747 Technical on Mortality of Northern Bobwhite Quail.

Treatment (mg ai/kg bw)		No. of Birds	Cumulative Mortality					
			day 1	day 2	day 3	day 4	day 14	day 17
Vehicle control		10	0	0	0	0	0	0
292		10	0	0	0	0	0	0
486		10	0	0	0	0	0	0
810		10	0	0	0	0	1	1
1350		10	0	0	0	0	0	0
2250		10	0	0	0	0	0	0
NOAEL		2250 mg ai/kg bw						
LD_{50}		>2250 mg ai/kg bw						
Reference chemical	mortality	N/A						
	LD_{50}	N/A						
	NOAEL	N/A						

B. SUBLETHAL TOXICITY ENDPOINTS:

There were no treatment-related signs of toxicity observed at the 292 or 486 mg ai/kg bw levels. Although one female from the 292 mg ai/kg bw level was noted as lethargic approximately 4 hours after dosing and again on day 3 of the test, no treatment-related effects were observed in birds from the 486 mg ai/kg level throughout the study. Therefore, this isolated effect observed at the 292 mg ai/kg level was considered incidental to treatment.

Ruffled appearance and lethargy were observed at the 810, 1350, and 2250 mg ai/kg bw levels, and these effects were regarded as related to treatment. At the 810 mg ai/kg bw level and excluding the effects observed in the single decedent hen, a ruffled appearance was observed in one female and two males beginning 3.5 hours following dosing and continuing off and on through day 3. All surviving birds appeared normal from day 4 until test termination. At the 1350 mg ai/kg bw level, a ruffled appearance and slight lethargy was observed in one male within 2.75 hours of dosing, and a ruffled appearance developed in all females from 2.75 to 3.5 hours of dosing. On the morning of day 1, five birds (sex not reported) displayed a ruffled appearance, and one bird displayed lethargy. A ruffled appearance persisted in one male through test termination, and was observed in one female from days 14-16. The remaining birds appeared normal from the morning of day 4 until test termination. At the 2250 mg ai/kg bw level, a ruffled appearance developed in all males between 2.5 and 4 hours of dosing. One of the males continued to display a ruffled appearance and/or lethargy through the morning of day 7. All other males displayed a ruffled appearance intermittently through day 6. One female was noted as ruffled on day 3. All birds appeared normal from the afternoon of day 7 through day 12. From the morning of day 13 through day 16, ruffled appearance was noted intermittently in as many as three birds. The NOAEL for clinical signs of toxicity was 486 mg ai/kg bw.

No treatment-related differences compared to the control were observed regarding body weight changes or feed consumption. Necropsy of birds sacrificed at study termination revealed areas of hyperemia in the small intestines of one male in the 2250 mg/kg dose group, which was not considered to be treatment-related. No other gross pathological findings were reported.

Table 4: Sublethal Effect of AE 0172747 Technical on Northern Bobwhite Quail.

Mean Body Weight Change, g									
Treatment, (mg ai/kg bw)		**Males**				**Females**			
		Days 0-3	**Days 3-7**	**Days 7-14**	**Days 14-17**	**Days 0-3**	**Days 3-7**	**Days 7-14**	**Days 14-17**
Vehicle control		3	0	-2	3	2	0	-2	3
292		1	1	-1	3	0	1	1	4
486		1	0	1	3	3	1	1	2
810		-2	2	2	2	2	-6[a]	-14[a]	2
1350		4	-1	1	1	1	0	1	2
2250		2	0	3	1	3	-3	2	1
NOAEL		2250 mg ai/kg bw				2250 mg ai/kg bw			
EC_{50}		Not determined				Not determined			
Reference chemical	effect: NOAEL: LD_{50}:	N/A				N/A			

[a] Primarily caused by the single euthanized hen that lost 33 g of weight between days 3 and 7, and 71 g between days 7 and 14.

Mean Feed Consumption, g/bird/day									
Treatment, (mg ai/kg bw)		Males				Females			
		Days 0-3	Days 4-7	Days 8-14	Days 15-17	Days 0-3	Days 4-7	Days 8-14	Days 15-17
Vehicle control		20	21	16	20	16	24	16	22
292		24	27	16	27	24	29	20	30
486		21	25	17	32	15	20	16	19
810		11	17	13	15	21	25	15	26
1350		14	24	16	21	16	25	15	20
2250		27	23	16	22	16	21	17	24
NOAEL		2250 mg ai/kg bw							
EC_{50}		Not determined							
Reference chemical	effect NOEL LD_{50}	N/A							

C. REPORTED STATISTICS:

As no treatment-related mortalities were observed, the LD_{50} was visually determined to be greater than the highest dosage tested. 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: Statistical analysis of the results was not required. The toxicity endpoints could be visually determined based on a clear lack of effects on body weight change, food consumption, and mortality. There were apparent effects on clinical effects, which were used to determine the NOAEL.

LD_{50}: >2250 mg ai/kg bw 95% C.I.: N/A
Probit slope: N/A 95% C.I.: N/A
NOAEL: 486 mg ai/kg bw
Endpoint(s) Affected: Clinical signs of toxicity

E. STUDY DEFICIENCIES:

There were no study deficiencies.

F. REVIEWER'S COMMENTS:

The reviewer's conclusions were identical to those of the study authors.

In-life dates were February 22 – March 11, 2002.

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

G. CONCLUSIONS:

This study is scientifically sound and is thus acceptable. No treatment-related mortality or effects on body weight or food consumption were observed, and no treatment-related gross pathological findings were observed at necropsy. Clinical signs of toxicity (ruffled appearance and or lethargy), however, were observed in birds from the ≥810 mg ai/kg bw levels.

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Probit slope: N/A 95% C.I.: N/A
NOAEL: 486 mg ai/kg bw
Endpoint(s) Affected: 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. *Avian Single-Dose Oral LD50 Test* 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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