Data Evaluation Report on the Acute Oral Toxicity of JAU 6476 Technical (Prothioconazole) on Northern Bobwhite Quail (*Colinus virginianus*)
PMRA Submission Number 2004-0843 EPA MRID Number 46246036

Data Requirement:	PMRA DATA CODE	9.6.2.1
	EPA DP Barcode	D303488
	OECD Data Point	IIA 8.1.1
	EPA MRID	46246036
	EPA Guideline	§71-1

Test material: JAU 6476 Technical **Purity:** 98.4%
Common name: Prothioconazole
Chemical name: IUPAC: **2-[2-(1-Chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3H-1,2,4-triazole-3-thione**
CAS: 2-[2-(1-Chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3H-1,2,4-triazole-3-thione
CAS No.: 178928-70-6
Synonyms: JAU6476

Primary Reviewer: Christie E. Padova **Signature:**
Staff Scientist, Dynamac Corporation **Date:** 8/18/04

QC Reviewer: Teri S. Myers **Signature:**
Staff Scientist, Dynamac Corporation **Date:** 9/20/04

Primary Reviewer: Kevin Costello, Geologist **Date:**
OPP/EFED/ERB - III

Secondary Reviewer(s): Christopher J. Salice **Date:** 7/27/2005
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Secondary Reviewer: Émilie Larivière **Date:** 9/12/2005
HC/PMRA/EAD Émilie Larivière 9/12/05

Reference/Submission No.: 2004-0843

Company Code: BCZ
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Date Evaluation Completed:

CITATION: Barfknecht, R. 1999. JAU6476 techn.ai:: Acute Oral Toxicity for Bobwhite Quail (*Colinus virginianus*). Unpublished study performed by Bayer AG Crop Protection Business Group, Leverkusen, Germany. Laboratory ID No. 2921561-6; Report No. BAR/LD028. Study sponsored by Bayer CropScience, Research Triangle Park, NC. Study initiated April 12, 1999 and completed July 17, 1999.

EXECUTIVE SUMMARY:

The acute oral toxicity of JAU 6476 Technical (98.4% prothioconazole) to 39-week old Northern Bobwhite quail (*Colinus virginianus*) was assessed over 14 days. JAU 6476 was administered to the birds via gelatin capsule at nominal concentrations of 0 (vehicle control), 200, 650, and 2000 mg a.i./kg bw.

No mortality was observed during the 14-day study in any test or control group. The 14-day LD_{50} was >2000 mg a.i./kg bw, which categorizes JAU 6476 Technical (prothioconazole) as practically non-toxic to Northern Bobwhite quail on an acute oral basis. Diarrhea was observed in males birds from the 650 and 2000 mg a.i./kg bw dose levels. A similar dose-related effect was not noted in females. The NOAEL for clinical signs of toxicity was 200 mg a.i./kg bw. No treatment-related effect on body weights were observed. The NOAEL for body weight changes was 2000 mg a.i./kg bw. A treatment-related effect on food consumption was observed in birds from the 2000 mg a.i./kg bw level between Days 0-3. The NOAEL for food consumption was 650 mg a.i./kg bw. No treatment-related abnormalities were observed at necropsy.

This toxicity study is scientifically sound and fulfills the guideline requirements for an acute toxicity study using the Northern Bobwhite quail (§71-1). This study is classified as ACCEPTABLE.

Results Synopsis

Test Organism Size/Age: Approximately 39 weeks old, 184-277 g (combined sexes; Day -1)

LD_{50}: >2000 mg a.i./kg bw
NOAEL: 200 mg a.i./kg bw
LOAEL: 650 mg a.i./kg bw
Endpoint(s) Affected: Clinical signs of toxicity (in males only) and food consumption
Most sensitive endpoint: Clinical signs of toxicity

I. MATERIALS AND METHODS

GUIDELINE FOLLOWED: The protocol followed procedures of the U.S. EPA Pesticide Assessment Guidelines, Subsection 71-1 (1982); MAFF Working Document No. 7/5; and OECD Guideline (*draft*, 1992). No deviations from §71-1 were noted.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. This study was conducted in accordance with Chemicals Law (ChemG; 1994) and OECD (1997) GLP standards.

