### Data Evaluation Report on the Reproductive Effects of AE 0172747 Technical on Mallard

Duck (Anas p PMRA Submissi			EPA MRID Number 466955-06
Data Requireme	ent:	PMRA Data Code EPA DP Barcode OECD Data Point EPA MRID EPA Guideline	{} D325337 {
Test material: Common name	AE 0172747 AE 0172747		<b>Purity:</b> 93.9%
Chemical name:		2-[2-Chloro-4-mesyl-3-((2,2,2,2-[2-Chloro-4-(methylsulfon cyclohexanedione	2-trifluoroethoxy)methyl)benzoyl]cyclohexane-1,3-dione yl)-3-[(2,2,2-trifluoroethoxy)methyl]-benzoyl]-1,3-
	CAS No.	335-104-84-2	
	Synonyms	Bayer AE 0172747	
Primary Review			Signature: Christia E. Padore.  Date: 6/6/06
Staff Scientist,	Dynamac Cor	poration	Date: 6/6/06
Secondary Revi Senior Scientist		. Myers Environmental Inc.	Signature: Jen 5 Mynn Date: 6/10/06
Primary Review EPA/OPP/EFE			Date: {
Secondary Rev {EPA/OECD/P		nette Martinez	Date: 7/19/06 Off
Reference/Subi	mission No.:	{}	
Company Code Active Code Use Site Catego	{		

Date Evaluation Completed: XX-XX-XXXX

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EPA PC Code

<u>CITATION</u>: Temple, D.L., *et al.* 2005. AE 0172747: A Subchronic Toxicity Study with the Mallard. Unpublished study performed by Wildlife International Ltd., Easton, MD. Laboratory Project No. 149-204. Study submitted by Bayer CropScience, Research Triangle Park, NC. Study initiated December 7, 2004 and submitted July 6, 2005.

DISCLAIMER: This document provides guidance for EPA and PMRA reviewers on how to complete a data evaluation record after reviewing a scientific study concerning the sub-chronic effects of a pesticide on avian species. It is not intended to prescribe conditions to any external party for conducting this study nor to establish absolute criteria regarding the assessment of whether the study is scientifically sound and whether the study satisfies any applicable data requirements. Reviewers are expected to review and to determine for each study, on a case-by-case basis, whether it is scientifically sound and provides sufficient information to satisfy applicable data requirements. Studies that fail to meet any of the conditions may be accepted, if appropriate; similarly, studies that meet all of the conditions may be rejected, if appropriate. In sum, the reviewer is to take into account the totality of factors related to the test methodology and results in determining the acceptability of the study.



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#### **EXECUTIVE SUMMARY**

The sub-chronic/one-generation reproductive toxicity of AE 0172747 Technical to 16 pairs per level of 33-week old mallard duck (*Anas platyrhynchos*) was assessed over approximately 8 weeks. AE 0172747 Technical was administered to the birds in the diet at nominal concentrations of 0 (vehicle control), 22, 65, and 185 mg ai/kg dw diet. Mean-measured concentrations were <5 (<LOD, control), 22.4, 65.4, and 198 mg ai/kg diet, respectively. The NOAEC could not be determined (<22.4 mg ai/kg diet) based on statistically-significant reductions in egg production at the lowest treatment level and female body weight gain at all treatment levels. Male body weight gain was significantly reduced at the two highest treatment levels. Food consumption was not reduced from control at any treatment level. These were the only endpoints monitored in this study.

This study deviated significantly from standard methods and appeared to be conducted for supplemental data purposes. Therefore, this study does not satisfy the guideline requirement for a mallard duck (*Anas platyrhynchos*) reproductive toxicity study. Furthermore, because adequate frozen storage stability data were not provided and ancillary factors confounded the ability to assess treatment related effects on egg production, the utility of the data is severely limited.

This study is not scientifically sound, does not satisfiy guideline requirements, and is thus classified as INVALID.

#### **Results Synopsis**

Test Organism Size/Age (mean Weight): 33-weeks old; 975-1388 g (combined sexes)

NOAEC: <22.4 mg ai/kg diet LOAEC: 22.4 mg ai/kg diet

Endpoint(s) Affected: body weights of males and females and egg production

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Duck (Anas platyrhynchos)

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#### I. MATERIALS AND METHODS

**GUIDELINE FOLLOWED:** 

The study protocol was based on procedures outlined in the U.S. EPA *Pesticide Assessment Guidelines*, §71-4; the U.S. EPA Ecological Effects Test Guideline OPPTS No. 850.2300; OECD Guideline No. 206; and ASTM Standard E1062-86. Deviations from OPPTS 850.2300 included:

- 1. Mortality of the adult birds during acclimation was not reported.
- The study design differed significantly from guidance. Most notable differences included the lack of a preegg-laying exposure period, and failure to monitor numerous required reproductive endpoints (since newlylaid eggs were counted and discarded). THIS AFFECTS THE VALIDITY OF THE STUDY.
- 3. Pen floor size was significantly less (3375 cm²/duck) than recommended (at least 10,000 cm²/duck). As cages were much smaller than recommended, documentation that reproductive parameters and health of birds are not adversely affected should be provided.
- The actual or expected field residue level was not reported, so it was unknown if the concentration range included this level.
- It was not reported if the acetone used in preparing the treated feed was allowed to completely evaporate prior to offering.
- Although adequate ambient 7-day feeder trough stability was demonstrated, frozen storage stability data were
  not generated. Premix batches were prepared every 3-4 weeks, and stored frozen in plastic bags until
  needed. THIS AFFECTS THE VALIDITY OF THE STUDY
- 7. Handling the birds for body weight measurements during the egg production phase may have impacted egg production results. Six of the 16 pair in the 22 mg ai/kg diet group appeared to go out of production following the second body weight measurements, and three hens in the 65 mg ai/kg level and two control hens appeared to be similarly impacted. THIS AFFECTS THE VALIDITY OF THE STUDY.

**COMPLIANCE:** 

Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. This study was conducted in compliance with GLP standards as published by the U.S. EPA 40 CFR Part 160 with the following exception: periodic analyses of water and feed for potential contaminants.

#### A. MATERIALS:

1. Test Material

AE 0172747 Technical

Description:

Beige powder

Lot No./Batch No.:

OP 2250027 / PFI 0215

**Purity:** 

93.9%

Stability of compound

<b>PMRA</b>	Subm	ission	Nun	nber :	<b></b> .

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Stability of compound under test conditions:

Stability was verified at all treatment levels under actual use conditions.

Samples were assessed after 7 days of ambient feeder storage during Week

1. Recoveries were 90-100% of initial measured concentrations.

(OECD recommends water solubility, stability in water and light, pKa, Pow, and vapor pressure of test compound)

Storage conditions of

test chemicals:

Ambient conditions

Physicochemical properties of AE 0172747 Technical.

Thysicochemical properties of AE 01/2/47 Technical.			
Parameter	Values	Comments	
Water solubility at 20°C	Not reported		
Vapor pressure	Not reported		
UV absorption	Not reported		
pKa	Not reported		
Kow	Not reported		

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#### 2. Test organism:

Table 1: Test organism.

Parameter	Details	Remarks Criteria
Species (common and scientific names):	Mallard duck (Anas platyrhynchos)	Birds were from the same hatch, and were phenotypically indistinguishable from wild birds.
		Recommended species include a wild waterfowl species, preferably the mallard (Anas platyrhynchos) or an upland game species, preferably the northern bobwhite (Colinus virginianus)
Age at Study Initiation:	33 weeks old	It was stated that birds were approaching their first breeding season.
	_	Birds approaching their first breeding season should be used.
Body Weight: (mean and range)	Males: Overall range (n=64) 975 to 1266 g, with group means of 1113 to 1137 g.  Females: Overall range (n=64) of 1003 to 1388 g, with group means	Body weights were recorded at weeks -2, 0, 2, 4, 6, and 8 (study termination).
	of 1133 to 1184 g.	Body weights should be recorded at test initiation and at biweekly intervals up to week eight or up to the onset of egg laying and at termination.
Source:	Whistling Wings, Inc. 113 Washington Street Hanover, IL	All birds should be from the same source.

#### **B. STUDY DESIGN:**

#### 1. Experimental Conditions

- a. Range-finding study: Test concentrations were selected in consultation with the Sponsor, based upon the results of a mallard reproduction study (Wildlife International Ltd., Project No. 149-194; concurrently-submitted as MRID 466955-05).
- b. Definitive Study

Table 2	Ex	perimental	Parameters.

