Data Evaluation Report on the Chronic Toxicity of JAU 6476 Technical (Prothioconazole) to Freshwater invertebrates - Daphnia sp.
PMRA Submission Number 2004-0843 EPA MRID Number 46246028

Data Requirement:	PMRA DATA CODE	9.3.3
	EPA DP Barcode	D303488
	OECD Data Point	IIA 8.3.2.1
	EPA MRID	46246028
	EPA Guideline	§72-4b

Test material: JAU 6476 Technical **Purity:** 98.8%
Common name: Prothioconazole
Chemical name: IUPAC: 3H-1,2,4-Triazole-3-thione.2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro (p. 7).
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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OPP/EFED/ERB - IV 7-17-05 **Date:** 7/17/2005

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CITATION: Hendel, B., and H. Sommer. 2001. Influence of JAU6476 (tech.) on the Reproduction Rate of Water Fleas. Unpublished study performed by Bayer AG Crop Protection Business Group, Crop Protection Development, Leverkusen, Germany. Laboratory ID No. E 3211982-6; Report No. HDB/rDm67. Study sponsored by Bayer CropScience, Research Triangle Park, NC. Study initiated November 8, 2000 and completed April 11, 2001.

EXECUTIVE SUMMARY:

The 21-day-chronic toxicity of JAU 6476 Technical (98.8% purity; Prothioconazole) to *Daphnia magna* was studied under static-renewal conditions. Nominal concentrations were 0 (negative and solvent controls), 0.56, 1.0, 1.8, 3.2, 5.6, 10.0, and 18.0 ppm, which corresponded to mean-measured concentrations of 0 (controls), 0.51, 1.02, 1.74, 3.37, 5.79, 10.5, and 15.6 ppm. The mean-measured concentrations were based on available measurement data. Eight media renewals were performed. "New" test media was sampled from all treatment levels at 0, 9, and 19 Days, and "old" test media (after 48 or 72 hours) was sampled from the control (both) and alternating toxicant levels (0.56, 1.8, and 5.6 ppm levels) on Days 2, 12, and 21 (the 18.0 ppm level was not sampled due to complete mortality on Day 1). Recoveries for all samples ranged from 86 to 109% of nominal concentrations indicating precision and stability. Toxicity endpoints were re-calculated using mean-measured concentrations; the study author used nominal concentrations.

After 21 days of exposure, mortality was 0% at the control, solvent control, and mean-measured 0.51 ppm treatment level, 10% at the 1.02 ppm level, 60% at the 1.74 ppm level, and 100% at the ≥3.37 ppm levels. The 21-day LC_{50} value (with 95% C.I.) was 1.57 (1.24-2.05) ppm and the NOAEC for mortality was 1.02 ppm.

The mean first day of reproduction was 9.3, 10.0, 10.1, 9.6, 9.9, and 11.0 for the negative control, solvent control, mean-measured 0.51, 1.02, 1.74, and 3.37 ppm treatment groups, respectively (no offspring were produced at higher levels). Offspring production was adversely affected by treatment at the **≥0.51 ppm** test levels. The sum of offspring per parent averaged 73.8, 80.3, 67.2, 64.3, and 51.3 for the negative control, solvent control, 0.51, 1.02, 1.74, and 3.37 ppm treatment groups, respectively. The number of offspring per parent and reproduction day averaged 5.84, 6.70, 5.62, 4.67, 3.99, and 0.96 for the negative control, solvent control, 0.51, 1.02, 1.74, and 3.37 ppm treatment groups, respectively. The subsequent NOAEC was 0.51 ppm for the number of offspring produced/parent/reproductive day.

A statistically-significant reduction compared to the solvent control in terminal lengths was observed at the ≥1.02 ppm test levels. Body lengths of surviving daphnids averaged 4.13, 4.06, 3.99, 3.81, and 3.70 mm for the negative control, solvent control, 0.51, 1.02, and 1.74 ppm treatment groups, respectively. The NOAEC for total length was 0.51 ppm. Terminal dry weight was not assessed in this study.

The study is scientifically sound and fulfills the guideline requirements for an aquatic invertebrate life cycle test with the *Daphnia magna* (§72-4b). Although not all "old" treatment solutions were analytically verified in this static-renewal design during the exposure period, analyzed treatment solutions indicated compound stability. Furthermore, the solvent was neither identified or quantified in the test media although there were no statistical effects of the solvent. Consequently, this study is classified as ACCEPTABLE. This study provides information that may be useful for risk assessment purposes. Mortality, reproduction, and growth were all affected by treatment with JAU 6476 Technical (Prothioconazole). Reproduction and growth were the most sensitive endpoints.

Results Synopsis:

Test Organism Age (eg. 1st instar): First instar, <24 hours old
Test Type (Flow through, Static, Static Renewal): Static-renewal

Mortality/immobilization:
NOAEC: 1.02 ppm
LOAEC: 1.74 ppm
LC_{50}: 1.57 ppm 95% C.I.: 1.24-2.05 ppm

Probit slope: 7.31 95% C.I.: 2.83-11.79

Time to First Brood Release
NOAEC: 3.37 ppm
LOAEC: >3.37 ppm

Sum of Offspring/Parent
NOAEC: 1.02 ppm
LOAEC: >1.02 ppm

Number of Offspring/Parent/Reproduction Day
NOAEC: 0.51 ppm
LOAEC: 1.02 ppm

Terminal Length
NOAEC: 0.51 ppm
LOAEC: 1.02 ppm

Terminal Dry Weight
NOAEC: Not determined
LOAEC: Not determined

Endpoint(s) Affected: Mortality, reproduction, and terminal length
Most sensitive endpoint(s): Reproduction and terminal length

I. MATERIALS AND METHODS

GUIDELINES FOLLOWED: The study protocol was based on procedures outlined in the OECD Guidelines for Testing of Chemicals, No. 211 (1998). Deviations from U.S. EPA FIFRA Guideline §72-4b include:

1. The storage conditions of the test chemical were not described.

2. The pretest health (including mortality) of the parental stock was not specified.

3. The hardness (196-214 mg/L as $CaCO_3$) and pH (7.6-8.5) were slightly higher than the recommended limits (160-180 mg/L as $CaCO_3$ and 7.6-8.0, respectively).