A. MATERIALS:

1. Test Material JAU 6476 Technical (prothioconazole)

Description: White powder

Lot No./Batch No.: 6233/0031 (mixed batch)

Purity:	98.4%
Stability of Compound Under Test Conditions:	N/A
Storage conditions of test chemicals:	Room temperature

OECD requires water solubility, stability in water and light, pK_a, P_{ow}, and vapor pressure of the test compound. OECD requirements were not reported.

2. **Test organism**:

Species:	Northern Bobwhite quail (*Colinus virginianus*)
Age at study initiation:	Approximately 39 weeks old
Weight at study initiation:	184-277 g (combined sexes; Day -1)
Source:	Morris Quail Farm, Goulds, FL

B. STUDY DESIGN:

1. Experimental Conditions

a. Range-finding Study: None reported.

b. Definitive Study:

Table 1. Experimental Parameters.

Parameter	Details	Remarks *Criteria*
Acclimation period: Conditions (same as test or not): Feeding: Health (any mortality observed):	At least 15 days Same as test Water and standard commercial quail diet (type 0729-Extrudat, batch no. 050599/1333 from the company Altromin, Lage, Germany) were provided, *ad libitum*. Not reported	Certificates of nutrient and contaminant analysis of the diet is provided in Appendices III and IV, p. 27. *EPA recommends that birds be pre-conditioned to the test facilities for at least 15 days.* *OECD recommends that birds be pre-conditioned to the test facilities for at least 7 days.*
Pen size and construction materials	Stainless steel wire mesh battery cages, 38 x 25 x 23 cm	Birds were housed individually. *EPA requires: pens must conform to good husbandry practices and should not create crowding stress.* *OECD lists no criteria for pen construction other than stating that pens should be suitable for the captive rearing of that species.*
Test duration	14 Days	*EPA requires a day for dosing and at least 14 days observation.*
Dose preparation Indicate method of confirmation of dose	The test substance was administered as a suspension in deionized water. N/A	
Mode of dose administration	Gelatin capsule	*Gavage or gelatin capsule.*
Dose levels nominal:	0 (vehicle control), 200, 650, and 2000 mg a.i./kg bw	
measured:	N/A	

Parameter	Details	Remarks *Criteria*
		EPA requires 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:	 Deionized water Negligible	 *EPA recommends that the test material 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 10/level	5 males and 5 females per treatment group. *EPA recommends 10 birds per treatment group and 10 birds for each control and vehicle group.*
No. of feed withholding days before dosing	15 hours	 *EPA recommends that food should be withheld for at least 15 hours prior to dosing.*
Test conditions Temperature: Relative humidity: Photo-period:	 15-30°C 35-75% Seasonal day lengths	Natural daylight reached the hall through windows in the roof and in one wall (p. 10). *EPA recommends that a 10 hr light/14 hr dark photo-period.*
Reference chemical, if used name: concentrations tested:	None used.	

2. Observations:

Table 2: Observations.

Parameter	Details	Remarks/Criteria
Parameters measured		

Parameter	Details	Remarks/Criteria
Parameters measured (mortality/individual body weight at test initiation and termination/ mean feed consumption/others)	- Mortality - Clinical signs of toxicity - Body weight - Feed consumption - Necropsy	*EPA recommends:* *Body weight measured at test initiation, on Day 14 and at end of the test if the test is extended beyond 14 days.* *Calculation of mortality. Mortality must NOT be more than 10% in controls.* *Feed consumption may 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. The test may have to be repeated if the problem persists.*
Groups on which necropsies were performed	All birds were subjected to necropsy.	*EPA recommends that gross necropsies be performed with inspections of the GI tract, liver, kidneys, heart, and spleen.*
Observation intervals	Mortality and signs of toxicity were observed hourly on the day of dosing and at least once daily thereafter. Body weights were determined on Days -1, 7, and 14. Feed consumption was determined on Days 3, 7, and 14.	
Were raw data included?	Yes, sufficient.	

II. RESULTS AND DISCUSSION:

A. MORTALITY:

No mortality was observed during the 14-day study in any test or control group (Table 1, p. 18). The 14-day LD_{50} was >2000 mg a.i./kg bw.

Table 3: Effect of JAU 6476 Technical (prothioconazole) on mortality of *Colinus virginianus*.

