

Data Evaluation Report on the acute toxicity of AE F132347 (Metabolite of Thidiazuron) to Rainbow Trout (*Oncorhynchus mykiss*)

PMRA Submission Number {.....}


EPA MRID Number 46203508

Data Requirement:


PMRA DATA CODE	
EPA DP Barcode	D294536
OECD Data Point	
EPA MRID	46203508
EPA Guideline	§72-1c

Test material: AE F132347 **Purity:** 97.4% (w:w)
Common name: Metabolite of thidiazuron
Chemical name: IUPAC: 1-Phenyl-3-(1,2,5-thiadiazol-3-yl)urea
CAS name: Not reported
CAS No.: Not reported
Synonyms: None reported

Primary Reviewer: Greg Hess
Staff Scientist, Dynamac Corporation

Signature: 
Date: 4/21/04

QC Reviewer: Christie E. Padova
Staff Scientist, Dynamac Corporation

Signature: 
Date: 4/23/04

Primary Reviewer: Bill Evans, Biologist
OPP/EFED/ERB - I



Date: 4/16/04

Secondary Reviewer(s):
{EPA/OECD/PMRA}

Date:

Reference/Submission No.:

Company Code:
Active Code:
EPA PC Code: 120301

Date Evaluation Completed:

CITATION: Blankinship, A.S., *et al.* 2003. AE F132347: A 96-Hour Static Acute Toxicity Test with the Rainbow Trout (*Oncorhynchus mykiss*). Unpublished study performed by Wildlife International, Ltd., Easton, MD. Laboratory Project No. 149A-156. Study sponsored by Bayer CropScience, Frankfurt am Main, Germany. Study initiated April 8, 2003 and completed June 30, 2003.



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EXECUTIVE SUMMARY:

In a 96-hour acute toxicity study, Rainbow Trout (*Oncorhynchus mykiss*) were exposed under static conditions to AE F132347 (a metabolite of thidiazuron) at nominal concentrations of 0 (negative and solvent controls), 0.63, 1.3, 2.5, 5.0, and 10 ppm. Mean-measured concentrations were <0.400 (<LOQ, controls), 0.59, 1.1, 2.3, 4.5, and 8.6 ppm a.i.

Following 96 hours of exposure, mortality was 0% in both control groups and the 0.59 through 2.3 ppm a.i. treatment groups, 10% in the 4.5 ppm a.i. group, and 80% in the 8.6 ppm a.i. group. The 96-hour LC₅₀ (with 95% C.I.) was 6.6 (5.7-7.7) ppm a.i., which categorizes AE F132347 (a metabolite of thidiazuron) as moderately toxic to Rainbow trout (*Oncorhynchus mykiss*) on an acute toxicity basis. Sub-lethal effects were mainly observed in surviving fish from the 8.6 ppm a.i. group; effects were first observed within 4 hours of exposure and continued through 96 hours, and included lethargy, surfacing, erratic swimming, loss of equilibrium, lying on the bottom of the test chamber, and/or floating at the surface. Lethargy was also observed in a single surviving fish at the 4.5 ppm a.i. level at 72 hours. The NOEC and LOEC, based on both mortality and sub-lethal effects, were 2.3 and 4.5 ppm a.i., respectively.

This study is scientifically sound and satisfies the guideline requirements for an acute toxicity study with Rainbow Trout (§72-1c). This study is classified as CORE.

Results Synopsis

Test Organism Size/Age (mean Weight or Length): 12 weeks old (reviewer-calculated); mean of 1.4 g (wet) and 5.6 cm (mean of 10 negative control fish at test termination)

Test Type (Flow-through, Static, Static Renewal): Static

96-Hour

LC₅₀: 6.6 ppm a.i. 95% C.I.: 5.7-7.7 ppm a.i.

NOEC: 2.3 ppm a.i.

LOEC: 4.5 ppm a.i.

Endpoints affected: Mortality and sub-lethal (same conclusions)

I. MATERIALS AND METHODS

GUIDELINE FOLLOWED: The study protocol was based on procedures outlined in the OECD Guideline No. 203 (1993); the U.S. EPA OPPTS No. 850.1075 (Draft, 1996); and ASTM Standard E729-88a (1994). Deviations from U.S. EPA §72-1 included:

1. Aeration of the test vessels was not addressed.
2. The water hardness (132 mg/L as CaCO₃) was three times higher than recommended (40-48 mg/L as CaCO₃).
3. The pH range (8.2-8.7) was greater than recommended (7.2-7.6).
4. The total organic carbon (TOC), particulate matter, and residual chlorine concentrations in the dilution water were not reported.