4. DO levels declined at all but the negative control level in "old" test media sampled on Days 12, 14, 16, 19, and 21 (Table 1.2, p. 15). Minimum levels of 3.2-3.3 mg/L were recorded on Day 21. Percent saturation levels were not provided for the "old" media, and no discussion of these findings was made by the study authors.

5. The study design differed from EPA guidance: in this static renewal study, 1 daphnid per test chamber was maintained, with ten replicate chambers per concentration (total of 10 daphnids/concentration). EPA guidance recommends 22 daphnids/level for static renewal studies, where seven test chambers should contain one daphnid each (to collect data on survival, growth, and reproduction), and three test chambers should contain five daphnids each (to collect data on survival only).

6. The type and quantity of solvent used in test solution preparation was not reported.

7. The LC_{50} (with 95% C.I.) was not determined.

8. The time to first brood release was not statistically analyzed.

9. Not all terminal growth measurements of surviving parental daphnid were measured. Terminal length is currently a required endpoint, and dry weight is a recommended endpoint. Terminal length was measured.

10. Not all "old" treatment solutions were analytically verified during the exposure period.

COMPLIANCE: Signed and dated GLP, Confidentiality, and Quality Assurance statements were provided. This study was conducted in accordance with the current version of Annex 1 of the Chemicals Law (Chem G; 1994) and the current OECD Principles of GLP.

A. MATERIALS:

1. Test Material JAU 6476 Technical (Prothioconazole)

Description: Light beige powder

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

Purity: 98.8%

Stability of Compound Under Test Conditions: The stability of JAU 6476 Technical in "old" test medium was verified on Days 2 (after 48 hours), 12 (after 72 hours), and 21 (after 72 hours). Samples were collected from the control (both sets), 0.56, 1.8 and 5.6 ppm test levels Recoveries were 86 to 106% of nominal concentrations (Table 9, p. 25). "New" test medium was verified on Days 0, 9, and 19. Samples were collected from the control (both sets), 0.56, 1.0, 1.8, 3.2, 5.6, 10.0, and 18.0 ppm test levels (the 10.0 and 18.0 ppm levels were not sampled on days 9 and 19due to complete mortality by 24 hours, and the 3.2 and 5.6 ppm levels were not sampled on day 19 due to complete mortality). Recoveries were 101 to 109% of nominal concentrations (Table 9, p. 25).

Storage conditions of test chemicals: Not reported.

OECD requires water solubility, stability in water and light, pKa, Pow, vapor pressure of test compound). The following OECD requirements were reported:

Water solubility: 7 mg/L (89 mg/L) [sic, p. 7]

2. Test organism:

Species: *Daphnia magna*

Age of the parental stock: Parental stock were 21- to 28-days old (from the fourth brood or later); first instars were <24 hours old

Source: In-house laboratory cultures (>10 years)

B. STUDY DESIGN:

1. Experimental Conditions

a. Range-finding Study: None reported. Nominal concentrations for the definitive study were reportedly based on the results of acute testing with daphnids (p. 10).

b. Definitive Study:

Table 1: Experimental Parameters

Parameter	Details	Remarks *Criteria*
Parental acclimation: Period:	Continuous in-house cultures were maintained (>10 years).	The organisms used for the definitive study were <24 hours old and were from the fourth brood or later. The parental stock were 21- to 28-days old at instar collection.
Conditions: (same as test or not)	Same as test	
Feeding:	*Daphnia* cultures were fed three times/week with single cell green algae *Scenedesmus subspicatus* and occasionally with commercial ornamental fish food (TetraMin®) in aqueous suspension.	
Health: (any mortality observed)	Not reported	
Test condition: Static renewal/flow through:	Static renewal	
Type of dilution system- for flow through method.	N/A	
Renewal rate for static renewal	Every 48 hours during the week, and at 72 hours over weekends.	

Parameter	Details	Remarks *Criteria*
		For flow-through study: consistent flow rate of 5-10 vol/24 hours, meter systems calibrated before study and checked twice daily during test period.
Aeration, if any	Not aerated during the exposure period.	*Dilution water should be aerated to insure DO concentration at or near 100% saturation. Test tanks should not be aerated.*
Duration of the test	21 days	*EPA requires 21 days for static renewal*
Test vessel Material: (glass/stainless steel) Size: growth/reproduction test: survival test: Fill volume: growth/reproduction test: survival test:	Glass beakers 250 mL Same 100 mL (4-cm depth) Same	The growth/reproduction and survival portions of the test were performed simultaneously in the same replicate test chambers/beakers. The beakers were covered with plexi glass plates. *1. Material: Glass, No. 316 stainless steel, or perfluorocarbon plastics* *2. Size: 250 mL with 200 mL fill volume is preferred; 100 mL with 80 mL fill volume is acceptable.* *OECD requires parent animals be maintained individually, one per vessel, with 50 - 100 mL of medium in each vessel.*
Source of dilution water	M7 Medium prepared using deionized water, mineral salts, and vitamins (components listed on p. 9). The water was aerated prior to use.	Results of analysis of the dilution water (July 2000) for contaminants are provided in Appendix III, pp. 56-59. *Unpolluted well or spring that has been tested for contaminants, or appropriate reconstituted water (see ASTM for details).*