Treatment (mg a.i./kg bw)		No. of birds	Cumulative mortality							
			day 1	day 2	day 4	day 6	day 8	day 10	day 12	day 14
Vehicle control		10	0	0	0	0	0	0	0	0
200		10	0	0	0	0	0	0	0	0
650		10	0	0	0	0	0	0	0	0
2000		10	0	0	0	0	0	0	0	0
NOAEL		2000 mg a.i./kg bw								
LD_{50}		>2000 mg a.i./kg bw								
Reference chemical	mortality	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	LD_{50}	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NOAEL	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

B. SUB-LETHAL TOXICITY ENDPOINTS:

Diarrhea was observed in all test and control females, and was not considered to be related to treatment (p. 13 and Table 1, p. 18). However, only males from the 650 (3 of 5 birds) and 2000 mg a.i./kg (5 of 5 birds) dose levels exhibited diarrhea, and therefore a treatment-related response could not be excluded. Therefore, the NOAEL for sub-lethal effects was 200 mg a.i/kg bw.

No treatment-related effect on body weights was observed (p. 13, and Tables 3 and 4, p. 19).

Mean Body Weight ± standard deviation, g						
Treatment, mg a.i./kg bw	Males			Females		
	Day -1	Day 7	Day 14	Day -1	Day 7	Day 14
Vehicle control	226.4±13.5	222.4±14.9	224.0±16.0	253.2±27.7	251.6±28.4	250.0±27.4
200	213.8±14.6	212.2±12.6	213.4±15.0	240.6±19.2	247.8±22.6	245.8±20.6
650	214.4±9.5	213.6±7.5	212.6±7.7	236.8±17.7	230.2±12.1	230.0±13.8
2000	214.2±19.0	210.6±18.8	211.8±19.4	259.2±10.4	256.0±11.9	256.8±9.7
NOAEL	2000 mg a.i./kg bw			2000 mg a.i./kg bw		
EC_{50}	Not determined			Not determined		

Reference chemical	effect: NOAEL: LD_{50}:	N/A	N/A	N/A	N/A	N/A	N/A

Based on visual inspection of the data, a treatment-related reduction in feed consumption was observed at the 2000 mg a.i./kg bw level between Days 0 and 3 (p. 13, and Tables 5 and 6, p. 20). The estimated consumption averaged 17.2 g/bird/day for the control group, and 18.9, 16.9, and 13.6 g/bird/day for the 200, 650, and 2000 mg a.i./kg bw levels, respectively. Thereafter, values were comparable to control values. The NOAEL for food consumption was 650 mg a.i./kg bw.

No treatment-related abnormalities were observed upon necropsy (p. 13 and Table 2, p. 18).

Mean Feed Consumption, g/bird/day				
Treatment, mg a.i./kg bw		**Days 0-3**	**Days 3-7**	**Days 7-14**
Vehicle control		517.0	798.0	1371.0
200		568.0	765.0	1260.0
650		507.0	866.0	1300.0
2000		409.0*	830.0	1337.0
NOAEL		2000 mg a.i./kg bw		
EC_{50}		Not determined		
Reference chemical	effect NOAEL LD_{50}	N/A		

*Notably different from control (not statistically analyzed).

C. REPORTED STATISTICS:

The LD_{50} could not be calculated because mortality did not exceed 50% at any test level. Body weight data were compared using the Mann-Whitney/Wilcoxon test for independent samples via STATGRAPHICS-Plus statistical software. Feed consumption data were not analyzed statistically, as there were no replicate data.

LD_{50}: >2000 mg a.i./kg bw
NOAEL: 200 mg a.i./kg bw
LOAEL: 650 mg a.i./kg bw
Endpoint(s) Affected: Clinical signs of toxicity (in males only) and food consumption
Most sensitive endpoint: Clinical signs of toxicity

D. VERIFICATION OF STATISTICAL RESULTS:

Statistical analyses were not conducted because mortality did not exceed 50% at any test level and no replicate data were provided for food consumption. The toxicity values were verified visually.

E. STUDY DEFICIENCIES:

There were no significant deviations from U.S. EPA Guideline §71-1 that affected the validity or acceptability of this study.

F. REVIEWER'S COMMENTS:

The reviewer's conclusions were identical to the study author's.

G. CONCLUSIONS:

This toxicity study is scientifically sound and fulfills the guideline requirements for an acute toxicity study using the Bobwhite quail (§71-1). The 14-day acute oral toxicity LD_{50} was >2000 mg a.i./kg bw, which categorizes JAU 6476 Technical (prothioconazole) as practically non-toxic to the Bobwhite quail. Based on treatment-related signs of toxicity in male birds (the most sensitive endpoint), the NOAEL was 200 mg/kg bw. This study is classified as ACCEPTABLE.

