Data Evaluation Report on the Acute Dietary Toxicity of JAU 6476 Technical (Prothioconazole) to Mallard Duck (*Anas Platyrhynchos*)

PMRA Submission Number 2004-0843 EPA MRID Number 46246040

Data Requirement:	PMRA DATA CODE	9.6.2.5
	EPA DP Barcode	D303488
	OECD Data Point	IIA 8.1.1
	EPA MRID	46246040
	EPA Guideline	§71-2b

Test material: JAU 6476 Technical **Purity:** 98.7%
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 name: 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

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Date: 8/25/04

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7-27-05

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Date: 9/14/2005
9/14/05

Reference/Submission No.: 2004-0843

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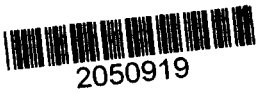
Date Evaluation Completed:

CITATION: Barfknecht, R. 2001. JAU6476 techn.: 5-Day Dietary LC50 to Mallard Duck (*Anas platyrhynchos*). Unpublished study performed by Bayer AG Crop Protection Business Group, Leverkusen, Germany. Laboratory ID No. E 2971562-2; Report No. BAR/LC010. Study sponsored by Bayer CropScience, Research Triangle Park, NC. Study initiated August 18, 1999 and completed February 13, 2001.



EXECUTIVE SUMMARY:

The acute dietary toxicity of JAU 6476 Technical (98.7% prothioconazole) to 10-day old Mallard duck (*Anas platyrhynchos*) was assessed over 8 days. JAU 6476 Technical was administered to the birds in the diet at nominal concentrations of 0 (negative control), 313, 625, 1250, 2500, and 5000 ppm. Mean-measured toxicant concentrations were 256, 555, 1180, 2532, and 5567 ppm a.i., respectively (control results not provided).

No treatment-related effects were observed with respect to mortality, clinical signs of toxicity, body weight, or feed consumption. In addition, no gross abnormalities were observed at necropsy. The 8-day acute dietary LC_{50} was >5567 ppm a.i., the highest concentration tested, which categorizes JAU 6476 Technical (prothioconazole) as practically non-toxic to the Mallard duck on an acute dietary basis. The NOAEC and LOAEC were 5567 and >5567 ppm a.i., respectively.

This toxicity study is scientifically sound and fulfills the guideline requirements for an avian dietary toxicity study using the Mallard duck (§71-2b). This study is classified as ACCEPTABLE.

Results Synopsis

Test Organism Size/Age : 10-days old; 67-139 g

LC_{50}: >5567 ppm a.i. 95% C.I.: N/A
NOAEC: 5567 ppm a.i.
LOEC: >5567 ppm a.i.
Endpoint(s) Affected: None

I. MATERIALS AND METHODS

GUIDELINE FOLLOWED: The study protocol was based on procedures outlined in the U.S. EPA Pesticide Assessment Guidelines, Series §71-2 (1982) and OECD Guideline No. 205 (1984). The following deviations from guideline §71-2 were noted:

1. Results of analysis of the control feed were not provided, and the LOD and/or LOQ were not provided.
2. The brooder temperature range (22-32°C) was less than recommended (about 35°C).
3. The photo-period was maintained on a 12-hour light/12-hour dark schedule, which is less than the minimum required photo-period of 14 hours of light/day.

These deviations do not affect the validity or acceptability of the study.

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: 98.7%

Stability of Compound Under Test Conditions: Stability of the test material was assessed prior to the definitive study in treated feed prepared at 313 and 5000 ppm and stored under actual test conditions (ambient temperature) for 24 hours or under frozen conditions for 29 days. After 24 hours of storage under actual use conditions, recoveries averaged 96 and 97% of initial concentrations for the 313 and 5000 ppm levels, respectively (p. 11). After 29 days of frozen storage, recoveries averaged 100% of initial values.

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: Mallard duck (*Anas platyrhynchos*)

Age at study initiation: 10 days

Weight at study initiation: 67-139 g

Source: Eggs were obtained from Geflügelzucht H. & E. Küberich (Wiesentheid, Germany) and hatched in the laboratory.