Parameter	Details	Remarks <i>Criteria</i>
Acclimation period:  Conditions (same as test or not):	Approx. 12 weeks total  Generally the same except for lighting. For the first 7 weeks of acclimation, the ducks were maintained on an 8-hour light/16-hour dark schedule. For the next 3 weeks, lighting was increased to 17 hours light/day to stimulate egg production. For the last 2 weeks of acclimation and during	The study author reported that immediately prior to test initiation, all birds were examined for physical injuries and general health, and that birds that did not appear healthy, either due to injury or inability to acclimate to laboratory conditions, or were outside the desired weight range for the test, were excluded from the study.
Feeding:	the definitive study, the lighting was increased an additional 15 minutes to further stimulate egg production.  Wildlife International Ltd. Game Bird Ration formulated by Cargill Animal Nutrition (Shippensburg, PA) and tap water were provided ad libitum.	Recommended observation period includes a 2-3 week health observation period prior to selection of birds for treatment. Generally, birds should be healthy without excess mortality. Feeding should be ad libitum, and sickness, injuries or mortality should be noted.
Health (any mortality observed):	Mortality not reported.	

Parameter	Details	Remarks
1 at ameter	Details	Criteria
<u>Test duration</u> pre-laying exposure: egg-laying exposure: withdrawal period, if used:	0 weeks 8 weeks N/A	Purposely, egg laying had commenced 2 weeks prior to the start of treatment.
willidrawai period, il used:	IV/A	Recommended pre-laying exposure duration: At least 10 weeks prior to the onset of egg-laying. Recommended exposure duration with egg-laying: At least 10 weeks. Recommended withdrawal period: If reduced reproduction is evident, a withdrawal period of up to 3 weeks should be added to the test phase.
Pen (for parental and offspring) size:	Parents (one pair) were housed in battery cages measuring 75 x 90 x 45 cm high. Offspring – N/A.	Pen floor size was significantly less (3375 cm <sup>2</sup> /duck) than recommended (at least 10,000 cm <sup>2</sup> /duck). As cages were much smaller than recommended,
construction materials:	Vinyl-coated wire mesh.  16 parental pens/treatment level.	documentation that reproductive parameters and health of birds are not adversely affected should be provided.
Number of his desired		Pens Pens should have adequate room and be arranged to prevent crosscontamination.  Materials Recommended materials include nontoxic material and nonbinding material, such as galvanized steel.  Number At least 5 replicate pens should be used for mallards housed in groups of 7. For other arrangements, at least 12 pens should be used, but considerably more may be used if birds are kept in pairs. Chicks should be housed according to parental grouping.
Number of birds per pen (male:female)	2 birds/pen (1 male:1 female)	One male and one female per pen should be used. For quail, one male and two females should be used. For ducks, two males and five females should be used.

Parameter	Details	Remarks  Criteria
Number of pens per group/treatment negative control: solvent control: treated:	N/A 16 pens 16 pens/treatment	At least 12-16 pens should be used, but considerably more if birds are kept in pairs.
Test concentrations (mg ai/kg diet) nominal: measured:	0 (vehicle control), 22, 65, and 180 mg ai/kg diet <5 ( <lod, 198="" 22.4,="" 65.4,="" ai="" and="" control),="" diet<="" kg="" mg="" td=""><td>Dietary concentrations were adjusted for purity of the test substance. Measured concentrations were determined at all levels during Weeks 1, 3, and 6. Mean-measured concentrations had coefficients of variation of 1.9-4.4% indicating relative precision among the samples.  Recommended test concentrations include at least two concentrations other than the control; three or more will provide a better statistical analysis. The highest test concentrations should show a significant effect or be at or above the actual or expected field residue level.</td></lod,>	Dietary concentrations were adjusted for purity of the test substance. Measured concentrations were determined at all levels during Weeks 1, 3, and 6. Mean-measured concentrations had coefficients of variation of 1.9-4.4% indicating relative precision among the samples.  Recommended test concentrations include at least two concentrations other than the control; three or more will provide a better statistical analysis. The highest test concentrations should show a significant effect or be at or above the actual or expected field residue level.
Maximum labeled field residue anticipated and source of information:	Not reported	The highest test concentrations should show a significant effect or be at or above the actual or expected field residue level. The source (i.e., maximum label rate in lb ai/A and ppm), label registration no., label date, and site should be cited]
Solvent/vehicle, if used type: amount:	Acetone and corn oil Approx. 0.8% (v:w - both)	Recommended solvents include corn oil or other appropriate vehicle not more than 2% of diet by weight

D	D. d. illa	Remarks	
Parameter	Details	Criteria	
Was detailed description and nutrient analysis of the basal diet provided? (Yes/No)	Yes. The basal ration contained at least 27% protein and 2.5% fat, and no more than 5% fiber. The diet was supplemented with limestone, to increase the calcium level to approximately 3%.	A commercial breeder feed or an equivalent that is appropriate for the test species is recommended.	
Preparation of test diet	The appropriate amount of test material was dissolved in acetone and corn oil using a magnetic stir plate, and quantitatively	It was not reported if the acetone (175 ml per premix) was allowed to completely evaporate prior to offering.	
	transferred to a bowl containing a portion of basal feed. The contents of the bowl were mixed on a Hobart mixer for approximately 15 minutes. The remainder of the basal ration was added, and the contents mixed for an additional 10 minutes. Premixes were prepared every 3-4 weeks, and if not used immediately after mixing, they were stored frozen in plastic bags.	A premixed diet containing the test substance should be mechanically mixed with basal diet. If an evaporative vehicle is used, it should be completely evaporated prior to feeding.	
	As needed, the appropriate premix was combined with additional basal ration and limestone and mixed in a Patterson-Kelly Twin Shell Blender for approximately 20 minutes.		
Indicate whether stability and homogeneity of test material in diet determined (Yes/No)	Yes		
Were concentrations in diet verified by chemical analysis?	Yes		

Parameter	Details	Remarks Criteria
Did chemical analysis confirm that diet was stable and homogeneous?	Yes, for ambient 7-day feeder storage. Frozen storage stability data were not generated (premix batches were prepared every 3 to 4 weeks and were stored frozen until needed).	Stability was assessed in treated feed prepared at all treatment levels after 7 days of ambient feeder storage during Week 1. Recoveries averaged 100, 100, and 90% of initial concentrations for the 22, 65, and 185 mg ai/kg diet levels, respectively.
	Yes	Homogeneity was assessed in treated feed prepared on Day 0 of Week 1 at the 22 mg ai/kg diet level. Six samples per level were collected: one sample per side from the top, middle, and bottom of the batch. The calculated coefficients of variation (CV=RSD) was 2.86%.
Feeding and husbandry	Feeding and husbandry conditions appeared to be adequate, given guideline recommendations.	
Test conditions (pre-laying) temperature: relative humidity: photoperiod:	20.2 ± 0.5 °C  37 ± 11%  8 hr light/day during 7-week acclimation; 17 hr light/day	Temperature and humidity were for the adult room during the entire study. The air handling system provided up to 15 room air volumes every hours.  Light intensity averaged
	during 3-week pre-egg laying period; 17.25 hr light/day during 2-week pre-treatment egg-laying period and treatment period.	approximately 244 lux (or 23 foot candles).  Recommended temperature: about 21°C (70°F) Recommended relative humidity: about 55% Recommended lighting First 8 weeks: 7 h per day. Thereafter: 16-17 h per day. At least 6 foot-candles are recommended at bird level.

Parameter	Details	Remarks Criteria
Egg Collection and Incubation		
Egg collection and storage collection interval: storage temperature: storage humidity;	Daily N/A	Eggs were discarded following counting.  Eggs should be collected daily; recommended egg storage temperature is approximately 16°C (61°F); recommended humidity is approximately 65%.  Recommended collection interval: daily
Were eggs candled for cracks prior to setting for incubation?	N/A	Eggs should be candled on day 0
Were eggs set weekly?	N/A	
When candling was done for fertility?	N/A	Quail: approx. day 11 Ducks: approx. day 14
When the eggs were transferred to the hatcher?	N/A	Bobwhite: usually day 21 Mallard: usually day 23
Hatching conditions temperature: humidity: photoperiod:	N/A	Recommended temperature is 39°C (102°F) Recommended humidity is 70%
Day the hatched eggs were removed and counted	N/A	Eggs for bobwhite should be removed on day 24; for mallard on day 27
Were egg shells washed and dried for at least 48 hrs before measuring?	N/A	

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Parameter	Details	Remarks	
1 at ameter	Details	Criteria	
Egg shell thickness no. of eggs used: intervals: mode of measurement:	N/A	Newly hatched eggs should be collected at least once every two weeks. Thickness of the shell plus membrane should be measured to the nearest 0.01 mm with 3 - 4 measurements per shell.	
Reference chemical, if used	None used		

#### 2. Observations:

Parameter	Details	Remarks
Parameters measured		
Parental (mortality, body weight, mean feed	- mortality	All adult birds were subjected to gross necropsy.
Egg collection and subsequent development (no. of eggs laid, no. of eggs cracked, shell thickness, no. of eggs set, no. of viable embryos, no. of live 3 week embryos, no. hatched, no. of 14-day survivors, average weight of 14-d old survivors, mortality, gross pathology, others)	- body weight - food consumption - signs of toxicity - necropsy - eggs laid	Recommended endpoints measured include:  Eggs laid/pen Eggs cracked/pen Eggs set/pen Viable embryos/pen Live 3-week embryos/pen Normal hatchlings/pen 14-day-old survivors/pen Weights of 14-day-old survivors (mean per pen) Egg shell thickness Food consumption (mean per pen) Initial and final body weight (mean per pen)
Indicate if the test material was regurgitated	No indications of dietary regurgitation.	