LD_{50}: >2000 mg a.i./kg bw
NOAEL: 200 mg a.i./kg bw
LOAEL: 650 mg a.i./kg bw
Endpoint(s) Affected: Clinical signs of toxicity (in males only) and food consumption
Most sensitive endpoint: Clinical signs of toxicity

III. REFERENCES:

Sachs, L. 1978. Angewandte Statistik, Springer Verlag, p. 420-422.

Statgraphics Plus for Windows. 1994-1996. Version 2.1. Serial No. 3869060. Statistical Graphics Corporation, Rockville, MD 20852, USA.

EAD Assessment of USEPA DER

Reviewer: Émilie Larivière (#1269); PMRA Date: September 12, 2005

PMRA Submission Number: 2004-0843

Study Type: Acute Oral Toxicity to Bobwhite Quail

Barfknecht, R. 1999. JAU6476 techn.ai:: Acute Oral Toxicity for Bobwhite Quail (*Colinus virginianus*). Unpublished study performed by Bayer AG Crop Protection Business Group, Leverkusen, Germany. Laboratory ID No. 2921561-6; Report No. BAR/LD028. Study sponsored by Bayer CropScience, Research Triangle Park, NC. Study initiated April 12, 1999 and completed July 17, 1999.

PMRA DATA CODE: 9.6.2.1
EPA DP Barcode: D303488
OECD Data Point: IA 8.1.1
EPA MRID: 46246036
EPA Guideline: §71-1

Reviewing Agency: US EPA

EAD Executive Summary:

The acute oral toxicity of JAU 6476 Technical (98.4% prothioconazole) to 39-week old Northern Bobwhite quail (*Colinus virginianus*) was assessed over 14 days. JAU 6476 was administered to the birds via gelatin capsule at nominal concentrations of 0 (vehicle control), 200, 650, and 2000 mg a.i./kg bw. The study followed procedures of the U.S. EPA Pesticide Assessment Guidelines, Subsection 71-1 (1982); MAFF Working Document No. 7/5; and OECD Guideline (*draft*, 1992) and was in compliance with German and OECD Principles of GLP. No mortality was observed during the 14-day study in any test or control group. The NOEL based on mortality is therefore 2000 mg a.i./kg bw, the highest dose tested. The 14-day LD_{50} was >2000 mg a.i./kg bw, which categorizes prothioconazole as practically non-toxic to Northern Bobwhite quail on an acute oral basis, according to the classification scheme of the U.S. EPA (1985). Diarrhea was observed in males birds from the 650 and 2000 mg a.i./kg bw dose levels. A similar dose-related effect was not noted in females. The NOEL for clinical signs of toxicity was 200 mg a.i./kg bw. No treatment-related effect on body weights were observed. The NOEL for body weight changes was 2000 mg a.i./kg bw. A treatment-related effect on food consumption was observed in birds from the 2000 mg a.i./kg bw level between Days 0-3. The NOEL for food consumption was 650 mg a.i./kg bw. No treatment-related abnormalities were observed at necropsy.

Results Synopsis

Test Organism Size/Age: Approximately 39 weeks old, 184-277 g (combined sexes; Day -1)

LD_{50}: >2000 mg a.i./kg bw
NOEL(mortality): 2000 mg a.i./kg bw (highest dose tested)
LOEL(mortality): >2000 mg a.i./kg bw
NOEL(diarrhea): 200 mg a.i./kg bw
LOEL(diarrhea): 650 mg a.i./kg bw
Endpoint(s) Affected: Clinical signs of toxicity (in males only) and food consumption
Most sensitive endpoint: Clinical signs of toxicity

EAD Comments:

1. The appropriate PMRA information (PMRA Submission Number, PMRA Data Code, PMRA company code, PMRA active ingredient code, PMRA use site category, OECD data point, name of PMRA secondary reviewer) was added to the EPA-DER as well as information on the chemical name (IUPAC name and synonym) available from the PMRA Chemistry review.

2. The standard deviation was added in the table of mean body weight, to provide information on the variation within treatments.

3. The EAD reviewer has verified the results visually and agrees with the conclusions of the EPA reviewer and the study author.

Study Acceptability: This toxicity study is scientifically sound and fulfills the guideline requirements for an acute toxicity study using the Northern Bobwhite quail. This study is classified as ACCEPTABLE.