Data Evaluation Report on the Acute Oral Toxicity of XDE-638 on Avian Species *Colinus virginianus*

PMRA Submission Number EPA MRID Number 45830928

Data Requirement:	PMRA DATA CODE	
	EPA DP Barcode	D288160
	OECD Data Point	
	EPA MRID	45830928
	EPA Guideline	§71-1

Test material: XDE-638 **Purity:** 97.5%
Common name: Penoxsulam
Chemical name: IUPAC: Not reported
CAS name: 2-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-C]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide
CAS No.: Not reported
Synonyms: Not reported

Primary Reviewer: Rebecca Bryan
Staff Scientist, Dynamac Corporation
Signature: Rebecca Bryan
Date: 10/17/03

QC Reviewer: Christie E. Padova
Staff Scientist, Dynamac Corporation
Signature: C. E Padova
Date: 10/17/03

Primary Reviewer: ~~William Erickson~~ - Biologist
OPP/EFED/ERB - III J. GOODYEAR
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Secondary Reviewer(s):
{EPA/OECD/PMRA}
Date:

Reference/Submission No.:

Company Code:
Active Code:
EPA PC Code: ~~199031~~ 119031

Date Evaluation Completed:

CITATION: Troup, R.R. and B.A. Medlicott. 1999. XDE-638: Avian Acute Oral Toxicity Test with Northern Bobwhite (*Colinus virginianus*). Unpublished study performed by Genesis Laboratories, Inc., Wellington, CO. Laboratory Study No. 99023. Study sponsored by Dow AgroSciences LLC, Indianapolis, IN. Study initiated August 6, 1999 and completed December 8, 1999.

EXECUTIVE SUMMARY:

The acute oral toxicity of XDE-638 (penoxsulam) to 20-week-old Northern Bobwhite quail (*Colinus virginianus*) was assessed over 14 days. XDE-638 was administered to the birds via oral capsule at nominal concentrations of 0, 400, 600, 900, 1350, and 2025 mg/kg bw.

No mortalities or treatment-related sub-lethal effects were observed during the study. There were no significant differences in body weights or feed consumption, and no abnormalities were observed at terminal necropsy. The 14-day acute oral LD_{50} is >2025 mg/kg bw, which categorizes XDE-638 as practically non-toxic to Northern Bobwhite quail on an acute oral basis.

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 CORE.

Results Synopsis

Test Organism Size/Age: 20-weeks old, 232-313 g (combined sexes)

LD_{50}: >2025 mg/kg bw
NOAEL: 2025 mg/kg bw
LOAEL: >2025 mg/kg bw
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 §71-1. There were no significant deviations from guideline §71.1.

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

A. MATERIALS:

1. Test Material XDE-638

Description: White solid

Lot No./Batch No.: ND05167938

Purity: 97.5%

Stability of Compound Under Test Conditions: N/A

Storage conditions of test chemicals: Ambient

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: 20 weeks old

Weight at study initiation: 232-313 g

Source: Barrett's Quail Farm, Houston, TX.

B. STUDY DESIGN:

1. Experimental Conditions

a) Range-finding Study: No range-finding study was reported.

b) Definitive Study:

Table 1. Experimental Parameters.

Parameter	Details	Remarks
		Criteria
Acclimation period:	15 days.	
Conditions (same as test or not):	Same as test.	*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.*
Feeding:	Dry, non-medicated Genesis Game Bird Ration (Ranch-Way, Inc.) and tap water were provided, *ad libitum*, during acclimation and testing.	
Health (any mortality observed):	General physical condition and suitability for testing were determined by a veterinarian prior to testing.	
Pen size and construction materials	Galvanized steel pens; 51 x 25 x 25.5 cm (floor surface area of 1275 cm^2).	*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	