B. STUDY DESIGN:

1. Experimental Conditions

a. Range-finding Study: None reported. It was reported that the chosen dietary concentrations selected for use in the definitive study were based on the findings obtained in previously-conducted quail studies (p. 10).

b. Definitive Study:

Table 1: Experimental Parameters

Parameter	Details	Remarks *Criteria*
Acclimation period: Conditions (same as test or not): Feeding: Health (any mortality observed):	10 days Same as test Water and standard commercial duck diet [type 07775-Extrudat (mash form), batch no. 210600/1118 from Altromin GmbH, Lage, Germany] were provided, *ad libitum*. No mortality was observed during acclimation.	Diet composition and results from analyses for food contaminants are provided in Appendices IV and V, pp. 25-26.
Pen size and construction materials	Stainless steel wire mesh battery cages, 70 x 100 cm (height not reported).	*EPA requires: about 35 x 100 x 24 cm*
Test duration	5 days with treated feed, and 3 days with"clean" feed (recovery period).	*EPA requires: 5 days with treated feed and at least 3 days observation with "clean" feed.*
Test concentrations nominal: measured:	 0 (negative control), 313, 625, 1250, 2500, and 5000 ppm a.i. 256, 555, 1180, 2532, and 5567 ppm a.i. (results of control analysis not reported)	Mean-measured concentrations were provided on p. 12. Recoveries were 82-111% of nominal concentrations. *Four minimum, 5 or 6 strongly recommended, in a geometric scale, unless LC_{50} > 5000 ppm.*

Parameter	Details	Remarks *Criteria*
Solvent/vehicle, if used type: amount:	None used	*EPA requires: Distilled water, corn oil, propylene glycol, 1% carboxymethylcellulose, or gum arabic. Solvent not more than 2%.*
Diet preparation and feeding	The appropriate amount of the test substance was directly admixed to the basal diet. No vehicles were used.	*EPA requires: Control group tested with diet containing the maximum amount of vehicle used in treated diets?*
Feed withholding period	None	
Indicate whether stability and homogeneity of test material in diet determined (Yes/No)	Yes	
Number of birds per replicate/group for negative control: for vehicle control: for treated:	 20 N/A 10	*EPA requires: 10 (strongly recommended)*
Number of replicates/group (if used) for negative control: for vehicle control: for treated:	 2 N/A 1	
Test conditions temperature: relative humidity(%): photoperiod:	 room: Not specified cages: 22-32°C 55-85% 12 hour light/12 hour dark photo-period	***Brooder temperature:*** *about 35°C (95°F)* ***Room temperature:*** *22-27°C (71-81°F)* ***Relative humidity:*** *30-80%* ***Photoperiod:*** *Minimum of 14 h of light.*
Reference chemical, if used	None used.	

2. Observations:

Table 2: Observations

Criteria	Details	Remarks *Criteria*
Parameters measured (mortality/body weight/ mean feed consumption/ others)	- Mortality - Clinical signs of toxicity - Body weights - Feed consumption - Necropsy	
Indicate the stability and homogeneity of test chemical in the diet	Stability: Verified. Stability of the test material was assessed in treated feed prepared at 313 and 5000 ppm and stored under actual test conditions (ambient temperature) for 24 hours or under frozen conditions for 29 days. After 24 hours of storage under actual use conditions, recoveries averaged 96 and 97% of initial concentrations for the 313 and 5000 ppm levels, respectively (p. 11). After 29 days of frozen storage, recoveries averaged 100% of initial values. Homogeneity: Verified. Homogeneity (five points from each batch) was assessed in treated feed prepared at 313 and 5000 ppm. Coefficients of variation (RSD) were 4.87 and 1.87%, respectively (p. 11).	Stability and homogeneity assessments were performed prior to the definitive test in treated feed prepared at 313 (low) and 5000 (high) ppm (pp. 10-11). The RSD of treated feed prepared at 313 ppm exceeded the acceptable limit of 5%.
Indicate if the test material was regurgitated	Regurgitation was not reported.	
Treatments on which necropsies were performed	All birds were subject to gross necropsy.	