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Parameter	Details	Remarks
Observation intervals (for various parameters)	Parental mortality and signs of toxicity were recorded once daily. Parental body weights were recorded at weeks -2 (beginning of the pre-treatment egg laying period), 0 (test initiation), 2, 4, 6, and 8 (adult termination). Parental food consumption was measured weekly throughout the test.	Body weights and food consumption should be measured at least biweekly
Were raw data included?	Yes	

#### II. RESULTS AND DISCUSSION:

#### A. MORTALITY:

No mortalities were observed in the control, 63, or 185 mg ai/kg diet groups. However, one incidental mortality occurred in the 22 mg ai/kg diet group. The single mortality was a female (pen 334) that was found dead during Week 2 without having exhibited prior clinical signs of toxicity. Necropsy revealed lesions on the right foot, cloudy air sacs, a firm, pale, and mottled liver, clear yellow fluid in the abdominal cavity, a regressing ovary, and cystic follicles of the reproductive tract. Necropsy of the pen-mate revealed small testes, but was otherwise unremarkable. This mortality was not considered to be related to treatment, and the NOAEC for adult mortality was 185 mg ai/kg diet.

Table 4: Effect of AE 0172747 Technical on Mortality of Mallard Duck.

Treatment		Observation Period								
(mg ai/kg diet) Mean-measured (and Nominal)	V	Veek 2	Week 4			Week 8				
Concentrations	No Male	. Dead Female	Nale Nale	o. Dead Female	N Male	o. Dead Female				
Control	0	0	0	0	0	0				
22.4 (22)	0	1	0	1	0	1				
65.4 (65)	0	0	0	0	0	0				
198 (185)	0	0	0	0	0	0				

#### **B. REPRODUCTIVE AND OTHER ENDPOINTS:**

Abnormal Effects/Behavior: No overt signs of toxicity were observed at any treatment level. Incidental clinical observations included those normally associated with injuries and pen wear; effects included feather loss and molting, food and head lesions, and occasional lameness. The NOAEC for clinical signs of toxicity was 185 mg ai/kg diet.

Food Consumption: No apparent treatment-related effects on feed consumption were observed at any treatment level. Although there was a statistically-significant increase (of 126% of control value) in feed consumption during Page 13 of 38

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Week 4 at the 65 mg ai/kg diet level, the difference was slight, and was neither concentration responsive nor consistent. The NOAEC for feed consumption was 250 mg ai/kg diet.

Body Weight: Slight, but statistically-significant reductions in body weights were observed in drakes from all treatment levels at Week 2, and continued throughout the study at the 185 mg ai/kg diet level. As body weights of drakes from the 22 and 65 mg ai/kg diet levels were similar to controls after Week 2 (indicating effect was transitory), only changes at the 185 mg ai/kg diet level were considered treatment-related. In hens, statistically-significant reductions in body weights were observed at Weeks 6 and 8; however, the reductions were partially reflective of the reproductive condition and/or incidental injury noted at study termination (see reproductive effects below). The subsequent NOAEC for adult body weight was 65 mg ai/kg diet.

Necropsy: There were no macroscopic findings at necropsy that were considered related to treatment.

Reproductive Effects: A treatment-related reduction in egg production was observed during the first 2 weeks of exposure at the 185 mg ai/kg diet level compared to the controls; the difference was statistically-significant at Week 1 (p<0.05). During the first 2 weeks of treatment, controls produced 95-100 eggs/week compared to 69 eggs/weeks from hens at the 185 mg ai/kg diet level. Weekly egg production increased during the third week to 80 eggs/week, which was comparable to control production (85 eggs/week). No statistically-significant differences from controls were observed on egg production at the 65 mg ai/kg diet level. At the 22 mg ai/kg diet level, egg production values appeared to have been impacted by handling stress during weight measurements. Six of the 16 pairs at this level appeared to go out of production (defined as at least 2 consecutive weeks of no eggs laid) following the second body weight measurement, and the difference in egg production was statistically-reduced from the control (42 versus 85 eggs/week) during Week 3 (42 versus 85 eggs/week) and overall (457 versus 707 total eggs laid). Three hens in the 65 mg ai/kg diet level and two hens in the control group appeared to be similarly impacted. The NOAEC for egg production was 65 mg ai/kg diet.

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Table 5: Reproductive and Other Parameters (nominal concentrations: study author-reported).

Parameter	Control	22 mg ai/kg	65 mg ai/kg	185 mg ai/kg	NOAEC/ LOAEC
Eggs laid/pen	Not reported				N/A
Eggs laid/hen/day	0.79	0.53*	0.68	0.75	65 mg ai/kg 185 mg ai/kg
Eggs cracked	N/A				N/A
Eggs set	N/A				N/A
Shell thickness (mm ± SD)	N/A				N/A
Viable embryos	N/A				N/A
Live 3-week embryos	N/A				N/A
No. of hatchlings/hen	N/A				N/A
No. of normal hatchlings	N/A				N/A
Hatchling weight (g ± SD)	N/A				N/A
14-day old survivors	N/A				N/A
14-day old survivors weight (g ± SD)	N/A				N/A
Mean food consumption (g/bird/day) <sup>(a)</sup>	186	195	214	201	185 mg ai/kg >185 mg ai/kg
Weight (g) of parent females at test initiation: at test termination:	1173 1157	1133 1048**	1184 1097	1159 1120	185 mg ai/kg >185 mg ai/kg
Weight (g) of parent males at test initiation: at test termination:	1137 1213	1117 1174	1115 1134	1113 1119*	65 mg ai/kg 185 mg ai/kg
Gross pathology	No treatment-	185 mg ai/kg >185 mg ai/kg			

N/A = Not statistically-analyzed.
(a) Reviewer-calculated from weekly data.

<sup>\*</sup> Statistically different from the control at p<0.05.

<sup>\*\*</sup> Statistically different from the control at p<0.01.

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#### C. REPORTED STATISTICS:

The following variables were statistically analyzed: adult body weight, adult feed consumption, and eggs laid. Each of the treatment groups was compared to the control group using an analysis of variance (ANOVA) followed by Dunnett's Multiple Comparison Procedure. Sample units were the individual pens within each experimental group, except adult body weights, where the sample unit was the individual bird. Nominal concentrations were used for all estimations.

#### D. VERIFICATION OF STATISTICAL RESULTS:

Statistical Method: Analysis was conducted using "chicks.sas" (Ver. 3; March 2002), a SAS program provided by EFED/OPP/USEPA. Data for all endpoints were examined graphically using box plots to determine if they exhibited a dose-dependent response, which was ultimately used to select the multiple comparison test to detect LOAEC and NOAEC. Data for each endpoint were tested to determine if their distributions were normal and if their variances were homogeneous using Shapiro-Wilk's and Levene's tests, respectively. Data that satisfied these assumptions were subjected to Dunnett's and William's tests and data that did not satisfy these assumptions were subjected to the non-parametric MannWhitney-U (with a Bonferroni adjustment) and Jonckheere's tests. Data for dead birds were excluded from the analyses. See Appendix I for output of reviewer's statistical verification and graphs for affected endpoints to support any reviewer-generated conclusions that may differ from those reported in the study.

NOAEC: <22.4 mg ai/kg LOAEC: 22.4 mg ai/kg

Most Sensitive Endpoint(s): eggs laid and female weight gain

Table 6: Reproductive and Other Parameters (mean-measured concentrations; reviewer-reported).