Parameter	Details	Remarks
		Criteria
		EPA requires a day for dosing and at least 14 days observation.
Dose preparation Indicate method of confirmation of dose	The calculated amount of test substance was measured into tared, empty gelatin capsules. The actual amount (g) of test substance administered was determined (Appendix A1, pp. 23-24).	
Mode of dose administration	Oral, via gelatin capsule.	
		Gavage or gelatin capsule.
Dose levels nominal: measured:	0 (vehicle control), 400, 600, 900, 1350, and 2025 mg/kg bw Not reported	
		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:	 N/A N/A	Each control bird received two empty gelatin capsules.
		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	5 males and 5 females/group
		EPA recommends 10 birds per treatment group and 10 birds for each control and vehicle group.
No. of feed withholding days before dosing	Birds were fasted for approximately 23 hours prior to dosing.	
		EPA recommends that food should be withheld for at least 15 hours prior to dosing.
Test conditions		Average light intensity was 2.9

Parameter	**Details**	**Remarks**
		Criteria
Temperature:	18-25°C (mean min. = 19°C; mean max. = 24°C)	foot-candles. Air exchange rate was 10-15 per hour.
Relative humidity:	36-85% (mean min. = 48%; mean max. = 69%)	*EPA recommends that a 10 hr light/14 hr dark photo-period.*
Photo-period:	10-hours light/14-hours dark.	
Reference chemical, if used name: concentrations tested:	None used.	

2. Observations:

Table 2: Observations.

Parameter	Details	Remarks/Criteria
Parameters measured		
Parameters measured (mortality/individual body weight at test initiation and termination/ mean feed consumption/others)	- Mortality - Clinical signs of toxicity - Individual body weights - Average feed consumption	*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	No regurgitation was observed on day of dosing.	*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	Four birds (2 males and 2 females) from the control and each treatment group were subject to a gross pathological examination.	*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: Twice daily. Body Weight: Days 0 (before dosing), 3, 7, and 14 Feed consumption: Days 0-3, 3-7, and 7-14.	
Were raw data included?	Raw data were included.	

II. RESULTS AND DISCUSSION:

A. MORTALITY:

No mortalities occurred during the study (Table I, p. 16).

Table 3: Effect of XDE-638 on mortality of *Colinus virginianus*.

Treatment (mg/kg bw)		No. of birds	Cumulative mortality		
			day 0	day 7	day 14
Vehicle control		10	0	0	0
400		10	0	0	0
600		10	0	0	0
900		10	0	0	0
1350		10	0	0	0
2025		10	0	0	0
NOAEL		2025 mg/kg bw			
LD_{50}		>2025 mg/kg bw			
Reference chemical	mortality	N/A	N/A	N/A	N/A
	LD_{50}	N/A	N/A	N/A	N/A
	NOAEL	N/A	N/A	N/A	N/A

B. SUB-LETHAL TOXICITY ENDPOINTS:

No treatment-related signs of toxicity were observed (Table I, p. 16). In addition, there were no significant differences in body weights or feed consumption during the study (Tables II and III, pp. 17-18). No post-mortem abnormal findings were observed that could be attributed to treatment (Table IV, p. 19).

Table 4: Sub-lethal effects of XDE-638 on *Colinus virginianus*.

Mean Body Weight, g					
Treatment, mg/kg bw		**Males and Females**			
		Day 0	**Day 3**	**Day 7**	**Day 14**
Vehicle Control		262	267	265	264
400		269	275	266	261
600		282	285	281	283
900		274	277	274	277
1350		273	276	273	274
2025		276	279	276	278
NOAEL		2025 mg/kg bw			
EC_{50}		>2025 mg/kg bw			
Reference chemical	effect: NOAEL: LD_{50}:	N/A	N/A	N/A	N/A

Mean Feed Consumption, g/bird/day				
Treatment, mg/kg bw		**Days 0-3**	**Days 3-7**	**Days 7-14**
Vehicle Control		17	16	16
400		18	16	15
600		18	17	17
900		18	18	17
1350		18	18	16
2025		17	17	16
NOAEL		2025 mg/kg bw		
EC_{50}		>2025 mg/kg bw		
Reference chemical	effect NOAEL LD_{50}	N/A	N/A	N/A

C. REPORTED STATISTICS:

Body weight and feed consumption data were analyzed by a Chi-square test for normality, followed by a Bartlett's test for homogeneity of variance. If a data set passed these tests, it was analyzed by ANOVA, followed by Dunnett's test to compare each treatment group with the control. Data sets which did not pass both tests were analyzed by Kruskal-Wallis' non-parametric ANOVA test, followed by Dunn's multiple comparison procedure. All analyses were conducted using TOXSTAT, v 3.4. The NOAEL and LD_{50} were estimated because there were no effects on mortality, feed consumption, or body weight.