Parameter	Details	Remarks *Criteria*
Water parameters: Hardness	11-12 °dH (196-214 mg/L $CaCO_3$)	The hardness and pH were slightly higher than the recommended limits of the EPA, but are acceptable according to OECD Guideline 211.
pH	7.6-8.5	
Dissolved oxygen	7.2-9.4 mg/L (≥approx. 85% saturation) in freshly prepared media; ≥3.2 mg/L in 48- or 72-hour old media (Tables 1.1 and 1.2, pp. 14-15)	DO levels declined at all but the negative control level in "old" test media sampled on Days 12, 14, 16, 19, and 21 (Table 1.2, p. 15). Minimum levels of 3.2-3.3 mg/L were recorded on Day 21. Percent saturation levels were not provided.
Temperature	19.9-20.7 °C	
Total Organic Carbon	<2 mg/L (July 2000)	
Particulate matter	Not specified	
Metals	Fe - 1.3 µg/L	
Pesticides	<0.05 µg/L (July 2000)	
Chlorine	<0.01 mg/L (July 2000)	
Interval of water quality measurements	DO and pH were measured at all test levels from "new" and "old" test media. Alkalinity, hardness, and conductivity were measured prior to each transfer of the parent daphnia. Temperature was measured continuously in one vessel (not specified) and in one control vessel at the "old" media samplings.	***hardness*** *160 to 180 mg/L as $CaCO_3$; OECD requires > 140 mg/L as $CaCO_3$* ***pH*** *7.6 to 8.0 is recommended. Must not deviate by more than one unit for more than 48 hours. OECD requires pH rang 6 - 9 and should not vary more than 1.5 units in any one test.* ***Dissolved Oxygen*** *Renewal: must not drop below 50% for more than 48 hours. Flow-through: ≥ 60% throughout test.* ***Temperature*** *20°C ± 2°C. Must not deviate from 20°C by more than 5°C for more than 48 hours. OECD requires range 18 - 22°C; temperature should not vary more than ± 2°C* *OECD requires total organic carbon < 2 mg/L*
Number of organisms:	10 daphnids/level	Did not follow recommended EPA test design, but followed OECD Guideline 211.
growth/reproduction test:	1 daphnid per replicate with 10 replicate chambers	*EPA requires 22 daphnids/level; 7 test chambers should contain 1 daphnid each, and 3 test chambers should contain 5 daphnids each.* *OECD requires minimum of 10 daphnids held individually for static tests. For flow-through tests, 40 animals divided into 4 groups of 10 animals at each test concentration.*
survival test:	(Not differentiated; same test chambers as above)	

Parameter	Details	Remarks *Criteria*
Application rates nominal: measured:	0 (negative and solvent controls), 0.56, 1.0, 1.8, 3.2, 5.6, 10.0, and 18.0 ppm "New" test media (without food or test animals) was sampled from all test levels at 0, 9, and 19 Days, and "old" test media (after 48 or 72 hours) was sampled from the control (both) and alternating toxicant levels (0.56, 1.8, and 5.6 ppm levels) on Days 2, 12, and 21 (Tables 8 and 9, p. 25). The 18.0 ppm level was not sampled due to complete mortality after 24 hours of exposure. Recoveries for all samples ranged from 86 to 109% of nominal concentrations indicating precision and stability; therefore, nominal concentrations are reported.	Fresh stock solutions were analyzed on Days 0, 9, and 19; recoveries were 100-103% of nominal concentrations (Table 7, p. 24). *EPA requires control(s) and at least 5 test concentrations; dilution factor not greater than 50%.* *OECD requires at least 5 test concentrations in a geometric series with a separation factor not exceeding 3.2.*
Solvent (type, percentage, if used)	Not specified	*EPA requires: solvent not to exceed 0.5 ml/L for static tests or 0.1 ml/L for flow-through tests. Acceptable solvents are dimethyl formamide, triethylene glycol, methanol, acetone and ethanol. OECD requires ≤ 0.1 ml/L*
Lighting	16:8 hour light/dark cycle.	Light intensity was approximately 1500 lux (p. 9). *EPA/OECD requires: 16 hours light, 8 hours dark.*
Feeding	Daphnids were fed daily with living single cell green algae (*Scenedesmus subspicatus*) at 0.2 mg TOC/100 mL test solution (1 x 10^8 cells/L).	On the first Friday (only), a three-fold amount was fed for the weekend. Thereafter, the daphnids were fed daily.

Parameter	Details	Remarks *Criteria*
Stability of chemical in the test system	Verified. The stability of JAU 6476 Technical in "old" test medium was verified on Days 2 (after 48 hours), 12 (after 72 hours), and 21 (after 72 hours). Samples were collected from the control (both sets), 0.56, 1.8 and 5.6 ppm test levels (the 18.0 ppm level was not sampled due to complete mortality after 24 hours of exposure). Recoveries were 86 to 106% of nominal concentrations (Table 9, p. 25).	Not all "old" treatment solutions (nominal 1.0, 3.2, and 10.0 ppm) were analytically verified during the exposure period.
Recovery of chemical: Frequency of measurement: LOD: LOQ:	101-109% of nominal "New" media sampled on Days 0, 9, and 19 Not reported 0.006 ppm	
Positive control {if used, indicate the chemical and concentrations}	see Reviewer's Comments section of this DER.	
Other parameters, if any	N/A	

2. Observations:

Table 2: Observations

Criteria	Details	Remarks *Criteria*
Data end points measured (list)	- Survival of first-generation daphnids - Number of young produced per adult per reproduction day - Total length - Observations of other effects	Dry weights should have been determined according to the EPA, but are not a requirement of OECD Guideline 211. *EPA requires:* *- Survival of first-generation daphnids,* *- Number of young produced per female,* *- Dry weight (recommended) and length (required)* of each first generation daphnid alive at the end of the test,* *- Observations of other effects or clinical signs.* **current requirement until the Agency provides specific guidance indicating otherwise (Pesticide Rejection Rate Analysis, p. 132).*
Observation intervals	Daphnids were observed daily. Offspring production was recorded daily beginning on Day 8 (first day of offspring production). Body length was determined at test termination.	
Were raw data included?	Yes	
Other observations, if any	N/A	

II. RESULTS AND DISCUSSION

A. MORTALITY:

After 21 days of exposure, mortality was 0% at the negative control, solvent control, and nominal 0.56 ppm level, 10% at the 1.0 ppm level, 60% at the 1.8 ppm level, and 100% at the ≥3.2 ppm levels (Tables 2.1 and 2.2, p. 17). A 21-day LC_{50} value was not determined. The NOAEC for mortality was 1.0 ppm.

Table 1: Effect of JAU 6476 Technical (Prothioconazole) on Growth and Survival of Daphnia sp.

Treatment, ppm Nominal Concn.	Mortality (Dead or Immobile)		Sum of Offspring per Parent	Offspring per Parent and Reproduction Day	Length (mm)
	No. Dead	%			
Negative control	0	0	73.8	5.84	4.13
Solvent control	0	0	80.3	6.70	4.06
0.56	0	0	67.2	5.62	3.99
1.0	1	10	64.3*	4.67*	3.81*
1.8	6	60	51.3*	3.99*	3.70*
3.2	10	100	---[1]	0.96*	---
5.6	10	100	---	---	---
10.0	10	100	---	---	---
18.0	10	100	---	---	---
NOAEC, ppm (nominal)	1.0		0.56	0.56	0.56
LOAEC, ppm (nominal)	1.8		1.0	1.0	1.0
MATC, ppm (nominal)	ND		ND	ND	ND
LC_{50}/EC_{50} (95% C.I.), ppm (nominal)	ND		ND	ND	ND

* Significantly different from pooled control ($\alpha = 0.05$).
[1] Offspring from parent animals which died during the test are excluded from the statistical evaluations of the sum of offspring per adult (p. 19).
ND - Not determined.