Parameter	Control	22.4 mg ai/kg	65.4 mg ai/kg	198 mg ai/kg	NOAEC/ LOAEC
Eggs laid/pen	44.2	28.6*	38.1	42.0	<22.4 mg ai/kg 22.4 mg ai/kg
Eggs cracked/pen	N/A	N/A	N/A	N/A	N/A
Eggs not cracked/eggs laid (%)	N/A	N/A	N/A	N/A	N/A
Eggs set/pen	N/A	N/A	N/A	N/A	N/A
Shell thickness	N/A	N/A	N/A	N/A	N/A
Eggs set/eggs laid (%)	N/A	N/A	N/A	N/A	N/A
Viable embryos/pen	N/A	N/A	N/A	N/A	N/A
Viable embryos/eggs set (%)	N/A	N/A	N/A	N/A	N/A
Live embryos/pen	N/A	N/A	N/A	N/A	N/A
Live embryos/viable embryos (%)	N/A	N/A	N/A	N/A	N/A
No. of hatchlings/pen	N/A	N/A	N/A	N/A	N/A

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No. of hatchlings/eggs laid (%)	N/A	N/A	N/A	N/A	N/A
No. of hatchlings/eggs set (%)	N/A	N/A	N/A	N/A	N/A
No. of hatchlings/live embryos (%)	N/A	N/A	N/A	N/A	N/A
Hatchling survival/pen	N/A	N/A	N/A	N/A	N/A
Hatchling survival/eggs set (%)	N/A	N/A	N/A	N/A	N/A
Hatchling survival/no. of hatchlings (%)	N/A	N/A	N/A	N/A	N/A
Hatchling weight (g)	N/A	N/A	N/A	N/A	N/A
Survivor weight (g)	N/A	N/A	N/A	N/A	N/A
Mean food consumption (g/bird/day)	186.1	195.3	214.1	201.1	198 mg ai/kg >198 mg ai/kg
Male weight gain (g)	75.8	53.5	19.3*	6.3*	22.4 mg ai/kg 65.4 mg ai/kg
Female weight gain (g)	-15.8	-76.4*	-87.4*	-39.3*	<22.4 mg ai/kg 22.4 mg ai/kg

<sup>\*</sup> Statistically different from the control at p<0.05.

#### E. STUDY DEFICIENCIES:

Treated premixes were prepared every 3 to 4 weeks and were stored frozen in plastic bags until needed; however, frozen storage stability data were not provided. This deficiency affects the scientific soundness of this study. In addition, notable deficiencies from OPPTS 850.2300 guideline included: the study methods deviated significantly from standard procedures (e.g., no pre-egg laying treatment period, 8-week duration, failure to incubate collected eggs and therefore measure numerous reproductive endpoints); pen floor size was significantly less (3375 cm²/duck) than recommended (at least 10,000 cm²/duck), and documentation that reproductive parameters and health of birds are not adversely affected were not provided; and handling of the birds for body weight measurements during the egg production phase may have adversely affected egg production. Other noted deviations from guidance were not considered significant by the reviewer.

#### F. REVIEWERS COMMENTS:

Results of the reviewer's statistical verification differed slightly from the study authors'. Both detected a statistically significant reduction in egg production at the lowest treatment level; however, the study author dismissed this effect because it was confounded by the adverse impact of handling adult birds during the egg production phase. Similarly, the study authors and reviewer detected significant reductions in male and female weight gain, but arrived at different conclusions for the NOAEC values. The study author dismissed reductions in male weight gain at the 65.4 mg ai/kg treatment level because they were reportedly transitory and dismissed reductions in female weight gain at all treatment levels because they were associated with reproductive condition and incidental injuries. The reviewer's toxicity values are reported in the Executive Summary and Conclusions sections.

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Although not specified in the report, this study appeared to have been conducted to provide supplemental data to further support and/or define the NOAEC and LOAEC values that were obtained from the standard avian reproduction study conducted using mallard ducks (concurrently-submitted MRID 466955-05).

Based on mean body weights and food consumption, the overall estimated daily dietary dose was calculated as 3.9, 12.5, and 33.5 mg ai/kg bw/day for the nominal 22, 65, and 185 mg ai/kg diet levels, respectively.

Matrix blanks were fortified at 10 or 200 mg ai/kg diet and analyzed concurrently with sample analysis. Recoveries ranged from 100-109% for all samples (mean range of 102-107%). Sample concentrations were not corrected for mean procedural recoveries.

Samples were analyzed by HPLC/UV. The analytical LOD and LOQ were 5 and 10 mg ai/kg diet, respectively.

In-life dates were December 21, 2004 to February 16, 2005.

#### G. CONCLUSIONS:

This study is not scientifically sound and is thus INVALID. Adequate freezer storage stability data were not provided. In addition, this study does not fulfill guideline requirements because it deviated significantly from standard methods and appeared instead to be for supplemental data purposes, the ducks were maintained in cages significantly smaller than recommended, and handling of the birds during the study for body weight measurements appeared to have adversely affected egg production. This study does not fulfill the guideline requirement for an avian reproduction study.

NOAEC: <22.4 mg ai/kg diet LOAEC: 22.4 mg ai/kg diet

Endpoint(s) Affected: body weights of males and females and egg production

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#### III. REFERENCES:

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APP	ENDIX	ı. oı	TP	UT OF RE	VIEW	ER'S ST	ATISTI	CAL VERIE	FICATI	ON:			
Mal	lard r	epro	, B	Bayer AE	0172	747, MR	ID 466	955-06					
	TRT	EL E		ENC_EL	ĒS	ES_EL	VE	VE_ES	LE	LE_VE	NH	NH_EL	
1	Ctrl	53										•	
2	Ctrl	51				•			•			• •	
3	Ctrl	56											
4	Ctrl	40							•				
5	Ctrl	46										•	
6	Ctrl	54											
7	Ctrl	50										•	
8	Ctrl	12											
9	Ctrl	43										•	
10	Ctrl	55											
11	Ctrl	5											
12	Ctrl	31											
13	Ctrl	54											
14	Ctrl	55											
15	Ctrl	58											
16	Ctrl	44					•						
17	Dosel	7										•	
18	Dosel	10					•						
19	Dosel	54					•						
20	Dosel	25			•		•						
21	Dose1	53			•		•					•	
22	Dose1	10					•						
23	Dosel	27											
24	Dose1	56											
25	Dosel	12											
26	Dose1	50		•					.•				

27       Dosel 40	66955-05
29 Dosel 31	
30 Dosel 17	
31 Dosel 25	
32 Dose1 8	
33 Dose2 55	
34 Dose2 20	
35 Dose2 54	
36 Dose2 1	
37 Dose2 17	•
38 Dose2 56	
39 Dose2 28	•
40 Dose2 53	
41 Dose2 12	
42       Dose2       49       . </td <td>•</td>	•
43       Dose2       21       . </td <td>•</td>	•
44 Dose2 46	
45 Dose2 43	•
46 Dose2 46	•
47 Dose2 56	
49 Dags 2 F 2	
48 Dose2 53	
	•
49 Dose3 37	•
50 Dose3 41	•
51 Dose3 50	•
52 Dose3 40	
53 Dose3 31	
54 Dose3 34	

PMR	A Submi	ssion	Number {	}	<del></del>			E	PA MRID	Number 4669	55-05
55	Dose3	37	•		•			•			
56	Dose3	57	ě							•	
57	Dose3	33									
			•	•	•	•	•	•		•	•
8	Dose3		•	•	•	•	•	•		•	•
59	Dose3	40	•	•	•	•	•	•		•	
50	Dose3	52	•		•		•	•		•	•
51	Dose3	46	•	•			•				
52	Dose3	49									
63	Dose3	31									
64	Dose3	56									
Mal	lard re	epro	, Bayer	AE0172	2747, MRID	46695	5-06				
PRI	TUOTH	OF R	AW DATA	(conti	inued)			CIIDI MAD	FOOD	times time	
	TRT AINF	NH_	LE HS	HS_H	rs H2_NH	THICK	TWTAH	SURVWT	FOOD	WTGAINM	
Ì	Ctrl					•			174	13	-25
2	Ctrl								281	50	~63
3	Ctrl						_		151	42	-131
1	Ctrl						·	•	198	48	43
5	Ctrl			•	•	•	•	•	156	181	-66
5	Ctrl			•	•	•	•	•			
7	Ctrl			•	•		•	•	197	90	-23
				•	•	•	•	•	207	33	47
8	Ctrl			•	•	•	•	•	158	199	-90
9	Ctrl				•	•	•	•	228	75	5
10	Ctrl				•				229	22	-29
11	Ctrl								154	81	-2
12	Ctrl								144	107	109
13	Ctrl								136	67	29
14	Ctrl				_				214	67	19
15	Ctrl						•	•	193	97	-45
16	Ctrl		•	•	•	•	•	•	157	41	-31
17	Dosel			•	•	•	•	•	200	121	-121
18	Dosel		• •	•	•	•	•	•	197	111	
19	Dosel			•	•	•	•	•			-41
20	Dosel				•	•	•	•	272	1	-115
21					•	•	•	•	216	45	50
	Dose1				•	•	•	•	281	102	-92
22	Dosel						•		229	134	-95
23	Dosel								143	-98	-42
24	Dosel								187	62	-27
25	Dosel								190	83	-155
26	Dosel								177	55	-74
27	Dosel								202	54	-115
28	Dosel				-	•	•	•	183	32	-36
29	Dosel			•	•	•	•	•	153	134	
30	Dosel			•	•	•	•	•	162	38	-63
31	Dose1			•	•	•	•	•			-110
32	Dosel			•	•	•	•		187	-72	-110
33				•	•	•	•	•	145	•	
رر	Dose2			•	•			•	346	36	-106