D. VERIFICATION OF STATISTICAL RESULTS:

Statistical analyses were not required, as there was no mortality in this study, and effects on food consumption and body weight could be visually determined.

LD_{50}: >2025 mg/kg bw
NOAEL: 2025 mg/kg bw
LOAEL: >2025 mg/kg bw
Endpoint(s) Affected: None

E. STUDY DEFICIENCIES:

No significant deviations from guideline §71-1 were observed.

F. REVIEWER'S COMMENTS:

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

G. CONCLUSIONS:

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 CORE. There were no treatment-related effects on mortality, sub-lethal effects, body weight, or food consumption, and necropsy after 14 days revealed no treatment-related abnormalities. The 14-day acute oral toxicity LD_{50} was >2025 mg/kg bw, which categorizes XDE-638 as practically non-toxic to Northern Bobwhite quail.

LD_{50}: >2025 mg/kg bw
NOAEL: 2025 mg/kg bw
LOAEL: >2025 mg/kg bw
Endpoint(s) Affected: None

III. REFERENCES:

No references were cited.

Data Requirement: PMRA DATA CODE

EPA DP Barcode	D288160
OECD Data Point	
EPA MRID	45830929
EPA Guideline	§71-1

Test material: XDE-638 **Purity:** 97.7%
Common name: Penoxsulam
Chemical name: IUPAC: Not reported
CAS name: 2-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-C]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide
CAS No.: Not reported
Synonyms: XR-638, X638177

Primary Reviewer: Rebecca Bryan
Staff Scientist, Dynamac Corporation
Signature:
Date: 10/17/03

QC Reviewer: Christie E. Padova
Staff Scientist, Dynamac Corporation
Signature:
Date: 10/17/03

Primary Reviewer: James J. Goodyear, Ph.D.
Biologist, ERB 3,
Environmental Fate and Effects Division
Office of Pesticide Programs, US EPA
Date:

Secondary Reviewer:
OPP/EFED/ERB3
Date:

Reference/Submission No.:
Company Code:
Active Code:
EPA PC Code: 119031

Date Evaluation Completed:

CITATION: Troup, R.R. 2001. XDE-638: Avian Acute Oral Toxicity Test with Mallard Ducks (*Anas platyrhynchos*). Unpublished study performed by Genesis Laboratories, Inc., Wellington, CO. Laboratory Study No. 01005. Study sponsored by The Dow Chemical Company for Dow AgroSciences LLC, Midland, MI. Study initiated June 8, 2001 and completed August 23, 2001.

EXECUTIVE SUMMARY:

The acute oral toxicity of Penoxsulam (penoxsulam) to 22-week-old Mallard duck (*Anas platyrhynchos*) was assessed for 14 days. Penoxsulam was administered to the birds by gavage at nominal concentrations of 0, 480, 686, 980, 1400, and 2000 mg/kg bw.

No mortalities or treatment-related sub-lethal effects were observed during the study. There were no significant differences in body weights or feed consumption, and no abnormalities were observed at terminal necropsy. The 14-day acute oral LD_{50} is >1900 mg/kg bw, which categorizes Penoxsulam as practically nontoxic to Mallard ducks on an acute oral basis.

This toxicity study is scientifically sound but does not fulfill the guideline requirements for an acute toxicity study using the Mallard duck (§71-1), because the levels were not measured. Therefore, the experimental concentrations cannot be determined. Even the reported nominal levels must be incorrect, since the test chemical is only 97.7% tgai. This study is classified as SUPPLEMENTAL. Since the nominal concentrations are very high, the study need not be repeated. The NOAEL, *etc.* will be recorded as > 1,900 mg/kg bw.