B. EFFECT ON REPRODUCTION AND GROWTH:

The first appearance of neonates occurred on Day 8 (Tables 1 through 9 of Appendix I, pp. 30-34). The mean first day of reproduction was 9.3, 10.0, 10.1, 9.6, 9.9, and 11.0 for the negative control, solvent control, nominal 0.56, 1.0, 1.8, and 3.2 ppm treatment groups, respectively (offspring produced at higher levels were not included due to significant treatment-related effects on parent survival). This endpoint was not statistically assessed by the study authors.

Offspring production was adversely affected by treatment at the ≥1.0 ppm treatment levels. At the 1.0 ppm level, aborted eggs were found, and at the 1.8 and 3.2 ppm levels, aborted eggs and dead offspring were found. The sum of offspring per parent averaged 73.8, 80.3, 67.2, 64.3, and 51.3 for the negative control, solvent control, nominal 0.56, 1.0, 1.8, and 3.2 ppm treatment groups, respectively (Table 4, p. 19). The number of offspring per parent and reproduction day averaged 5.84, 6.70, 5.62, 4.67, 3.99, and 0.96 for the negative control, solvent control, nominal 0.56, 1.0, 1.8, and 3.2 ppm treatment groups, respectively (Table 5, p. 20). For

both endpoints, data were significantly different from the pooled control at concentrations ≥1.0 ppm, according to the study author. The subsequent NOAEC was 0.56 ppm as reported by the study author.

A statistically-significant reduction compared to the pooled control in terminal lengths was observed at the ≥1.0 ppm test levels (p. 22 and Table 3, p. 18). Body lengths of surviving daphnids averaged 4.13, 4.06, 3.99, 3.81, and 3.70 mm for the negative control, solvent control, nominal 0.56, 1.0, and 1.8 ppm treatment groups, respectively. Treatment levels ≥3.2 ppm were not measured due to 100% mortality prior to test termination. The NOAEC for total length was 0.56 ppm.

C. REPORTED STATISTICS:

The sum of offspring per parent, the number of offspring per parent per reproduction day, and terminal lengths of surviving adult daphnia were statistically analyzed. For all endpoints, the negative control and solvent control groups were analyzed using the Kolmogorrof-Smirnov test for normality and the Bartlett's test for homogeneity of variances. The data were then subjected to ANOVA followed by the Student t-test. Negative and solvent control data were pooled for all statistical analyses due to a lack of significant differences for all endpoints.

All data sets were determined to be normal (Kolmogoroff-Smirnoff test) and homogenous (Bartlett's test), and were analyzed by ANOVA followed the Student's t-test. Statistical analyses were performed via "Multi-Test" statistical software for MS-DOS using nominal concentrations.

Mortality/immobilization:
NOAEC: 1.0 ppm
LOAEC: 1.8 ppm
LC_{50}: Not determined 95% C.I.: Not determined
Probit slope: Not determined

Time to First Brood Release
NOAEC: Not determined
LOAEC: Not determined

Sum of Offspring/Parent
NOAEC: 0.56 ppm
LOAEC: 1.0 ppm

Number of Offspring/Parent/Reproduction Day
NOAEC: 0.56 ppm
LOAEC: 1.0 ppm

Terminal Length
NOAEC: 0.56 ppm
LOAEC: 1.0 ppm

Endpoint(s) Affected: Mortality, offspring production, and terminal length
Most sensitive endpoint(s): Offspring production and terminal length

D. VERIFICATION OF STATISTICAL RESULTS:

For all endpoints, the solvent control and mean-measured concentrations were used for statistical analyses. The 21-day LC_{50} was calculated using the probit method via TOXANAL statistical software. The NOAEC for survival of adults compared to the solvent control was determined using Fisher's exact test. Reproduction (sum of offspring per parent, the number of offspring per parent per reproduction day, and the first day of reproduction) and terminal length data were determined to be normally distributed and the variances were homogeneous. NOAEC and LOAEC values for all endpoints were determined using ANOVA followed by William's multiple comparison test. The above statistical analyses were performed via TOXSTAT statistical software. All treatment levels ≥1.74 ppm were excluded from statistical verification for number of offspring/parent/reproduction day due to significant treatment-related effects on parental survival at levels ≥1.74 ppm; treatment levels ≥5.79 ppm were excluded for time to first brood and treatment levels above 1.02 ppm were excluded from analyses of sum of offspring/parent and terminal length due to adult mortality.

Mortality/immobilization:
NOAEC: 1.02 ppm
LOAEC: 1.74 ppm
LC_{50}: 1.57 ppm 95% C.I.: 1.24-2.05 ppm
Probit slope: 7.31 95% C.I.: 2.83-11.79

Time to First Brood Release
NOAEC: 3.37ppm
LOAEC: >3.37 ppm

Sum of Offspring/Parent
NOAEC: 1.02 ppm
LOAEC: >1.02 ppm

Number of Offspring/Parent/Reproduction Day
NOAEC: 0.51 ppm
LOAEC: 1.02 ppm

Terminal Length
NOAEC: 0.51 ppm
LOAEC: 1.02 ppm

Terminal Dry Weight
NOAEC: Not determined
LOAEC: Not determined

Endpoint(s) Affected: Mortality, reproduction, and terminal length
Most sensitive endpoint(s): Reproduction and terminal length

E. STUDY DEFICIENCIES:

This study fulfills the guideline requirements for an aquatic invertebrate life-cycle study using *daphnia magna* (§72-4b). This study is classified as ACCEPTABLE.