PMI	RA Submiss	ion Num	ber {	.}			EF	'A MRID N	ımber 466	955-05
				,	-					
34	Dose2	•						143	56	12
35	Dose2				•	•		194	-83	-185
36	Dose2	•						142	80	-36
37	Dose2	•						157	64	-3
38	Dose2							289	-6	86
39	Dose2				•			205	62	-148
40	Dose2							194	-47	-81
41	Dose2							143	106	-196
42	Dose2	•						228	-4	-174
43	Dose2	•	•					224	-5	-2
44	Dose2		•					225	23	-155
45	Dose2		•	•	•	•		236	22	-169
46	Dose2		•		•			176	- 6	-4
47	Dose2							310	0	-127
48	Dose2			•	•			213	10	-110
49	Dose3							185	-7	~169
50	Dose3			•				141	0	-31
51	Dose3			•				203	- 4	-95
52	Dose3							211	15	-64
53	Dose3							222	-71	44
54	Dose3	-					•	212	17	-47
55	Dose3	•		•		•	•	137	94	57
56	Dose3	•						153	21	-27
57	Dose3	•						171	-23	29
58	Dose3			٠.				251	135	-56
59	Dose3							160	-60	87
60	Dose3							241	12	-125
61	Dose3	•						250	-20	-51
62	Dose3							222	-75	-58
63	Dose3					• .		257	26	-129
64	Dose3	•	•	•	•			202	40	6

PMRA Submission Number {.....}

EPA MRID Number 466955-05

Mallard repro, Bayer AE0172747, MRID 466955-06 ANALYSIS RESULTS FOR VARIABLE EL ( Eggs Laid ) TESTS OF ASSUMPTIONS FOR PARAMETRIC ANALYSIS Shapiro-Wilks test for Normality of Residuals -- alpha-level=0.01 Levenes test for homogeneity of variance(absolute residuals) -- alpha-Use parametric analyses if neither test rejected, otherwise non-parametric analyses. Shapiro-Wilks Shapiro-Wilks Levenes Levenes Conclusion
Test Stat P-value Test Stat P-value
0.969 0.106 3.671 0.017 USE NON-PARAMETRIC TESTS \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* BASIC SUMMARY STATISTICS Level N Mean StdDev StdErr Coef of Var 95% Conf.Interval Ctrl 16 44.19 15.67 3.92 35.46 35.84, 52.54 Dosel 16 28.56 17.55 4.39 61.43 19.21, 37.91 Dose2 16 38.13 18.47 4.62 48.44 28.28, 47.97 Dose3 16 42.00 8.61 2.15 20.50 37.41, 46.59 Min Level Median Max %of Control(means) %Reduction(means) Ctrl 50.50 5.00 58.00 .

Dosel 26.00 7.00 56.00 64.64

Dose2 46.00 1.00 56.00 86.28

Dose3 40.00 31.00 57.00 95.05 35.36 13.72 4.95 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* NON-PARAMETRIC ANALYSES - use alpha-level=0.05 for all tests Kruskal-Wallis test - equality among treatment groups Degrees of Freedom TestStat P-value 7.70 0.053 MannWhit(Bon) - testing each trt median signif. less than control Jonckheere - test assumes dose-response relationship, testing negative trend

Level	Median	MannWhit(Bon	adjust)p-value	Jonckheere p-value
Ctrl	50.50			
Dosel	26.00		0.037	0.009
Dose2	46.00		0.635	0.189
Dose3	40.00		0.259	0.398
Dosel Dose2	26.00 46.00	·	0.037 0.635	0.009 0.189

SUMMARY	NOEC	LOEC
MannWhit (Bonf adjust)	<pre><lowest dose<="" pre=""></lowest></pre>	Dose1
Jonckheere	Dose3	>highest dose

EPA MRID Number 466955-05

	_	_	-								
Mallard repro	. Baver	AE0172747.	MRID 46695	5-06							
Mallard repro, Bayer AE0172747, MRID 466955-06 ANALYSIS RESULTS FOR VARIABLE NEG_EC ( Eggs Cracked )											
IMMBIGIO NECORIO FON VANIABBE NECEBO ( Eggs CIECARO )											
TESTS OF ASSUMPTIONS FOR PARAMETRIC ANALYSIS											
					-level=0 01						
Shapiro-Wilks test for Normality of Residuals alpha-level=0.01											
Levenes test for homogeneity of variance(absolute residuals) alpha-											
level=0.05											
Use parametric analyses if neither test rejected, otherwise non-parametric											
analyses. Shaniro-Wilks Shaniro-Wilks Louones Conclusion											
Shapirc-Wilks Shapiro-Wilks Levenes Levenes Conclusion Test Stat P-value Test Stat P-value											
				P-value	NO DERE BOD BEOM						
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Dose2 0	•	•			. , .						
Dose3 0		•	•		. ,						
		Min	Max ₹	of Control (me	eans)						
%Reduction(me	eans)										
Ctrl											
Dosel											
Dose2		•									
Dose3											
Mallard repro	, Bayer	AE0172747,	MRID 46695	5-06							
ANALYSIS RESU					)						
			, ,	( , , ( , , ,	•						
TESTS OF ASSU	JMPTIONS	FOR PARAMET	TRIC ANALYS	IS							
Shapiro-Wilks	test fo	r Normality	v of Residu	als alpha	-level=0.01						
Levenes test	for homo	geneity of	variance(a	bsolute resid	duals) alpha-						
level=0.05		50		2001400 1001	2220) alpa						
Use parametri	c analys	es if neith	ner test re	jected, other	rwise non-parametric						
analyses.				jected, cene.	inibe non parametric						
Shapiro-Wil	ks Shap	iro-Wilks	Levenes	Levenes	Conclusion						
Test Stat	P-	value	Test Star	P-value	Concidition						
	-				NO DATA FOR TEST						
•		•	•	•	NO BATA TON 1251						
*****	*****	*****	*****	*****	******						
**											
BASIC SUMMARY	STATIST	ics									
Level N	Mean		StdErr	Coef of Va	r 95% Conf.Interval						
Ctrl 0	ricuii	3 cape v	OCCEPT	COEI OI Va.							
Dosel 0	•	•	•	•	• , •						
Dose2 0	•	•	•	•	• , .						
Dose3 0	•	•	•	•	. , .						
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Level	Median	Min	May &	af C+1 /							
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Ctrl	alls)										
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Dose2	•	•	•	•	•						
Dose3		•	•	•	•						
20363		•		•	•						
			D 2¢ - ¢	7.0							

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				MRID 466955 Eggs Se				
Shapiro-Levenes level=0.	Wilks test 05 metri	test for home	or Normality ogeneity of	variance(ab	(S als alpha osolute resi jected, othe	duals)	alpha-	
Shapir	o-Wil	ks Shar	piro-Wilks -value	Levenes	Levenes	Conclusi	.on	
rest.	Stat	r	·	rest stat		NO DATA	FOR TES	Т
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BASIC SU				0. 17	~ ~ ~ ~	050		
Level				StdErr	Coef of Va	ar 95%	Conf.In	terval
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Dose2		•	•	•	•		. ,	•
Dose3	0	•	•	•	•		. ,	•
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Level		Median	Min	Max %	of Control(n	neans)		
%Reducti	on (me	ans)						
Ctrl		•	•	•	•		•	
Dosel		•	•	•	•		•	
Dose2		•	•	•	•		-	
Dose3		•	•	•	•		•	
ANALYSIS TESTS OF Shapiro-	RESU ASSU Wilks test	LTS FOR MPTIONS test f	VARIABLE E FOR PARAME or Normalit	TRIC ANALYS: y of Residu	sSet/EggsLai	a-level=0.		
Use para	metri	c analy	ses if neit	her test re	jected, othe	erwise nor	n-parame	tric
analyses Shapir		ks Sha	oiro-Wilks	Levenes	Levenes	Conclusi	on	
					P-value			·m
•			•	•	•	NO DATA	FOR TES	' 1
******	****	*****	*****	*****	*****	*****	****	*****
**								
BASIC SU	V G KIMMI	י כייאיידכי	TTCC					
Level		Mean		StdErr	Coef of Va	n 0 E e	Conf In	+1
-		mean	Stabev	SCUELL	COGI OI V	aL 908	CONT. II.	rervar
Ctrl		•	•	•	•		• ,	•
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Dose2		•	.•	•	•		. ,	•
Dose3	0	•	•	•	•		. ,	•
Level %Reducti			Min	Max %	of Control(	neans)		
	on (me	:a115)						
Ctrl		•	٠	•	•		•	
Dosel		•	•	•	•		•	
Dose2		•	•	•	•		•	
				Page 26 of	38			

