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WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Tebuconazole. Review of Dog Chronic Toxicity Study.
Tox Chem No. 463P
PC-Code 128997
Submission Nos. S406879, S406875, S406862, S431101, S431102, S431100.
MRID Nos. 420306-01 & 425372-01 (Supplemental submission).
Case Nos. 194438, 280819, 280785.
Action Nos. 231, 251.
DP Barcode Nos. D171226, D171220, D171189, D185645, D185646, D185644.
ID No. 9F03818, 9H05575, 9F03724.

From: Alberto Protzel, Ph.D. 7/22/93
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

To: Ms. Susan Lewis/Mr. Benjamin Chambliss
Product Manager, Team 21.
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Thru: James N. Rowe, Ph.D., Head James N. Rowe 7/30/93
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D., Chief 8/4/93
Toxicology Branch II
Health Effects Division (H7509C)

ACTION: Review of the following study on the chemical HWG 1608 (Tebuconazole) Technical submitted by Miles Inc. :

Safety Evaluation of HWG 1608: Chronic (1 Year) Feeding Study in Dogs [Miles Report No. 99673 with MRID 420306-01 (Main Study) and Miles Report 99673-1 with MRID 425372-01 (Supplementary Data)].

CONCLUSION:

Tebuconazole was administered to pure-bred beagle dogs of both sexes for a period of up to 12 months in the diet at levels of 0, 100 ppm (LDT), and 150 ppm (HDT).

This study defines a systemic LOEL of 150 ppm (based on adrenal effects in both sexes) and a systemic NOEL of 100 ppm. The NOEL of 100 ppm defined by this study is higher than the original NOEL of 40 ppm defined in the initial minimum dog study (MRID 407009-40). This study, taken together with the initial chronic dog study [Mobay Report 95690, EPA MRID 407009-40] is classified as MINIMUM.

The current RfD for tebuconazole (0.01 mg/kg/day) is based on the original dog study, with the lower NOEL of 40 ppm.

DETAILED CONSIDERATIONS:

The present report is a follow-up of an initial 12-month dog oral study (Mobay Report 95690, EPA MRID 407009-40) reviewed on 1/3/89. The initial dog study (at dietary levels of 0, 40, 200 and 1000/2000 ppm) defined a systemic LOEL of 200 ppm (based on ocular lesions and hepatic toxicity in either sex) and a systemic NOEL of 40 ppm. The present study used lower dose levels to further define the NOEL for tebuconazole (HWG 1608).

Tebuconazole was administered to pure-bred beagle dogs of both sexes for a period of up to 12 months in the diet at levels of 0, 100 ppm (LDT), and 150 ppm (HDT). resulting in mean respective compound intakes of 0, 2.96 and 4.39 mg/kg body weight/day (males) and 0, 2.94, and 4.45 mg/kg body weight/day (females).

Histopathology examination indicated the adrenal gland as a target organ at 150 ppm in both sexes. In males there was hypertrophy of adrenal zona fasciculata cells amounting to 4/4 at 150 ppm and to 0/4 at 100 ppm and in controls. Other adrenal findings in males included fatty changes in the zona glomerulosa (3/4) and lipid hyperplasia in the cortex (2/4) at 150 ppm vs. 1/4 for both effects at 100 ppm and control dogs.

In females there was hypertrophy of zona fasciculata cells of the adrenal amounting to 4/4 at 150 ppm and to 0/4 at 100 ppm and 1/4 in controls. Fatty changes in the zona glomerulosa of the female adrenal amounted to 2/4 at 150 ppm and to 1/4 at 100 ppm and in controls.

This study defines a systemic LOEL of 150 ppm (based on adrenal effects in both sexes) and a systemic NOEL of 100 ppm. The NOEL of 100 ppm defined by this study is higher than the original NOEL of 40 ppm defined in the initial dog study (MRID 407009-40).

cc: Nan Gray HED/CCB (H7509C); George Ghali HED/PRS (H7509C)

C10471

Reviewed by: Alberto Protzel, Ph.D.
Review Section III, Toxicology Branch II(H7509C)
Secondary Review by: James N. Rowe, Ph.D.
Review Section III, Toxicology Branch II(H7509C)

Alberto Protzel 7/22/93
James N. Rowe 7/30/93

DATA EVALUATION RECORD

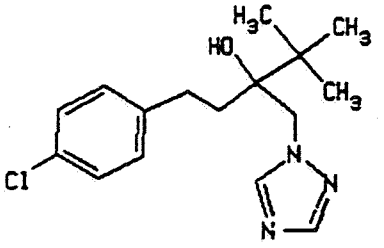
STUDY TYPE: 12-Month dog (oral)
Species: Dog (beagle)
EPA Guideline 83-1

TOX. CHEM. NO: 463P

EPA IDENTIFICATION NO.: EPA MRID Nos. 420306-01 (Main volume) and 425372-01 (Supplemental data).