Dissolved oxygen levels declined at all but the negative control level in "old" test media sampled on Days 12,

14, 16, 19, and 21 (samples collected prior to renewal). Minimum levels of 3.2-3.3 mg/L were recorded on Day 21. Percent saturation levels were not provided for the "old" media, and no discussion of these findings was made by the study authors. However, although these levels are likely below 50% saturation, it is not likely that they existed for >48 hours, and therefore this deficiency is considered minor.

All other deficiencies were considered minor and did not affect the validity or acceptability of this study.

F. REVIEWER'S COMMENTS:

The reviewer re-calculated toxicity endpoints based on mean-measured concentrations based on all available measurements. Overall conclusions were similar although the NOAEC as determined by the reviewer's statistical analysis is lower. Presumably, this may be due to using only the solvent control for the analysis.

A method validation was conducted concurrently with test solution analysis. However, results from these injections were only provided in terms of peak area (Table E3, p. 65).

The study authors reported (p. 26) that an acute toxicity test was performed on October 19, 2000 under the same conditions using the reference substance $K_2Cr_2O_7$ (potassium dichromate), reagent grade (test concentrations: 0.75,1.00, 1.33, 1.78, 2.37 and 3.16 mg/L). The 24 hour EC_{50} (with 95% C.I.) was 1.55 (1.30-1.85) ppm, which was within the required range of 0.9-1.9 ppm. The gradient of the regression line (after Litchfield & Wilcoxon) was s = 1.45.

G. CONCLUSIONS:

The study is scientifically sound and fulfills the guideline requirements for an aquatic invertebrate life cycle test with the *Daphnia magna* (§72-4b). Although not all "old" treatment solutions were analytically verified in this static-renewal design during the exposure period, analyzed solutions indicated that the chemical was stable. Furthermore, the solvent was neither identified or quantified in the test media although there were no statistical differences between controls. Consequently, this study is classified as ACCEPTABLE. This study provides information that may be useful for risk assessment purposes. Mortality, reproduction, and growth were all affected by treatment with JAU 6476 Technical (Prothioconazole). Reproduction and growth were the most sensitive endpoints.

Mortality/immobilization:
NOAEC: 1.02 ppm
LOAEC: 1.74 ppm
LC_{50}: 1.57 ppm 95% C.I.: 1.24-2.05 ppm
Probit slope: 7.31 95% C.I.: 2.83-11.79

Time to First Brood Release
NOAEC: 3.37 ppm
LOAEC: >3.37 ppm

Sum of Offspring/Parent
NOAEC: 1.02 ppm
LOAEC: >1.02 ppm

Number of Offspring/Parent/Reproduction Day
NOAEC: 0.51 ppm
LOAEC: 1.02 ppm

Terminal Length
NOAEC: 0.51 ppm
LOAEC: 1.02 ppm

Terminal Dry Weight
NOAEC: Not determined
LOAEC: Not determined

Endpoint(s) Affected: Mortality, reproduction, and terminal length
Most sensitive endpoint(s): Reproduction and terminal length

III. REFERENCES:

No references were cited.

APPENDIX 1. OUTPUT OF REVIEWER'S STATISTICAL VERIFICATION:

LC50:
An Approximate LC50 for this set of data is: 1.567766

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS	
4	9.447589E-02	1.55496	1.164492	
2.01592				

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H	GOODNESS OF FIT PROBABILITY
8	.3752746	1	.9996271

SLOPE = 7.312179
95 PERCENT CONFIDENCE LIMITS = 2.832763 AND 11.7916

LC50 = 1.567766
95 PERCENT CONFIDENCE LIMITS = 1.242565 AND 2.05008

LC10 = 1.050989
95 PERCENT CONFIDENCE LIMITS = .5419436 AND 1.306492
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NOAEC and LOAEC for parent survival:

SUMMARY OF FISHER'S EXACT TESTS

GROUP	IDENTIFICATION	NUMBER EXPOSED	NUMBER DEAD	SIG (P=.05)
	CONTROL	10	0	
1	.51	10	0	
2	1.02	10	1	
3	1.74	10	6	*
4	3.37	10	10	*
5	5.79	10	10	*
6	10.5	10	10	*
7	15.6	10	10	*

Growth
Daphnia - Adult Length
File: pdapleng.dat Transform: NO TRANSFORM

ANOVA TABLE

SOURCE	DF	SS	MS	F
Between	3	0.524	0.175	4.082
Within (Error)	29	1.241	0.043	
Total	32	1.766		

Critical F value = 2.93 (0.05,3,29)
Since F > Critical F REJECT Ho: All equal

Daphnia - Adult Length
File: pdapleng.dat Transform: NO TRANSFORM

BONFERRONI t-TEST - TABLE 1 OF 2 Ho:Control<Treatment

GROUP	IDENTIFICATION	TRANSFORMED MEAN	MEAN CALCULATED IN ORIGINAL UNITS	T STAT	SIG
1	solv control	4.055	4.055		
2	0.51	3.985	3.985	0.757	
3	1.02	3.811	3.811	2.566	*
4	1.74	3.700	3.700	2.900	*

Bonferroni t table value = 2.23 (1 Tailed Value, P=0.05, df=29,3)

Daphnia - Adult Length
File: pdapleng.dat Transform: NO TRANSFORM

BONFERRONI t-TEST - TABLE 2 OF 2 Ho:Control<Treatment

GROUP	IDENTIFICATION	NUM OF REPS	Minimum Sig Diff (IN ORIG. UNITS)	% of CONTROL	DIFFERENCE FROM CONTROL
1	solv control	10			
2	0.51	10	0.207	5.1	0.070
3	1.02	9	0.212	5.2	0.244
4	1.74	4	0.273	6.7	0.355

Daphnia - Adult Length
File: pdapleng.dat Transform: NO TRANSFORM

WILLIAMS TEST (Isotonic regression model) TABLE 1 OF 2

GROUP	IDENTIFICATION	N	ORIGINAL MEAN	TRANSFORMED MEAN	ISOTONIZED MEAN
1	solv control	10	4.055	4.055	4.055
2	0.51	10	3.985	3.985	3.985
3	1.02	9	3.811	3.811	3.811
4	1.74	4	3.700	3.700	3.700

Daphnia - Adult Length
File: pdapleng.dat Transform: NO TRANSFORM

WILLIAMS TEST (Isotonic regression model) TABLE 2 OF 2

IDENTIFICATION	ISOTONIZED MEAN	CALC. WILLIAMS	SIG P=.05	TABLE WILLIAMS	DEGREES OF FREEDOM
solv control	4.055				
0.51	3.985	0.757		1.70	k= 1, v=29
1.02	3.811	2.565	*	1.78	k= 2, v=29
1.74	3.700	2.900	*	1.81	k= 3, v=29

s = 0.207
Note: df used for table values are approximate when v > 20.