Observation intervals	Mortality and signs of intoxication were observed twice daily on the first day of exposure, and at least once daily thereafter. Food consumption was determined daily, and body weights were recorded on Days 0, 5, and 8.	
Were raw data included?	Yes, adequate.	

II. RESULTS AND DISCUSSION:

A. MORTALITY:

No mortality occurred during the study in any control or treatment group (Table 1, p. 16). The 8-day LC_{50} was >5000 ppm a.i.

Table 3: Effect of JAU 6476 Technical (prothioconazole) on mortality of Mallard duck.

Treatment, ppm a.i. mean-measured (and nominal)		No. of birds per treatment	Cumulative mortality							
			Days							
			1	2	3	4	5	6	7	8
Control		20	0	0	0	0	0	0	0	0
256 (313)		10	0	0	0	0	0	0	0	0
555 (625)		10	0	0	0	0	0	0	0	0
1180 (1250)		10	0	0	0	0	0	0	0	0
2532 (2500)		10	0	0	0	0	0	0	0	0
5567 (5000)		10	0	0	0	0	0	0	0	0
NOAEC		5000 ppm a.i.								
LC_{50}		>5000 ppm a.i.								
Reference chemical:	mortality	N/A								
	LC_{50}	N/A								
	NOAEC	N/A								

B. SUB-LETHAL TOXICITY ENDPOINTS:

No sub-lethal effects were observed (Table 2, p. 16).

No treatment-related effect on body weight changes were observed (p. 14 and Tables 3 and 4, pp. 17-18).

No treatment-related effect on food consumption was evident (p. 14 and Tables 5 and 6, p. 18). Food consumption was slightly reduced during the first three days of exposure at the 2500 ppm level; however, a dose-dependent relationship was not observed. Calculated mean test substance intakes were 18.5, 44.2, 88.7, 158.0, and 404.9 mg/bird/day for the 313, 625, 1250, 2500, and 5000 ppm a.i. treatment groups, respectively.

No gross pathological lesions were observed at necropsy (Table 7, p. 19).

Table 4: Sub-lethal effects of JAU 6476 Technical (prothioconazole) on Mallard duck.

Treatment, ppm a.i. mean-measured (and nominal)		Observation				
		Mean Body Weight ± standard deviation, g (and Body Weight Changes, %)			Food consumption (g/bird/day)	
		Day			Day	
		0	5	8	0-4	5-7
Control		104.7±16.5	223.7±34.0 (+113.6%)	282.5±48.8 (+26.3%)	75.1	77.4
256 (313)		95.1±9.8	217.3±30.4 (+128.5%)	281.0±31.7 (+29.3%)	72.2	76.8
555 (625)		106.6±21.5	232.0±43.7 (+117.6%)	295.3±58.3 (+27.3%)	79.6	77.6
1180 (1250)		95.7±14.1	210.0±38.4 (+119.4%)	264.7±49.8 (+26.0%)	75.2	78.0
2532 (2500)		100.9±21.1	208.9±45.3 (+107.0%)	282.6±70.6 (+35.3%)	62.4	79.6
5567 (5000)		105.2±19.5	224.4±37.7 (+113.3%)	276.1±53.6 (+23.0%)	72.7	76.8
NOAEC		5000 ppm				
EC_{50}		Not reported				
Reference chemical	NOAEC	N/A				
	EC_{50}	N/A				

C. REPORTED STATISTICS:

The LC_{50} could not be calculated because mortality did not exceed 50% at any test level. The NOAEC and LOEC levels for body weight and food consumption data were determined visually. Nominal concentrations were reported by the study author.

LC_{50}: >5000 ppm
NOAEC: 5000 ppm
LOEC: >5000 ppm
Endpoint(s) Affected: None

D. VERIFICATION OF STATISTICAL RESULTS:

The LC_{50} could not be calculated because mortality did not exceed 50% at any test level. The NOAEC and LOEC levels for body weight and food consumption data were determined visually. Toxicity estimates are based on the mean measured concentrations.