TEST MATERIAL: HWG-1608 Technical

SYNONYMS/STRUCTURE: Tebuconazole; α-[2-(4-Chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1H -1,2,4-triazole-1-ethanol



STUDY NUMBER: 99673 (Main volume) and 99673-1 (Supplemental data).

TESTING FACILITY: Toxicology Department Miles Inc. P.O. Box 40. Elkhart, IN 46515. Bericht NR. R 4781.

TITLE OF REPORT: Safety Evaluation of HWG 1608: Chronic (1 year) feeding study in dogs.

AUTHOR: M.C. Porter, V. Jasty, C.M. Troup, and R.E. Hartnagel, Jr.

REPORT ISSUED: June 28, 1989 (Main study) and October 5, 1992 (Supplemental data).

CONCLUSIONS:

The present report is a follow-up of an initial 12-month dog oral study (Mobay Report 95690, EPA MRID 407009-40) reviewed on 1/3/89. The initial dog study (at dietary levels of 0, 40, 200 and 1000/2000 ppm) defined a systemic LOEL of 200 ppm (based on ocular lesions and hepatic toxicity in either sex) and a systemic NOEL of 40 ppm. The present study used lower dose levels to further define the NOEL for tebuconazole (HWG 1608).

Tebuconazole was administered to pure-bred beagle dogs of both sexes for a period of up to 12 months in the diet at levels of 0, 100 ppm (LDT), and 150 ppm (HDT). resulting in mean respective compound intakes of 0, 2.96 and 4.39 mg/kg body

weight/day (males) and 0, 2.94, and 4.45 mg/kg body weight/day (females).

Histopathology examination indicated the adrenal gland as a target organ at 150 ppm in both sexes. In males there was hypertrophy of adrenal zona fasciculata cells amounting to 4/4 at 150 ppm and to 0/4 at 100 ppm and in controls. Other adrenal findings in males included fatty changes in the zona glomerulosa (3/4) and lipid hyperplasia in the cortex (2/4) at 150 ppm vs. 1/4 for both effects at 100 ppm and control dogs.

In females there was hypertrophy of zona fasciculata cells of the adrenal amounting to 4/4 at 150 ppm and to 0/4 at 100 ppm and 1/4 in controls. Fatty changes in the zona glomerulosa of the female adrenal amounted to 2/4 at 150 ppm and to 1/4 at 100 ppm and in controls.

This study defines a systemic LOEL of 150 ppm (based on adrenal effects in both sexes) and a systemic NOEL of 100 ppm. The NOEL of 100 ppm defined by this study is higher than the original NOEL of 40 ppm defined in the initial dog study (MRID 407009-40).

CLASSIFICATION: This study, taken together with the initial chronic dog study (Mobay Report 95690, EPA MRID 407009-40), is classified as Minimum.

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A. Materials: (A photocopy of the methods is included as Attachment 1).

1. Test compound: HWG 1608 (Tebuconazole, technical grade). Description: None given. Batch No.: 16013/86 supplied by Bayer AG, Wuppertal, West Germany. Purity: Not given; however, the study protocol indicated that purity of batch 16013/86 was 96%. Contaminants: not listed.

2. Test animals: Species: dog. Strain: Pure-bred beagle. Age: nearly 6 months. Mean weight (at week 0): males, 6.1-9.2 kg; females, 5.3-7.3 kg. At week 0 the animals were within ±20% of the mean weight for each sex, except for the 100 ppm male 1348 which exceeded the mean by about 23%. Source: White Eagle Laboratories Inc. Doylestown, PA.

B. Study Design:

1. Dose Selection:

The present report is a follow-up of an initial 12-month dog oral study (Mobay Report 95690, EPA MRID 407009-40) reviewed by J.N. Rowe on 1/3/89. The initial dog study (at dietary levels of 0, 40, 200 and 1000/2000 ppm) was classified as Core minimum and defined a systemic LOEL of 200 ppm (based on ocular lesions and hepatic toxicity in either sex) and a systemic NOEL of 40 ppm. The present study was done at dose levels of 0, 100 and 150 ppm to further define the NOEL for tebuconazole.

2. Animal assignment:

The animals were assigned randomly to the test groups shown in Table 1. A 7-day (males) to 8-day (females) period of acclimation was allowed between receipt of shipment and start of treatment.

Table 1. Dosing groups for 1-year toxicity study of HWG 1608[a] in dogs.