Daphnia - Sum of Offspring per Parent
File: pdaphsum.dat Transform: NO TRANSFORMATION

ANOVA TABLE

SOURCE	DF	SS	MS	F
Between	2	1408.438	704.219	3.138
Within (Error)	26	5835.700	224.450	
Total	28	7244.138		

Critical F value = 3.37 (0.05,2,26)
Since F < Critical F FAIL TO REJECT Ho: All equal

Daphnia - Number of offspring per adult per repro day
prothio daphnia - offspring per repro day
File: pdaphrep.dat Transform: NO TRANSFORMATION

ANOVA TABLE

SOURCE	DF	SS	MS	F
Between	3	41.849	13.950	6.281
Within (Error)	36	79.953	2.221	
Total	39	121.802		

Critical F value = 2.92 (0.05,3,30)
Since F > Critical F REJECT Ho: All equal

prothio daphnia - offspring per repro day
File: pdaphrep.dat Transform: NO TRANSFORMATION

BONFERRONI t-TEST - TABLE 1 OF 2 Ho:Control<Treatment

GROUP	IDENTIFICATION	TRANSFORMED MEAN	MEAN CALCULATED IN ORIGINAL UNITS	T STAT	SIG
1	solv control	6.702	6.702		
2	.51	5.620	5.620	1.623	
3	1.02	4.665	4.665	3.056	*
4	1.74	3.986	3.986	4.075	*

Bonferroni t table value = 2.21 (1 Tailed Value, P=0.05, df=36,3)

prothio daphnia - offspring per repro day
File: pdaphrep.dat Transform: NO TRANSFORMATION

BONFERRONI t-TEST - TABLE 2 OF 2 Ho:Control<Treatment

GROUP	IDENTIFICATION	NUM OF REPS	Minimum Sig Diff (IN ORIG. UNITS)	% of CONTROL	DIFFERENCE FROM CONTROL
1	solv control	10			
2	.51	10	1.475	22.0	1.082
3	1.02	10	1.475	22.0	2.037
4	1.74	10	1.475	22.0	2.716

prothio daphnia - offspring per repro day
File: pdaphrep.dat Transform: NO TRANSFORMATION

WILLIAMS TEST (Isotonic regression model) TABLE 1 OF 2

GROUP	IDENTIFICATION	N	ORIGINAL MEAN	TRANSFORMED MEAN	ISOTONIZED MEAN
1	solv control	10	6.702	6.702	6.702
2	.51	10	5.620	5.620	5.620
3	1.02	10	4.665	4.665	4.665
4	1.74	10	3.986	3.986	3.986

prothio daphnia - offspring per repro day
File: pdaphrep.dat Transform: NO TRANSFORMATION

WILLIAMS TEST (Isotonic regression model) TABLE 2 OF 2

IDENTIFICATION	ISOTONIZED MEAN	CALC. WILLIAMS	SIG P=.05	TABLE WILLIAMS	DEGREES OF FREEDOM
solv control	6.702				
.51	5.620	1.623		1.69	k= 1, v=36
1.02	4.665	3.056	*	1.77	k= 2, v=36
1.74	3.986	4.075	*	1.79	k= 3, v=36

s = 1.490
Note: df used for table values are approximate when v > 20.

Daphnia - First Day of Reproduction

chronic tox prothio daphnia first brood
File: prodaph1.dat Transform: NO TRANSFORM

ANOVA TABLE

SOURCE	DF	SS	MS	F
Between	4	11.080	2.770	1.244
Within (Error)	45	100.200	2.227	
Total	49	111.280		

Critical F value = 2.61 (0.05,4,40)
Since F < Critical F FAIL TO REJECT Ho: All equal

chronic tox prothio daphnia first brood
File: prodaph1.dat Transform: NO TRANSFORM

BONFERRONI t-TEST - TABLE 1 OF 2 Ho:Control<Treatment

GROUP	IDENTIFICATION	TRANSFORMED MEAN	MEAN CALCULATED IN ORIGINAL UNITS	T STAT	SIG
1	solv control	10.000	10.000		
2	0.56	10.100	10.100	-0.150	
3	1	9.600	9.600	0.599	
4	1.8	9.900	9.900	0.150	
5	3.2	11.000	11.000	-1.499	

Bonferroni t table value = 2.33 (1 Tailed Value, P=0.05, df=40,4)

EAD Assessment of USEPA DER

Reviewer: Émilie Larivière (#1269); PMRA Date: August 23, 2005

PMRA Submission Number: 2004-0843

Study Type: Chronic (Life-Cycle) Toxicity to *Daphnia* sp.

Hendel, B., and H. Sommer. 2001. Influence of JAU6476 (tech.) on the Reproduction Rate of Water Fleas. Unpublished study performed by Bayer AG Crop Protection Business Group, Crop Protection Development, Leverkusen, Germany. Laboratory ID No. E 3211982-6; Report No. HDB/rDm67. Study sponsored by Bayer CropScience, Research Triangle Park, NC. Study initiated November 8, 2000 and completed April 11, 2001.

PMRA DATA CODE	9.3.3
EPA DP Barcode	D303488
OECD Data Point	IIA 8.3.2.1
EPA MRID	46246028
EPA Guideline	§72-4b

Reviewing Agency: U.S. EPA

EAD Executive Summary:

The 21-day-chronic toxicity of JAU 6476 Technical (98.8% purity; Prothioconazole) to *Daphnia magna* was studied under static-renewal conditions. The study was conducted following OECD Guideline 211, and in compliance with German and OECD Principles of GLP. Nominal concentrations were 0 (negative and solvent controls), 0.56, 1.0, 1.8, 3.2, 5.6, 10.0, and 18.0 mg a.i./L, which corresponded to mean-measured concentrations of 0 (controls), 0.51, 1.02, 1.74, 3.37, 5.79, 10.5, and 15.6 mg a.i./L. The mean measured concentrations were based on available measurement data. Eight media renewals were performed. "New" test media was sampled from all treatment levels at 0, 9, and 19 Days, and "old" test media (after 48 or 72 hours) was sampled from the control (both) and alternating toxicant levels (0.56, 1.8, and 5.6 mg a.i./L levels) on Days 2, 12, and 21 (the 18.0 mg a.i./L level was not sampled due to complete mortality on Day 1). Recoveries for all samples ranged from 86 to 109% of nominal concentrations indicating precision and stability. Toxicity endpoints were re-calculated using mean-measured concentrations; the study author used nominal concentrations.