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

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COMPLIANCE: Signed and dated GLP, Confidentiality, and Quality Assurance statements were provided. This study was conducted in accordance with GLP standards of the U.S. EPA (40 CFR Part 160), OECD, and Japan MAFF (p. 3).

A. MATERIALS:

1. Test Material AE F132347 (a metabolite of thidiazuron)

Description: Rust-colored powder

Lot No./Batch No.: GMT 216P (Product code: AE F132347 00 1B97 0001)

Purity: 97.4% (w:w) a.i.

Stability of Compound Under Test Conditions: The stability of the test substance in the dilution water during the course of the study was assessed by analytical determination at 0, 48, and 96 hours. Concentrations declined slightly during the 96-hour study (Table 1, p. 18). Recoveries were 87.1-108% of nominal concentrations at 0 hours, 71.3-103% of nominal at 48 hours, and 67.8-99.6% of nominal at 96 hours (Table 1, p. 18). Declines lessened as the concentration increased: mean 96-hour recoveries represented decreases of 21, 19, 16, 11 and 2.4% of 0-hour recoveries at the nominal 0.63, 1.3, 2.5, 5.0, and 10 ppm test concentrations, respectively (reviewer-calculated).

Storage conditions of test chemicals: Stored frozen.

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: Rainbow Trout (*Oncorhynchus mykiss*)

Age at test initiation: 12 weeks old (reviewer-calculated, hatched on May 15, 2003)

Weight at study initiation: Not provided; the blotted wet weight of 10 negative control fish measured at test termination averaged 1.4 g (range of 0.84-1.7 g).

Length at study initiation: Not provided; the length of 10 negative control fish measured at test termination averaged 5.6 cm (range of 4.8-6.0 cm).

Source: Thomas Fish Company, Anderson, CA.

B. STUDY DESIGN:

1. Experimental Conditions

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a. Range-finding Study: The definitive nominal test concentrations were selected in consultation with the sponsor, and were based upon the results of an exploratory range-finding toxicity test. The results of the range-finding study were not reported (p. 9).

b. Definitive Study

Table 1. Experimental Parameters

Parameter	Details	Remarks
		Criteria
Acclimation period:	At least 14 days prior to testing	<hr/> <i>EPA requires: minimum 14 days; no feeding during test OECD requires minimum of 12 days.</i>
Conditions: (same as test or not)	Same as test	
Feeding:	Fed commercially-prepared diet supplied by Zeigler Brothers Inc., Gardners, PA. Fish were not fed two days prior to and during testing.	
Health: (any mortality observed)	During the 48 hours prior to testing, fish showed no signs of disease, stress or mortality.	
Duration of the test	96-hour	<hr/> <i>EPA/OECD requires: 96 hour</i>

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Parameter	Details	Remarks
		Criteria
Test condition static/flow through	Static	
Type of dilution system- for flow through method.	N/A	<i>EPA: Must provide reproducible supply of toxicant, with a consistent flow rate of 5-10 vol/24 hours, and meter systems calibrated before study and checked twice daily during test period</i>
Renewal rate for static renewal	N/A	
Aeration, if any	Not reported	<i>EPA requires: no aeration; OECD permits aeration</i>
<u>Test vessel</u>		
Material: (glass/stainless steel)	Stainless steal aquaria with stainless steal cover 38 L 25 L (18.9-cm depth)	<i>EPA requires: Size 19 L (5 gal) or 30 x 60 x 30 cm Fill volume: 15-30 L of solution</i>
Size:		
Fill volume:		
Source of dilution water	The dilution water was freshwater obtained from an on-site laboratory well (40-m deep). The well water was sand-filtered, aerated, then filtered (0.45 µm) again prior to use.	<i>EPA 1975; Soft reconstituted water or water from a natural source, not dechlorinated tap water; OECD permits dechlorinated tap water.</i>