E. STUDY DEFICIENCIES:

There were no significant deviations from U.S. EPA Guideline §71-2 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, fulfills the guideline requirements for an avian dietary study using the Mallard duck (§71-2b), and is classified as ACCEPTABLE. Based on the results of this study, JAU 6476 Technical (prothioconazole) is categorized as practically non-toxic to Mallard duck on an acute dietary basis.

LC_{50}: >5567 ppm a.i.
NOAEC: 5567 ppm a.i.
LOAEC: >5567 ppm a.i.
Endpoint(s) Affected: None

III. REFERENCES:

None cited.

EAD Assessment of USEPA DER

Reviewer: Émilie Larivière (#1269); PMRA Date: September 14, 2005

PMRA Submission Number: 2004-0843

Study Type: Acute Dietary Toxicity to Mallard Duck

Barfknecht, R. 2001. JAU6476 techn.: 5-Day Dietary LC50 to Mallard Duck (*Anas platyrhynchos*). Unpublished study performed by Bayer AG Crop Protection Business Group, Leverkusen, Germany. Laboratory ID No. E 2971562-2; Report No. BAR/LC010. Study sponsored by Bayer CropScience, Research Triangle Park, NC. Study initiated August 18, 1999 and completed February 13, 2001.

PMRA DATA CODE: 9.6.2.5
EPA DP Barcode: D303488
OECD Data Point: IIA 8.1.1
EPA MRID: 46246040
EPA Guideline: §71-2b

Reviewing Agency: US EPA

EAD Executive Summary:

The acute dietary toxicity of JAU 6476 Technical (98.7% prothioconazole) to 10-day old Mallard duck (*Anas platyrhynchos*) was assessed over 8 days. JAU 6476 Technical was administered to the birds in the diet at nominal concentrations of 0 (negative control), 313, 625, 1250, 2500, and 5000 mg/kg. Mean measured toxicant concentrations were 256, 555, 1180, 2532, and 5567 mg a.i./kg food, respectively (control results not provided). The study was conducted following U.S. EPA Pesticide Assessment Guidelines, Series §71-2 (1982) and OECD Guideline No. 205 (1984) and was in compliance with German and OECD Principles of GLP.

No treatment-related effects were observed with respect to mortality, clinical signs of toxicity, body weight, or feed consumption. In addition, no gross abnormalities were observed at necropsy. The 8-day acute dietary LC_{50} was >5567 mg a.i./kg food, the highest concentration tested, which categorizes prothioconazole as practically non-toxic to the Mallard duck on an acute dietary basis, according to the classification scheme of the U.S. EPA (1985). The NOEC and LOEC were 5567 and >5567 mg a.i./kg food, respectively.

Results Synopsis

Test Organism Size/Age : 10-days old; 67-139 g

LC_{50}: >5567 mg a.i./kg food 95% C.I.: N/A
NOEC: 5567 mg a.i./kg food
LOEC: >5567 mg a.i./kg food
Endpoint(s) Affected: None

Evaluator 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 to the Table with body weight data, to include information on the variation within treatments.

3. OECD Guideline 205 recommends having 12 to 16 hours of light per day, therefore the lighting used in this study is acceptable.

4. U.S. EPA OPPTS 850.2200 requires a temperature gradient in the pen of approximately 38 to approximately 22 °C in order to allow young birds to seek a proper temperature. Temperature requirements for young birds typically decline over this range from birth through the first several weeks of life. OECD Guideline 205 recommends temperature ranges for mallard duck which span from 22 to 35°C, depending on the age of the birds. The temperature in the test is therefore acceptable.

5. The EAD reviewer agrees with the conclusions of the study author and the EPA reviewer.

Study Acceptability: This toxicity study is scientifically sound and fulfills the guideline requirements for an avian dietary toxicity study using the Mallard duck. This study is classified as ACCEPTABLE.