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PMRA Submission	Number {	}			EPA MRI	ID Number	466955-05
Dose3	•	•	•	•		•	
Mallard repro ANALYSIS RESU					)		
TESTS OF ASSU Shapiro-Wilks Levenes test level=0.05 Use parametri	test for for homog	Normality geneity of	y of Residu variance(a	als alpha bsolute resi	duals) -	- alpha-	
analyses. Shapiro-Wil	ks Shapi	ro-Wilks	Levenes	Levenes P-value	Conclus	ion	
		, aruc		,	NO DATA	FOR TES	ST
*****	*****	*****	*****	*****	*****	*****	*****
** BASIC SUMMARY	STATIST	CS					
Level N			StdErr	Coef of Va	er 95%	Conf.Ir	nterval
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Dosel 0	•	•	•	•		. ,	
Dose2 0	•	•	•	•		· r	•
Dose3 0	•	•	•	•		• ,	•
Level %Reduction(me		Min	Max %	of Control(m	neans)		
Ctrl	•	•	•	•			
Dose1		•	•	•	-	•	
Dose2		•	•	•		•	
Dose3	•	•	•	•		•	
Mallard repro					ggsSet (%	·	
TESTS OF ASSU Shapiro-Wilks Levenes test level=0.05	test for	r Normalit	y of Residu	als alpha			-
Use parametri analyses.	c analyse	es if neitl	her test re	ejected, othe	erwise no	n-parame	etric
Shapiro-Wil Test Stat	ks Shap	iro-Wilks value	Levenes Test Stat	Levenes P-value	Conclus	ion	
•		•	•		NO DATA	FOR TES	ST
*****	*****	*****	*****	*****	*****	*****	*****
BASIC SUMMARY	STATIST:	rcs					
Level N	Mean	StdDev	StdErr	Coef of Va	ar 95%	Conf.Ir	nterval
Ctrl 0	•	•	•	•		. ,	
Dosel 0	•	•		•		,	•
Dose2 0	•	•		•		. ,	
Dose3 0	•	•		•		. ,	•
Level %Reduction(me	Median	Min	Max %	of Control(m	means)		
Ctrl		•					
Dosel	•			ē			
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PMRA Submissio	n Number {	<u>}</u>			EPA MRID Number 466955-05
Dose2					
Dose3	•	•	•	•	•
Mallard repr ANALYSIS RES	o, Bayer ULTS FOR	AE0172747, VARIABLE L	MRID 46695 E ( Live E	5-06 Embryo(d21) )	
TESTS OF ASS Shapiro-Wilk	s test fo	r Normalit	y of Residu	als alpha	
Levenes test level=0.05	ior nome	geneity or	variance(a	osolule resi	iduals) alpha-
-	ic analys	ses if neit	her test re	ejected, othe	erwise non-parametric
analyses.	_				
Shapiro-Wi	lks Shap	oiro-Wilks	Levenes	Levenes	Conclusion
rest Sta	.t P-	-value		P-value	NO DATA FOR TEST
•		•	•	•	NO DATA FOR TEST
	*****	******	*****	*****	*******
* *					
BASIC SUMMAR			011-37	0.5	050 6-04 701-00-7
Ctrl 0			Statrr		er 95% Conf.Interval
Dosel 0		•	•	•	• , •
Dosel 0		•	•	•	• •
Dose3 0		•	•	•	• , •
- 5555	•	•		-	, ,
Level	Median	Min	Max %	of Control(	means)
Reduction(m	neans)				
Ctrl		•	•		
Dosel	•	•	•	•	•
Dose2	•	•	•	•	•
Dose3	•	•	•	•	•
Mallard repr	. Paus	VEU113111	MDID 1660E	: 5 _ O. 6	
					bleEmbryo (%) )
MAIDIDID REC	0013 1010	VARIANDED D	p_	CEMETYO, VIGI	Sichmoly (0)
TESTS OF ASS	SUMPTIONS	FOR PARAME	TRIC ANALYS	SIS	
				als alpha	
	for home	geneity of	variance(a	absolute res:	iduals) alpha-
level=0.05					
	ric analys	ses if neit	her test re	ejected, othe	erwise non-parametric
analyses. Shapiro-Wi	lka Char	siro-Wilks	Levenes	Levenes	Conclusion
Test Sta	.t D.	-value	Test Stat		Conclusion
	1	·	·		NO DATA FOR TEST
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BASIC SUMMAR			0+ 15	C	050 05 7 1
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Dosel 0	•	•	•	•	• •
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	•	•	-	•	• , •
Level	Median	Min	Max 8	of Control(	means)
%Reduction(m	neans)				
Ctrl	•	•	•	•	•
			Page 28 of	`38	

Duck ( <i>Anas pla</i> PMRA Submission					EPA MRID Number 466955-05
Dosel	•	•	•	•	•
Dose2			•	•	•
Dose3		•	•	•	. •
Mallard repro					
level=0.05	test for for homoge	Normality eneity of	y of Residua variance(ab	als alpha solute resi	a-level=0.01 duals) alpha- erwise non-parametric
analyses.					
Shapiro-Wil	ks Shapi:	ro-Wilks	Levenes	Levenes	Conclusion
rest Stat	; P-V	alue	Test Stat	r-value	NO DATA FOR TEST
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·*************	*****	****	*****	******	**********
BASIC SUMMARY					
Level N	Mean	StdDev	StdErr	Coef of Va	ar 95% Conf.Interval
Ctrl 0					. , .
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Dose2 0 Dose3 0	•	÷.	•	:	: ; :
Level Reduction(me	eans)	Min	Max %	of Control(r	neans)
Ctrl	•	•	•	•	•
Dosel	•	•	•	•	•
Dose2	•	•	•	•	•
Dose3			•	•	•
	JLTS FOR V.	ARIABLE N	H_EL ( Numi	perHatched/H	EggsLaid (%) }
level=0.05	s test for for homog	Normalit eneity of	y of Residua variance(a)	als alpha osolute resi	iduals) alpha-
Jse parametri analyses.	ic analyse	s if neit	her test re	jected, othe	erwise non-parametric
Shapiro-Wil Test Stat	lks Shapi	ro-Wilks	Levenes	Levenes	Conclusion
Test Stat		alue	Test Stat	P-value	NO DATA FOR TEST
***********	*****	*****	*****	*****	********
BASIC SUMMARY	/ STATTSTT	CS			
			StdErr	Coef of Va	ar 95% Conf.Interval
Ctrl 0			•		: , .
Dosel 0					. , .
Dose2 0			•	•	
Dose3 0	·	:			. , .
Level EReduction(me	Median	Min		of Control(	means)
			Page 29 of	38	

PMRA Submission	,			· · · · · · · · · · · · · · · · · · ·	EPA MRII	Number 46	695 <u>5</u> -05
Ctrl							
Dosel	•	•	•	•		•	
Dose2	•	•	•	•		•	
Dose3	•	•	•	•		•	
Doses	•	•	•	•		•	
	o, Bayer AE01 ULTS FOR VARI				gsSet (%	) )	
Shapiro-Wilks Levenes test level=0.05	UMPTIONS FOR stest for No for homogene	ermality of tity of var	Residuals iance(abso	olute resid	luals)	alpha-	
Use parametr: analyses.	ic analyses i	f neither	test rejec	cted, other	wise non	-parametr	ric
Shapiro-Wil	lks Shapiro-	Wilks L	evenes	Levenes	Conclusi	on	
Test Stat	t P-valu	ie Te	st Stat	r-value	NO DATA	FOR TEST	
	*****						
**		* * * * * * * * * *	****		*****	*******	****
	Y STATISTICS						
Level N	Mean Sto	Dev S	tdErr (	Coef of Var	95%	Conf.Inte	erval
Ctrl 0			•			. ,	
Dosel 0						. ,	
Dosel 0 Dose2 0				_		. ,	
Dose3 0				:		. ,	
	Median N	Min M	lax %of	Control (me	ans)		
Reduction (me	eans)						
Ctrl		•					
Dosel							
Dose2							
Dose3			•				
ANALYSIS RES	o, Bayer AE01 ULTS FOR VARI UMPTIONS FOR	ABLE NH_LE	. ( Number	rHatched/Li	_		
Levenes test Level=0.05	s test for No	eity of var	iance(abso	olute resid	duals)	alpha-	
analyses.	ic analyses i		_			-	10
Shapiro-Will Test Star	lks Shapiro- t P-valu	Wilks L me Te	evenes st Stat	Levenes P-value	Conclusi	on	
•				,	NO DATA	FOR TEST	
	*****	*****	*****	*****	*****	****	****
**							
	Y STATISTICS						_
		iDev S	tdErr (	Coef of Var	95%	Conf.Inte	erval
Ctrl 0		•	•			. ,	
Dosel 0						. ,	
Dose2 0						. ,	
Dose3 0	•	•				. ,	
		J	Page 30 of 38				
			-				