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Parameter	Details	Remarks
		Criteria
Water parameters: Hardness	132 mg CaCO ₃ /L	<p>The hardness and pH were higher than recommended.</p> <p>Total alkalinity was 188 mg/L as CaCO₃.</p> <p>Results of the analysis of the well water on July 31, 2002 for pesticides, organics, and metals are provided in Appendix 3, pp. 28-29.</p> <hr/> <p>Hardness and pH EPA requires hardness of 40-48 mg/L as CaCO₃ and pH of 7.2-7.6. OECD allows hardness of 10-250 mg/L as CaCO₃ and pH between 6 and 8.5.</p> <p>Dissolved Oxygen <u>Renewal</u>: ≥60% during 1st 48 hrs and ≥40% during 2nd 48 hrs <u>Flow-through</u>: ≥60% through out test. OECD requires at least 80% saturation value.</p> <p>Temperature EPA requires 12°C for coldwater species and 17-22°C for warmwater species. OECD requires range of 21 - 25°C for bluegill and 13-17°C for rainbow trout.</p> <p>EPA water quality measured at beginning of test and every 48 hours</p>
pH	8.2-8.7	
Dissolved oxygen	6.7-9.5 mg/L (≥62% saturation)	
Total Organic Carbon	Not reported	
Particulate Matter	Not reported	
Metals	See Appendix 3, p. 29.	
Pesticides	<LOD	
Chlorine	Not reported	
Temperature	11.2 to 13.1°C	
Intervals of water quality measurement	The DO, pH and temperature were measured in both replicate aquaria at 0-, 24-, 48-, 72- and 96-hours. Temperature was also measured continuously in one negative control aquaria.	

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Parameter	Details	Remarks
		Criteria
<p><u>Concentration of test material:</u> nominal:</p> <p>measured:</p>	<p>0 (negative and solvent controls), 0.63, 1.3, 2.5, 5.0, and 10.0 ppm</p> <p><0.400 (<LOQ, controls), 0.59, 1.1, 2.3, 4.5, and 8.6 ppm a.i.</p>	<p>Mean-measured concentrations are provided in Table 1, p. 18. Although slight decreases were observed at all test levels, reviewer-calculated high-low ratios were ≤ 1.44, which indicates acceptable variability.</p> <p>Stock solutions were adjusted for purity of the test material (p. 12).</p> <p><i>EPA/OECD requires: Control and five treatment levels. Each conc. should be 60% of the next highest conc., and should be in a geometric series</i></p>
Solvent (type, percentage, if used)	Dimethyl formamide (DMF), 0.1 mL/L	<p><i>EPA requires: Not to exceed 0.5 mL/L for static tests or 0.1 mL/L for flow-through tests; OECD requires solvent, exceed 100 mg/L.</i></p>
<p><u>Number of fish/replicates:</u> negative control:</p> <p>solvent control:</p> <p>treated:</p>	<p>20 fish, divided into two replicates containing 10 fish each</p> <p>20 fish, divided into two replicates containing 10 fish each</p> <p>20 fish, divided into two replicates containing 10 fish each</p>	<p><i>EPA: ≥ 10/concentration; OECD requires at least 7 fish/concentration</i></p>
Biomass loading rate	0.56 g fish/L	<p><i>Static: ≤ 0.8 g/L at $\leq 17^\circ\text{C}$, ≤ 0.5 g/L at $> 17^\circ\text{C}$; flow-through: ≤ 1 g/L/day; OECD requires maximum of 1 g fish/L for static and semi-static with higher rates accepted for flow-through</i></p>
Lighting	16-hours light/8-hours dark, with a 30-minute transition period.	<p>Light intensity of 381 lux at the water surface during daylight hours.</p> <p><i>EPA requires: 16 hours light/8 hours dark; OECD requires 12 -16 hours photoperiod.</i></p>

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Parameter	Details	Remarks
		Criteria
Feeding	Animals were not fed during testing.	<i>EPA/OECD requires: No feeding during the study</i>
Recovery of chemical	98.8-100% of nominal	Based on quality control matrix spikes fortified at 0.600, 3.00, or 10.0 ppm and analyzed concurrently with the samples (Appendix 4.5, p. 35).
Level of Quantitation	0.400 ppm a.i.	
Level of Detection	Not reported	
Positive control {if used, indicate the chemical and concentrations}	N/A	
Other parameters, if any	N/A	

2. Observations:

Table 2: Observations

Criteria	Details	Remarks/Criteria
Parameters measured including the sub-lethal effects/toxicity symptoms	Mortality and sub-lethal effects	
Observation intervals	at 4 hours and every 24 hours thereafter	<i>(EPA/OECD requires: minimally every 24 hours)</i>
Were raw data included?	Yes, sufficient	
Other observations, if any	N/A	

II. RESULTS AND DISCUSSION:

A. MORTALITY:

By 96-hours, mortality was 0% in both control groups and the 0.59 through 2.3 ppm a.i. treatment groups, 10% in the 4.5 ppm a.i. group, and 80% in the 8.6 ppm a.i. group (Table 4, p. 21). The 96-hour LC₅₀ (with 95% C.I.) was 6.7 (5.7-7.9) ppm a.i. (Table 5, p. 22). The NOEC based on mortality data was 2.3 ppm a.i.