After 21 days of exposure, mortality was 0% at the control, solvent control, and mean measured 0.51 mg a.i./L treatment level, 10% at the 1.02 mg a.i./L level, 60% at the 1.74 mg a.i./L level, and 100% at the ≥3.37 mg a.i./L levels. The 21-day LC_{50} value (with 95% C.I.) was 1.57 (1.24-

2.05) mg a.i./L and the NOAEC for mortality was 1.02 mg a.i./L.

The mean first day of reproduction was 9.3, 10.0, 10.1, 9.6, 9.9, and 11.0 for the negative control, solvent control, mean-measured 0.51, 1.02, 1.74, and 3.37 mg a.i./L treatment groups, respectively (no offspring were produced at higher levels). No significant differences were observed between the treatment levels and the solvent control. The sum of offspring per parent averaged 73.8, 80.3, 67.2, 64.3, and 51.3 for the negative control, solvent control, 0.51, 1.02, 1.74, and 3.37 mg a.i./L treatment groups, respectively. The number of offspring per parent and reproduction day averaged 5.84, 6.70, 5.62, 4.67, 3.99, and 0.96 for the negative control, solvent control, 0.51, 1.02, 1.74, and 3.37 mg a.i./L treatment groups, respectively. The NOAEC values were >3.37, 1.02 and 0.51 mg a.i./L for the time to first brood, the sum of offspring per parent and the number of offspring produced/parent/reproductive day, respectively.

A statistically-significant reduction compared to the solvent control in total length was observed at the ≥1.02 mg a.i./L test levels. Body lengths of surviving daphnids averaged 4.13, 4.06, 3.99, 3.81, and 3.70 mm for the negative control, solvent control, 0.51, 1.02, and 1.74 mg a.i./L treatment groups, respectively. The NOAEC for total length was 0.51 mg a.i./L.

Result Synopsis:

Test Organism Age (eg. 1st instar): First instar, <24 hours old
Test Type (Flow through, Static, Static Renewal): Static-renewal

Mortality/immobilization:
NOAEC: 1.02 mg a.i./L
LOAEC: 1.74 mg a.i./L
LC_{50}: 1.57 mg a.i./L 95% C.I.: 1.24-2.05 mg a.i./L
Probit slope: 7.31 95% C.I.: 2.83-11.79

Time to First Brood Release
NOAEC: 3.37 mg a.i./L
LOAEC: >3.37 mg a.i./L (treatment levels >3.37mg a.i./L produced no offspring)

Sum of Offspring/Parent
NOAEC: 1.02 mg a.i./L
LOAEC: >1.02 mg a.i./L (treatment levels >1.02 mg a.i./L had no surviving adults after 21 days and were not included in this statistical analysis)

Number of Offspring/Parent/Reproduction Day
NOAEC: 0.51 mg a.i./L
LOAEC: 1.02 mg a.i./L

Total Length

NOAEC: 0.51 mg a.i./L
LOAEC: 1.02 mg a.i./L

Endpoint(s) Affected: Mortality, reproduction, and terminal length
Most sensitive endpoint(s): Reproduction and terminal length

1. The appropriate PMRA information (PMRA Submission Number, PMRA Data Code, PMRA company code, PMRA reviewer, PMRA active ingredient code, PMRA use site category, OECD data point) was added to the DER. Information on the chemical name (CAS name and synonym) available from the PMRA Chemistry review was also added.

2. The water hardness and the pH were within the limits recommended by the OECD guideline. A comment was added in the Comments section in Table 1, under Water parameters for clarification purposes.

3. The OECD guideline requires that at least 10 animals, held individually, be used in semi-static tests. The Remark on test design in Table 1 for the Number of Organisms was modified to clarify that eventhough the design did not follow EPA guidance, it was conducted according to OECD Guideline 211.

4. OECD Guideline 211 requires that the dissolved oxygen concentration be above 3 mg/L at the beginning and during the test. The dissolved oxygen levels measured ranged from 7.2-9.4 mg/L in freshly prepared media and ranged from 3.2-9.0 mg/L in 48- or 72-hour old media.

5. Measuring old solutions in all treatment vessels is not required according to OECD guideline 211 if the concentration is expected to remain within ±20 percent of the nominal concentration. As a minimum, the highest and lowest concentrations are to be analysed when freshly prepared and at the time of renewal on one occasion during the first week of the test and repeated at weekly intervals thereafter.

6. Measurements of dry weight are not required under OECD Guideline 211. A clarification has been added to the Remarks column in Table 2.

7. The EAD reviewer verified the statistical analyses for time to first brood, adult length, sum of offspring/parent and number of offspring/parent/reproduction day. The NOAEC was determined using ANOVA when assumptions of normality and homogeneity of variances were met. Kruskal-Wallis One-Way ANOVA on Ranks was run otherwise. The analyses for time to first brood and for the sum of offspring/parent/reproduction day were conducted using treatments up to and including 3.37 mg a.i./L, as all individuals up to this treatment level produced young. The 3.37 mg a.i./L and higher treatment levels were not included in the analysis for sum of offspring/parent as no adults survived to the end of the study. The outcome of analyses

performed by the EAD reviewere were the same as those of the EPA reviewer. Probit analysis was used to estimate the LC_{50}/EC_{50} value for adult mortality/immobility. The results of the EAD reviewer were almost identical to the LC_{50}/EC_{50} value reported by the EPA reviewer. The value reported by the EPA reviewer is acceptable.

Study Acceptability: The study is scientifically sound, and fulfills the guideline requirements for an aquatic invertebrate life cycle test with the *Daphnia magna*.