Duck (Anus plutythytichos)	
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		,		<del></del>			
Level	Median	Min	Max %	of Control(n	neans)		
%Reduction(	means)			·	·		
Ctrl		•	•	•		•	
Dosel Dose2	•	•	•	•		•	
Dose2 Dose3	•	•	•	•		•	
Doses	•	•	•	•		•	
Mallard rep ANALYSIS RE				55-06 .ng Survival	(d14) )		
			<b>.</b> .				
TESTS OF AS				SIS Mals alpha	- 1 arro 1 - (	0.1	
Levenes tes				absolute resi			
	ric analys	es if neit	her test re	ejected, othe	erwise no	on-parame	tric
analyses. Shapiro-W	ilks Shap	iro-Wilks	Levenes	Levenes	Conclus	sion	
		value	Test Stat	P-value	אר האת	1 FOD TEC	T
•		•	•	•	NO DATE	TON 123	
*****	*****	*****	*****	******	******	*****	*****
BASIC SUMMA							
Level N	Mean	StdDev	StdErr	Coef of Va	ar 959	Conf.In	terval
Ctrl 0						. ,	
Dosel 0 Dose2 0	•	•	•	•		. ,	
		•	•	•		. ,	•
Dose3 0	•	•	•	•		. ,	•
Level	Median	Min	Max 9	of Control(	neans)		
%Reduction(				•	·		
Ctrl							
Dosel							
Dose2	•	•	•			•	
Dose3	•	•	•	•		•	
Mallard rep	ro, Bayer	AE0172747,	MRID 46695	55-06 cchingSurviva	-1 /FC-	-+ (8)	
ANALISIS KE	SOLIS FOR	AWINDPE U	S_ES ( nat	-CHINGSULVIV	11/Eggsse	EL (6) )	
TESTS OF AS							
Shapiro-Wil	ks test fo	r Normalit	y of Residu	als alpha	a-level=(	0.01	
Levenes tes level=0.05	t for homo	geneity of	variance(a	absolute res	iduals) -	alpha-	
	ric analys	es if neit	her test re	ejected, othe	erwise no	on-parame	tric
Shapiro-W Test St		iro-Wilks value	Levenes	Levenes P-value	Conclus	sion	
rest st	at r-	value	rest stat		אַר האַדע	A FOR TES	т
		•					
*****	******	******	******	*****	*****	*****	*****
BASIC SUMMA	RY STATIST	ICS					
Level N	Mean	StdDev	StdErr	Coef of Va	ar 959	Conf.In	terval
Ctrl 0						. ,	
Dosel 0	-	•				. ,	
Dose2 0 Dose3 0	•		•			. ,	
Doses 0	•	•				. ,	•
			Page 21 of	20			

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Level	Mod	41.75	Min	Mav	%of Control(m	ieane l		
%Reduction			11111	Hax	801 CONC. O. (10	iedii3/		
	on (mean:	5)						
Ctrl		•	•	•	•		•	
Dosel		•	•	•	•		•	
Dose2			•	•	•		•	
Dose3				•			•	
Mallard :	repro.	Baver A	E0172747,	MRID 466	955-06			
ANALYSTS	RESULT	S FOR V	ARIABLE H	S NH (H	atchingSurviva	1/Number	Hatched {	કુ) )
	NEDODI.						,	
TECTC OF	A CCIIMD	TTONC E	OR DARAME	TRIC ANAL	YSTS			
					duals alpha	-102201-0	0.1	
		r nomog	seneity or	variance	(absolute resi	iduals) -	- alpha-	
level=0.0		_						
		analyse	s if neit	her test	rejected, other	rwise no	n-paramet	ric
analyses								
Shapir	o-Wilks	Shapi	ro-Wilks	Levene	s Levenes at P-value	Conclus	ion	
Test	Stat	P-7	ralue	Test St	at P-value			
						NO DATA	FOR TEST	•
*****	****	*****	*****	*****	*****	*****	*****	*****
* *								
BASIC SU	MMARV S	יים אוד ביים	CS					
				S+ 4E~~	Coef of Va	958	Conf Int	erval
							COIII.III	CIVAI
CCTI	0	•	•	•	•		• ,	•
Dosel Dose2	0	•	•	•	•		. ,	•
			•		•		. ,	•
Dose3	0				•		. ,	•
Level	Me	dian	Min	Max	%of Control(n	neans)		
%Reduction		s)						
Ctrl			•	•			•	
Dosel					,			
Dose2								
Dose3								
Mallard	repro.	Baver A	AE0172747.	MRID 466	955-06			
					ggshell thick	iess l		
	TIED OF I	0 101.			990.1011 (1110)11	.000 /		
##C#C \P	ACCIIMD	TIONS I	משעמשעם שטב	TRIC ANAL	VCTC			
					duals alpha	- 11-0	01	
		r nomog	geneity of	variance	(absolute resi	iduais) -	- alpha-	
level=0.		_						
		analyse	es if neit	her test	rejected, other	erwise no	n-paramet	ric
analyses								
Shapir	o-Wilks	Shapi	iro-Wilks	Levene	es Levenes	Conclus	ion	
Test	Stat	P-7	value	Test St	at P-value			
			-			NO DATA	FOR TEST	r
*****		*****	·****	*****	****	*****	*****	******
* *								
		ተመንተመመ	res					
BASIC SU	MMARY S			C+ 4F~~	Coef of W	- OF 0	Conf To	orus 1
BASIC SU	MMARY S	TATIST: ean	ICS StdDev	StdErr	Coef of V	ar 95%	Conf.Int	terval
BASIC SU Level Ctrl	MMARY S N M			StdErr	Coef of Va	ar 95%	Conf.Int	terval
BASIC SU Level Ctrl Dosel	MMARY S N M O			StdErr	Coef of Va	ar 95%		terval
BASIC SU Level Ctrl Dosel	MMARY S N M			· ·	•	ar 95%		cerval
BASIC SU Level Ctrl Dosel	MMARY S N M O			StdErr Page 32	•	ar 95%		cerval

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Dose3 0	•					. ,	
	Median	Min	Max %	of Control(m	eans)		
%Reduction(me	eans)						
Ctrl	•	•				•	
Dosel			•	•		•	
Dose2		•	•	•		•	
Dose3	•	•	•	•		•	
Mallard repro					it )		
TESTS OF ASSU Shapiro-Wilks Levenes test level=0.05 Use parametr:	s test fo for homo	r Normality geneity of	y of Residu variance(a	aals alpha absolute resi	duals) -	- alpha-	ric
analyses.	_			Levenes		-	
Test Stat	. P-	value	Test Stat	P-value			
•		•	•		NO DATA	FOR TEST	ſ
********	*****	******	*****	******	*****	*****	*****
BASIC SUMMARY	Y STATIST	ICS					
Level N	Mean	StdDev	StdErr	Coef of Va	ır 95%	Conf.Int	cerval
Ctrl 0			•			• ,	
Dosel 0	•		•			. ,	
Dose2 0	•	•		•		. ,	
Dose3 0	•	•	•	•		. ,	•
Level %Reduction(me	Median eans)	Min	Max 9	of Control(m	neans)		
Ctrl							
Dosel	•	•	•				
Dose2		•	•	•			
Dose3	•	•	•	•			
Mallard repro	D, Bayer ULTS FOR	AE0172747, VARIABLE SU	MRID 46695 URVWT ( Su	55-06 Irvivor Wt (c	114) )		
TESTS OF ASSI Shapiro-Wilks Levenes test level=0.05	for homo	r Normality geneity of	y of Residu variance(a	als alpha absolute resi	duals) -	- alpha-	
Use parametri analyses.							ric
Shapiro-Wil Test Stat	lks Shap P-	iro-Wilks value	Levenes Test Stat	P-value	Conclus		
•		•	•	•	NO DATA	FOR TEST	Γ
************  ** BASIC SUMMARY			*****	******	*****	*****	******
Level N Ctrl O	Mean .	StdDev	StdErr	Coef of Va	ır 95%	Conf.Int	erval
Dosel 0	•	•	•	•		. ,	
			Page 33 of	38			

PMRA Sub	missi	on Number {	}	EPA N	EPA MRID Number 466955-05				
	_								
Dose2	Q	•	•	•	•		,	•	
Dose3	0	Ē	•			•	,	•	
Level		Median	Min	Max	%of Control(means)				
%Reducti	on (r	means)							
Ctrl							٠.		
Dosel		•	•						
Dose2					•				
Dose3					•				