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Table 3: Effect of AE F132347 on mortality of Rainbow Trout (*Oncorhynchus mykiss*).

Treatment, ppm a.i. Measured and (nominal) concn.	No. of fish at start of study	Observation Period					
		0-48 Hours		72 Hours		96 Hours	
		No Dead	% mortality	No Dead	% mortality	No Dead	% mortality
Negative control	20	0	0	0	0	0	0
Solvent control	20	0	0	0	0	0	0
0.59 (0.63)	20	0	0	0	0	0	0
1.1 (1.3)	20	0	0	0	0	0	0
2.3 (2.5)	20	0	0	0	0	0	0
4.5 (5.0)	20	0	0	1	5	2	10
8.6 (10)	20	7	35	14	70	16	80
NOEC (mortality)	2.3 ppm a.i.						
LC ₅₀ (95% C.I.)	6.7 (5.7-7.9) ppm a.i.						
Positive control, if used mortality: LC ₅₀ :	N/A	N/A	N/A	N/A	N/A	N/A	N/A

B. NON-LETHAL TOXICITY ENDPOINTS:

Sub-lethal effects were generally observed in surviving fish from the 8.6 ppm a.i. group; effects were first observed within 4 hours of exposure and continued through 96 hours (Table 4, p. 21). Effects included lethargy, surfacing, erratic swimming, loss of equilibrium, lying on the bottom of the test chamber, and/or floating at the surface. Lethargy was also observed in a single surviving fish at the 4.5 ppm a.i. level at 72 hours. No signs of toxicity were observed in either control group, or in the 0.59 through 2.3 ppm a.i. test groups during the study. The NOEC and LOEC, based on sub-lethal effects, were 2.3 and 4.5 ppm a.i., respectively.

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Table 4. Sub-lethal effects of AE F132347 on Rainbow Trout (*Oncorhynchus mykiss*).

Treatment, ppm a.i. Measured and (nominal) concn.	Observation Period				
	endpoint at 4 Hours	endpoint at 24 Hours	endpoint at 48 Hours	endpoint at 72 Hours	endpoint at 96 Hours
	% affected ^a	% affected	% affected	% affected	% affected
Negative control	AN	AN	AN	AN	AN
Solvent control	AN	AN	AN	AN	AN
0.59 (0.63)	AN	AN	AN	AN	AN
1.1 (1.3)	AN	AN	AN	AN	AN
2.3 (2.5)	AN	AN	AN	AN	AN
4.5 (5.0)	AN	AN	5% - Lethargic	AN	AN
8.6 (10)	80% - Lethargic 20% - Surfacing	45% - Lethargic 35% - Lying on bottom 10% - Floating at surface 10% - Erratically swimming 10% - Loss of equilibrium 10% - Surfacing	46% - Erratically swimming 38% - Lying on bottom 15% - Floating at surface	17% - Lying on bottom 17% - Lethargic 17% - Erratically swimming 17% - Loss of equilibrium	75% - Erratic swimming 75% - Loss of equilibrium 25% - Lying on bottom
NOEC (sub-lethal)	2.3 ppm a.i.				
LOEC (sub-lethal)	4.5 ppm a.i.				
EC ₅₀	Not determined				
Positive control, if used % sub-lethal effect: EC ₅₀ :	N/A	N/A	N/A	N/A	N/A

^a The percent of affected fish was reviewer-calculated from number affected based on number of surviving fish (Table 4, p. 21).

AN - All surviving fish appeared normal.

C. REPORTED STATISTICS:

The 96-hour LC₅₀ (with 95% C.I.) was calculated using the probit analysis method via a computer program (Stephan, C.E., 1978). The 96-hour NOEC and LOEC values were determined by visual observation based on mortality and sub-lethal effects data. Mean-measured concentrations were used for all determinations.

96-Hour

LC₅₀: 6.7 ppm a.i.