Results Synopsis

Test Organism Size/Age: 22-weeks old, 816-1420 g (combined sexes)

LD_{50}: >1900 mg/kg bw
NOAEL: 1900 mg/kg bw
LOAEL: >1900 mg/kg bw
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 §71-1. Deviations from guideline §71.1 were observed:

The vehicle concentration (HPLC water plus 2% carboxymethylcellulose) was approximately 1.4% (reviewer-calculated from control data provided in Appendix A1, pp. 23-24; the actual dose administered divided by the bird weight x 100), which exceeded the recommended limit of 1.0%. This deviation was not considered to have an effect on the validity or acceptability of the study.

The concentrations of the doses were not measured or even corrected for the reported concentration of the experimental material. This deviation was serious.

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

A. MATERIALS:

1. **Test Material** Penoxsulam

   Description: White powder

   Lot No./Batch No.: B-765-44

   Purity: 97.7%

   Stability of Compound Under Test Conditions: N/A

   Storage conditions of test chemicals: Ambient

   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: 22weeks old

   Weight at study initiation: 816-1420 g

   Source: Whistling Wings, Hanover, IL

B. STUDY DESIGN:

1. **Experimental Conditions**

   a) Range-finding Study: No range-finding study was reported.

   b) Definitive Study:

Table 1. Experimental Parameters.

Parameter	Details	Remarks *Criteria*
Acclimation period:	17days.	
Conditions (same as test or not):	Same as test.	*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.*
Feeding:	Dry, non-medicated Turkey and Gamebird Grower (Ranch-Way, Inc.) and tap water were provided, *ad libitum*, during acclimation and testing.	
Health (any mortality observed):	General physical condition and suitability for testing were determined by a veterinarian prior to testing.	
Pen size and construction materials	Plastic-coated steel wire pens; 61 x 76 x 46 cm (floor surface area of 4636 cm^2).	
		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	A single dosing solution was prepared using Penoxsulam and HPLC water and 2% carboxymethylcellulose.	
Indicate method of confirmation of dose	The actual amount (mL) of test substance administered was determined (Appendix A1, pp. 23-24).	
Mode of dose administration	Oral, via gavage.	
		Gavage or gelatin capsule.

Parameter	Details	Remarks *Criteria*
Dose levels nominal: measured:	0 (vehicle control), 480, 686, 980, 1400, and 2000 mg/kg bw Not reported	*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:	2% Carboxymethylcellulose and HPLC water Approximately 1.4% (mL/g bw)	Reviewer-calculated from the control group by dividing the actual dose administered by the bird weight (x 100). *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	5 males and 5 females/group *EPA recommends 10 birds per treatment group and 10 birds for each control and vehicle group.*
No. of feed withholding days before dosing	Birds were fasted for approximately 25 hours prior to dosing.	 *EPA recommends that food should be withheld for at least 15 hours prior to dosing.*
Test conditions Temperature: Relative humidity: Photo-period:	 17-30°C (mean min. = 18°C; mean max. = 24°C) 27-77% (mean min. = 37%; mean max. = 60%) 10-hours light/14-hours dark.	Average light intensity was 7.6 foot-candles. Air exchange rate was 10-15 per hour. *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		
Parameters measured (mortality/individual body weight at test initiation and termination/ mean feed consumption/others)	- Mortality - Clinical signs of toxicity - Individual body weights - Average feed consumption	*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	Not 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	Four birds (2 males and 2 females) from the control and each treatment group were subject to a gross pathological examination.	Except in the 686 mg/kg bw treatment group where 1 male and 3 females were used. *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: Twice daily. Body Weight: Days 0 (before dosing), 3, 7, and 14 Feed consumption: Days 0-3, 3-7, and 7-14.	
Were raw data included?	Raw data were included.	

II. RESULTS AND DISCUSSION:

A. MORTALITY:

No mortalities occurred during the study (Table I, p. 16).

Table 3: Effect of Penoxsulam on mortality of *Anas platyrhynchos*.