				0172747, RIABLE FO			-06 Consumptio	on )			
Shapiro Levenes level=0	TESTS OF ASSUMPTIONS FOR PARAMETRIC ANALYSIS Shapiro-Wilks test for Normality of Residuals alpha-level=0.01 Levenes test for homogeneity of variance(absolute residuals) alpha-level=0.05 Use parametric analyses if neither test rejected, otherwise non-parametric										
analyse	s. ro-Wil	ko	- Chaniz	oWilka	Τ.0	venes	Levenes	Concl	lusion		
	t Stat			o-Wilks lue		t Stat	P-value		1431011		
0	.965		0.0	66	1	.060	0.373	USE I	PARAMETRI	C TESTS	
*****	*****	****	****	******	***	*****	*****	*****	*****	*****	**
**											
BASIC S											
Level				tdDev		dErr	Coef of	Var 9	95% Conf.		
Ctrl	16	186.	06	39.46		.87	21.21		165.03,		
Dosel	16 16	195.	25 06	39.73 60.00		.93	20.35 28.03		174.08, 182.09,		
	16			39.65		.91	19.71		180.00,		
00363	10	201.	13	55.05		• >1	13.71		100.00,	222.20	
Level		Medi	an	Min	Ма	x %c	f Control	(means)			
%Reduct	ion (me	eans)									
Ctrl				36.00		.00					
Dosel		188.			281		104.94		-4.		
Dose2		209.		42.00		.00	115.05		-15.		
Dose3		207.	00 1	37.00	25/	.00	108.10		-8.	10	
*****	*****	****	*****	*****	***	*****	*****	*****	*****	*****	* *
* *											
PARAMET	RIC AN	NALYS	ES	- use alp	ha-1	evel=0.	05 for al	1 tests			
Ana	lysis	of V	arianc	e (ANOVA)	- 0	verall	F-test				
Nu	merato	or df	De	nominator	df	F-st	at	P-value			
	3			60		1.0	16	0.373			
			. 1				4.3				
							s than co			<b></b>	
							ionship, risons, n				
lakey	CWO	sided	ceses	, all pos	3101	e compa	11130115, 11	ot useu	TOT NOEC	OI LOEC	
Level	Mear	n D	unnett	Isotoni	.c W		:		Tukey p-	values	
		р	-value	mean		p-value	Dosel	Dose2	Dose3	Dose4	
Dose5											
Ctrl	186.0	06	•	199.13	3	•		•	•	•	
Dosel	195.2	2.5		199.13		0.865					
Dosei	195.2	25	•	199.13	5	0.865	•	•	•	•	
Dose2	214.0	16		199.13	3	0.891					
			-	100.10		0.001	•	•	•	•	
Dose3	201.1	13		199.13	3	0.904					
SUMMAR				NOE		. ,	LOEC				
Dunn พ.ก.	iett				lowes se3	t dose	Dosel	at daa-			
M T T T	T 01112			DC	JSE3		>111gne	st dose			

PMRA Submission Number {.....}

EPA MRID Number 466955-05

Mallard repro, Bayer AE0172747, MRID 466955-06 ANALYSIS RESULTS FOR VARIABLE WTGAINM ( Male wt gain ) TESTS OF ASSUMPTIONS FOR PARAMETRIC ANALYSIS Shapiro-Wilks test for Normality of Residuals -- alpha-level=0.01 Levenes test for homogeneity of variance(absolute residuals) -- alphalevel=0.05 Use parametric analyses if neither test rejected, otherwise non-parametric analyses. Shapiro-Wilks Shapiro-Wilks Levenes Levenes Conclusion P-value Test Stat Test Stat P-value 0.981 0.448 0.426 0.735 USE PARAMETRIC TESTS \*\*\*\* BASIC SUMMARY STATISTICS Level N Mean StdDev Ctrl 16 75.81 51.97 StdErr Coef of Var 95% Conf.Interval 
 Ctrl
 16
 75.81
 51.97
 12.99
 68.55

 Dosel
 15
 53.47
 68.84
 17.78
 128.76

 Dosel
 16
 19.25
 47.89
 11.97
 248.78

 Dosel
 16
 6.25
 54.82
 13.70
 877.05
 68.55 48.12, 103.51 91.59 44.77 15.34, -6.27, -22.96, 35.46 Level Median Min Max %of Control(means) %Reduction(means) 67.00 13.00 199.00 55.00 -98.00 134.00 16.00 -83.00 106.00 Ctrl 67.00 70.52 29.48 Dose1 Dose2 25.39 74.61 Dose3 6.00 -75.00 135.00 8.24 91.76 \*\*\*\*\*\*\*\*\*\* PARAMETRIC ANALYSES - use alpha-level=0.05 for all tests Analysis of Variance (ANOVA) - overall F-test Numerator df Denominator df F-stat P-value 3 5.09 0.003 Dunnett - testing each trt mean signif. less than control Williams - test assumes dose-response relationship, testing negative trend Tukey - two-sided tests, all possible comparisons, not used for NOEC or LOEC Level Mean Dunnett Isotonic Williams Tukey p-values D

		p-value	mean	p-value	Dosel	Dose2	Dose3	Dose4
Dose5								
Ctrl	75.81	•	75.81	•				•
Dosel	53.47		53.47	0.163				
Dose2	19.25	•	19.25	0.003				
Dose3	6.25	•	6.25	<.001	•			
SUMMARY Dunnett Williams		NOEC <lowest dose<br="">Dose1</lowest>		LOEC Dosel Dose2				

PMRA Submission Number {.....}

EPA MRID Number 466955-05

Mallard repro, Bayer AE0172747, MRID 466955-06 ANALYSIS RESULTS FOR VARIABLE WTGAINF ( Female wt gain ) TESTS OF ASSUMPTIONS FOR PARAMETRIC ANALYSIS Shapiro-Wilks test for Normality of Residuals -- alpha-level=0.01 Levenes test for homogeneity of variance (absolute residuals) -- alphalevel=0.05 Use parametric analyses if neither test rejected, otherwise non-parametric analyses. Shapiro-Wilks Shapiro-Wilks Levenes Levenes Conclusion Test Stat P-value Test Stat P-value 0.983 0.542 2.309 0.086 USE PARAMETRIC TESTS \* BASIC SUMMARY STATISTICS 
 StdDev
 StdErr
 Coef of Var
 95% Conf.Interval

 58.73
 14.68
 -371.41
 -47.11, 15.48

 51.18
 13.21
 -66.98
 -104.74, -48.06

 85.69
 21.42
 -98.07
 -133.04, -41.71

 71.11
 17.78
 -180.89
 -77.20, -1.42
 Level N Mean StdDev Ctrl 16 -15.81 58.73

Dosel 15 -76.40 51.18

Dosel 16 -87.38 85.69

Dosel 16 -39.31 71.11 58.73 -180.89 Level Median Min Max %of Control(means) %Reduction(means) 

 Ctrl
 -24.00
 -131.00
 109.00

 Dosel
 -92.00
 -155.00
 50.00

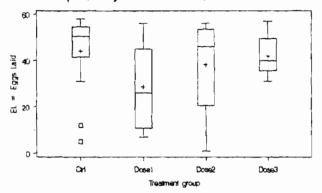
 Dose2
 -103.00
 -196.00
 86.00

 483.16 552.57 -383.16 -452.57 -49.00 -169.00 Dose3 87.00 248.62 -148.62\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* PARAMETRIC ANALYSES - use alpha-level=0.05 for all tests Analysis of Variance (ANOVA) - overall F-test Numerator df Denominator df F-stat P-value 3 3.74 0.016 · Dunnett - testing each trt mean signif. less than control Williams - test assumes dose-response relationship, testing negative trend Tukey - two-sided tests, all possible comparisons, not used for NOEC or LOEC

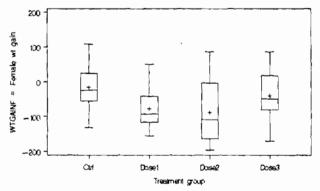
Level	Mean	Dunnett	Isotonic	Williams		Tukey p-values		
Dose5		p-value	mean	p-value	Dosel	Dose2	Dose3	Dose4
Ctrl	-15.81		-15.81					
Dosel	-76.40		-67.51	0.022 .				
Dose2	-87.38		-67.51	0.021				
Dose3	-39.31		-67.51	0.022				•
SUMMARY Dunnett Williams			NOEC <lowest dose<br=""><lowest dose<="" td=""><td>LOEC Dosel Dosel</td><td></td><td></td><td></td></lowest></lowest>		LOEC Dosel Dosel			

#### **Box Plots:**

Mallard repro, Bayer AE0172747, MRID 466955-06



Mallard repro, Bayer AE0172747, MRID 466955-06



Mallard repro, Bayer AE0172747, MRID 466955-06