95% C.I.: 5.7-7.9 ppm a.i.

Probit slope: 7.6

NOEC: 2.3 ppm a.i.

LOEC: 4.5 ppm a.i.
Endpoints affected: Mortality and sub-lethal (same conclusions)

D. VERIFICATION OF STATISTICAL RESULTS:

The 96-hour LC₅₀ was determined using the moving average method via TOXANAL statistical software after pooling the control groups. The NOEC was visually determined as the highest concentration which exhibited no significant (<10%) mortality or sub-lethal effects. All toxicity values were determined in terms of the reported mean-measured treatment concentrations.

96-Hour

LC₅₀: 6.6 ppm a.i. 95% C.I.: 5.7-7.7 ppm a.i.
NOEC: 2.3 ppm a.i.
LOEC: 4.5 ppm a.i.
Endpoints affected: Mortality and sub-lethal (same conclusions)

E. STUDY DEFICIENCIES:

There were no significant deviations from U.S. EPA guideline §72-1c that affected the acceptability or validity of this study.

F. REVIEWER'S COMMENTS:

Results of the reviewer's statistical verification were nearly identical to those of the study authors'. The reviewer's 96-hour LC₅₀ was slightly lower with a slightly narrower 95% confidence interval than the study authors' reported value, presumably due to the different statistical methods used. Therefore, the reviewer's lower LC₅₀ value is reported in the Executive Summary and Conclusions sections of this DER because it is a more conservative estimate of the acute toxicity of AE F132347 to Rainbow Trout.

The concentrations of AE F132347 declined slightly at all test levels during the 96-hour study (Table 1, p. 18). At 0 hours, recoveries were 87.1-108% of nominal values. By 96-hours, mean recoveries were 77.9-85.9% of nominal values. Declines decreased with increasing concentration, and were 21 to 2.4% of initial values (reviewer-calculated). However, although slight declines were observed, overall variability was within acceptable limits, with high-low ratios of ≤ 1.44 (reviewer-calculated). Therefore, these differences were not considered to be significant with respect to the results of the study.

The nominal 0.63, 1.3, and 2.5 ppm test solutions appeared clear and colorless at test initiation and termination (p. 12). The 5.0 and 10 ppm test solutions were clear with a tan tint and very fine particles on the surface at test initiation, and were clear and colorless with a small amount of fine brown precipitate in the test chambers at test termination.

G. CONCLUSIONS:

This study is scientifically sound and satisfies the guideline requirements for an acute toxicity study with freshwater fish, cold water species (§72-1c). This study is classified as CORE. The 96-hour LC₅₀ (with 95% C.I.) was 6.6 (5.7-7.7) ppm a.i., which classifies AE F132347 (a metabolite of thidiazuron) as moderately toxic to Rainbow Trout (*Oncorhynchus mykiss*) on an acute toxicity basis. The NOEC (for mortality and sub-lethal effects) was 2.3 ppm a.i.

96-Hour

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LC₅₀: 6.6 ppm a.i. 95% C.I.: 5.7-7.7 ppm a.i.
NOEC: 2.3 ppm a.i.
LOEC: 4.5 ppm a.i.
Endpoints affected: Mortality and sub-lethal (same conclusions)

III. REFERENCES:

- Organization for Economic Co-Operation and Development (OECD). 1993. Guideline for the Testing of Chemicals. *Guideline 203: Fish Acute Toxicity Test*, Adopted by Council on 12 July 1992.
- U.S. Environmental Protection Agency. 1996. *Fish Acute Toxicity Test, Freshwater and Marine*. Series 850 - Ecological Effects Test Guidelines (*draft*), OPPTS Number 850.1075.
- ASTM Standard E729-88a. 1994. *Standard Guide for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians*. American Society for Testing and Materials.
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APPENDIX I. OUTPUT FROM REVIEWER'S STATISTICAL VERIFICATION:

TOXANAL RESULTS: CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS	
1	.1713618	6.585459	5.735354	7.741769

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H	GOODNESS OF FIT PROBABILITY
7	.2019991	1	.9999093

SLOPE = 7.573672
95 PERCENT CONFIDENCE LIMITS = 4.169738 AND 10.97761

LC50 = 6.654648
95 PERCENT CONFIDENCE LIMITS = 5.669661 AND 7.86431

LC10 = 4.523129
95 PERCENT CONFIDENCE LIMITS = 3.154707 AND 5.370233