Treatment (mg/kg bw)		No. of birds	Cumulative mortality		
			day 0	day 7	day 14
Vehicle control		10	0	0	0
480		10	0	0	0
686		10	0	0	0
980		10	0	0	0
1400		10	0	0	0
2000		10	0	0	0
NOAEL		1900 mg/kg bw nominal (adjusted)			
LD_{50}		>1900 mg/kg bw nominal (adjusted)			
Reference chemical	mortality	N/A	N/A	N/A	N/A
	LD_{50}	N/A	N/A	N/A	N/A
	NOAEL	N/A	N/A	N/A	N/A

B. SUB-LETHAL TOXICITY ENDPOINTS:

No treatment-related signs of toxicity were observed (Table I, p. 16). In addition, there were no significant differences in body weights or feed consumption during the study (Tables II and III, pp. 17-18). No postmortem abnormal findings were observed (Table IV, p. 19).

Table 4: Sub-lethal effects of Penoxsulam on *Anas platyrhynchos*.

Mean Body Weight, g					
Treatment, mg/kg bw		**Males and Females**			
		Day 0	**Day 3**	**Day 7**	**Day 14**
Vehicle control		1088	1111	1110	1097
480		1043	1067	1071	1065
686		1123	1153	1163	1112
980		1032	1059	1052	1035
1400		1119	1138	1135	1130
2000		1097	1134	1135	1111
NOAEL		1900 mg/kg bw (adjusted)			
EC_{50}		>1900 mg/kg bw (adjusted)			
Reference chemical	effect: NOAEL: LD_{50}:	N/A	N/A	N/A	N/A

Mean Feed Consumption, g/bird/day				
Treatment, mg/kg bw		**Days 0-3**	**Days 3-7**	**Days 7-14**
Vehicle control		82.8	94.3	99.1
480		80.9	71.9	80.3
686		64.7	83.7	85.4
980		76.0	69.9	72.9
1400		78.5	77.5	90.5
2000		86.7	94.5	93.0
NOAEL		2000 mg/kg bw nominal		
EC_{50}		>2000 mg/kg bw nominal		
Reference chemical	effect NOAEL LD_{50}	N/A	N/A	N/A

C. REPORTED STATISTICS:

Body weight and feed consumption data were analyzed with a Chi-square test for normality, followed by Bartlett's test for homogeneity of a variance. All data's sets passed these tests, and were analyzed by ANOVA, followed by Dunnett's test to compare each treatment group with the control. All analyses were conducted using TOXSTAT, v 3.4. The NOAEL and LD_{50} were estimated because there were no effects on mortality, feed consumption, or body weight.

D. VERIFICATION OF STATISTICAL RESULTS:

Statistical analyses were not required, as there was no mortality in this study, and effects on food consumption and body weight could be visually determined.

LD_{50}: >1900 mg/kg bw
NOAEL: 1900 mg/kg bw
LOAEL: >1900 mg/kg bw
Endpoint(s) Affected: None

E. STUDY DEFICIENCIES:

The dose levels were not measured. They weren't even adjusted for the least nominal TGAI (97.7%).

F. REVIEWER'S COMMENTS:

The reviewer's conclusions are that the guideline requirements were not met because of the failure to measure the per cent active ingredient. This deficiency makes the study "Supplemental," but, since the dosages were high and since there were no observed adverse effects, the study does not have to be repeated.

G. CONCLUSIONS:

This toxicity study is scientifically sound but does not fulfill the guideline requirements for an acute toxicity study using the Northern Bobwhite quail (§71-1). This study is classified as SUPPLEMENTAL. Since there were no treatment-related effects on mortality, sub-lethal effects, body weight, or food consumption, and necropsy after 14 days revealed no treatment-related abnormalities, the study does not have to be repeated. The 14-day acute oral toxicity LD_{50} will be adjusted to >1900 mg/kg bw, which categorizes Penoxsulam as practically nontoxic to Mallard duck.

LD_{50}: >1900 mg/kg bw
NOAEL: 1900 mg/kg bw
LOAEL: >1900 mg/kg bw
Endpoint(s) Affected: None

III. REFERENCES:

No references were cited.