Statistical Verification Performed by EAD reviewer

Sum of offspring/parent

One Way Analysis of Variance Tuesday, August 23, 2005, 14:46:55

Data source: Data 1 in Notebook

Normality Test: Passed (P > 0.200)

Equal Variance Test: Passed (P = 0.644)

Group Name	N	Missing	Mean	Std Dev	SEM
solvent	10	0	80.300	18.031	5.702
0.56 mg/L	10	0	67.200	15.789	4.993
1.0 mg/L	9	0	64.333	9.124	3.041
1.8 mg/L	4	0	51.250	16.297	8.148

Source of Variation	DF	SS	MS	F	P
Between Groups	3	2755.732	918.577	4.016	0.017
Residual	29	6632.450	228.705		
Total	32	9388.182			

The differences in the mean values among the treatment groups are greater than would be expected by chance; there is a statistically significant difference (P = 0.017).

Power of performed test with alpha = 0.050: 0.647

The power of the performed test (0.647) is below the desired power of 0.800.
You should interpret the negative findings cautiously.

Multiple Comparisons versus Control Group (Dunnett's Method) :

Comparisons for factor: treatment

Comparison	Diff of Means	q'	P	P<0.050
solvent vs. 1.8 mg/L	29.050	3.247	--	Yes
solvent vs. 1.0 mg/L	15.967	2.298	--	No
solvent vs. 0.56 mg/L	13.100	1.937	--	Do Not Test

Note: The P values for Dunnett's and Duncan's tests are currently unavailable except for reporting that the P's are greater or less than the critical values of .05 and .01.

A result of "Do Not Test" occurs for a comparison when no significant difference is found between two means that enclose that comparison. For example, if you had four means sorted in order, and found no difference between means 4 vs. 2, then you would not test 4 vs. 3 and 3 vs. 2, but still test 4 vs. 1 and 3 vs. 1 (4 vs. 3 and 3 vs. 2 are enclosed by 4 vs. 2: 4 3 2 1). Note that not testing the enclosed means is a procedural rule, and a result of Do Not Test should be treated as if there is no significant difference between the means, even though one may appear to

exist.

Number of offspring/parent/reproduction day

One Way Analysis of Variance Tuesday, August 23, 2005, 14:51:56

Data source: Data 1 in Notebook

Normality Test: Passed (P = 0.012)

Equal Variance Test: Passed (P = 0.617)

Group Name	N	Missing	Mean	Std Dev	SEM
solvent	10	0	6.702	1.449	0.458
0.56 mg/L	10	0	5.620	1.176	0.372
1.0 mg/L	10	0	4.665	1.587	0.502
1.8 mg/L	10	0	3.986	1.698	0.537
3.2 mg/L	10	0	0.962	0.855	0.270

Source of Variation	DF	SS	MS	F	P
Between Groups	4	188.482	47.121	24.504	<0.001
Residual	45	86.534	1.923		
Total	49	275.016			

The differences in the mean values among the treatment groups are greater than would be expected by chance; there is a statistically significant difference (P = <0.001).

Power of performed test with alpha = 0.050: 1.000

Multiple Comparisons versus Control Group (Dunnett's Method) :

Comparisons for factor: treatments

Comparison	Diff of Means	q'	P	P<0.050
solvent vs. 3.2 mg/L	5.740	9.256	--	Yes
solvent vs. 1.8 mg/L	2.716	4.380	--	Yes
solvent vs. 1.0 mg/L	2.037	3.285	--	Yes
solvent vs. 0.56 mg/L	1.082	1.745	--	No

Note: The P values for Dunnett's and Duncan's tests are currently unavailable except for reporting that the P's are greater or less than the critical values of .05 and .01.

Time to First Brood

One Way Analysis of Variance Tuesday, August 23, 2005, 15:25:09

Data source: Data 1 in Notebook

Normality Test: Failed (P = <0.001)

Test execution ended by user request, ANOVA on Ranks begun

Kruskal-Wallis One Way Analysis of Variance on Ranks Tuesday, August 23, 2005, 15:25:09

Data source: Data 1 in Notebook

Group	N	Missing	Median	25%	75%
solvent	10	0	10.000	9.000	10.000
0.56 mg/L	10	0	10.000	9.000	11.000
1.0 mg/L	10	0	9.000	9.000	9.000
1.8 mg/L	10	0	9.000	9.000	10.000
3.2 mg/L	10	0	12.000	9.000	13.000

H = 4.949 with 4 degrees of freedom. (P = 0.293)

The differences in the median values among the treatment groups are not great enough to exclude the possibility that the difference is due to random sampling variability; there is not a statistically significant difference (P = 0.293)

EPA PROBIT ANALYSIS PROGRAM
USED FOR CALCULATING LC/EC VALUES
Version 1.5

Adult mortality

Number Conc.	Exposed	Observed Number Resp.	Proportion Responding	Proportion Responding	Predicted Proportion Adjusted for Controls
0.5100	10	0	0.0000	0.0000	0.0002
1.0200	10	1	0.1000	0.1000	0.0861
1.7400	10	6	0.6000	0.6000	0.6297
3.3700	10	10	1.0000	1.0000	0.9925
5.7900	10	10	1.0000	1.0000	1.0000
10.5000	10	10	1.0000	1.0000	1.0000
15.6000	10	10	1.0000	1.0000	1.0000

Chi - Square for Heterogeneity (calculated) = 0.140
Chi - Square for Heterogeneity

(tabular value at 0.05 level) = 11.070

Mu = 0.195281
Sigma = 0.136758

Parameter	Estimate	Std. Err.	95% Confidence Limits
Intercept	3.572069	0.524455	(2.544138, 4.600000)
Slope	7.312183	2.285208	(2.833175, 11.791191)

Theoretical Spontaneous Response Rate = 0.0000

daphniachronic

Estimated LC/EC Values and Confidence Limits

Point	Exposure Conc.	95% Confidence Limits Lower	Upper
LC/EC 1.00	0.754	0.238	1.028
LC/EC 5.00	0.934	0.406	1.195
LC/EC 10.00	1.047	0.537	1.303
LC/EC 15.00	1.131	0.646	1.388
LC/EC 50.00	1.568	1.243	2.050
LC/EC 85.00	2.173	1.753	4.131
LC/EC 90.00	2.347	1.861	4.981
LC/EC 95.00	2.632	2.023	6.608
LC/EC 99.00	3.262	2.345	11.332