Group number	Dose (ppm)	Main Group		Interim Sacrifice	
		Males	Females	Males	Females
1 Control	0	4	4[b]	N/A	N/A
2 (LDT)	100	4	4	"	"
3 (HDT)	150	4	4	"	"

[a] The original study [MRID 407009-40] was performed with HWG 1608 at dietary levels of 0, 40, 200, and 1000/2000 ppm.
[b] One female (#1360) was sacrificed on day 70 due to protracted elevated body temperature, anorexia, and deteriorating physical condition. Female #1365, from the same shipment of animals, replaced #1360 on study day 70.

3. Diet preparation

Diets were prepared every 2 to 4 weeks. Prepared diets were placed in labelled, tightly sealed containers and stored at room temperature. Just prior to feeding

each day, tap water (100 mL) was thoroughly mixed with the diet to increase palatability and minimize inhalation. Samples of treated food were analyzed for stability (dry form and wetted form) prior to study initiation and for test article concentration at time of diet preparation just prior to study initiation, during the second week of feeding and approximately every 2 or 3 months thereafter. Explicit tests for homogeneity were not reported.

To analyze for stability in dry test diets, prepared diets containing test material at 100 or 150 ppm were stored for up to 8 weeks in closed containers at ambient temperature. Random samples were obtained for analysis at the storage periods indicated in Table 2. As shown in Table 2, samplings obtained at up to 8 weeks do not deviate from the zero-time values by more than 10.6%.

Table 2. Assessment of stability in dry test diets[a]

Storage period. (Weeks)	Results for nominal concentrations of: 100 ppm		150 ppm	
	Mean ppm	% Deviation[b]	Mean ppm	%Deviation
0 (Initial)	103.2	-	155.9	-
1	100.8	-2.3	152.3	-2.3
2	99.4	-3.7	151.6	-2.8
4	100.0	-3.2	154.5	-0.9
6	89.4	-10.6	136.1	-9.3
8	96.4	-6.6	143.6	-7.9

[a] Data from (Appendix B) p. 54 of the Study Report.
[b] % Deviation from initial value.

To analyze for stability of wetted diets, samples of dry diet (300 g, amount consumed by dogs over a 24-hour period) containing 100 or 150 ppm test material were mixed with water (100 mL) and were analyzed for active ingredient after standing at room temperature for 48 hours prior to analysis. As shown below in Table 3, the mean value deviated by 3% or less from the nominal concentration.

Table 3. 48-Hour stability of wetted test diets[a]

Nominal Concentration (ppm)	Observed concentration mean ± S.D[b]. (ppm)	% Deviation
100	97.0 ± 1.9 (n=3)	-3.0%
150	147.0 ± 7.7 (n=3)	-2.0%

[a] Data from (Appendix B) p. 53 of the Study Report.
[b] Standard deviation (S.D.) for the 100-ppm value was reported by the Registrant, the S.D. for the 150-ppm value was calculated by the reviewer.

Concentration of test material was analyzed in diets prepared on the dates

indicated in Table 4. For each analysis five random samples were obtained for each dose level. As shown in Table 4, mean analytical values remained within 4.0% of the nominal at 100 ppm and within 4.3% of nominal at 150 ppm. These values are within acceptable variability for test substance concentrations.

Table 4. Analytical concentrations of HWG 1608 during testing[a]

Date of diet. preparation	Results for nominal concentrations of: 100 ppm		150 ppm	
	Mean ± S.D (ppm)	%Deviation[b]	Mean ± S.D.(ppm)	%Deviation
7/28/87	99.9 ± 5.6	-0.1	153.5 ± 2.1	+2.3
8/12/87	97.0 ± 1.9	-3.0	147.0 ± 9.4	-2.0
10/13/87	99.3 ± 3.6	-0.7	143.5 ± 5.7	-4.3
1/7/88	96.5 ± 4.2	-3.5	144.5 ± 6.5	-3.6
4/7/88	96.0 ± 1.8	-4.0	144.9 ± 2.5	-3.4
6/30/88	102.6 ± 10.1	+2.6	154.5 ± 9.0	+3.0

[a] Data from (Appendix B) pages 55 & 56 of the Study Report.
[b] % Deviation of mean from nominal value.

4. Statistics:

Body weights, food consumption, organ weights were analyzed using Dunnett's method. Clinical Pathology data were analyzed using the method of Bare (et al., 1978). Additionally, clinical pathology data were analyzed with Dunnett's method and the results were submitted in the supplementary volume (MRID 425372-01).

5. Compliance Statements:

A statement of data confidentiality (none claimed) and a flagging statement according to the criteria of 40 CFR 158.34 were included. Signed and dated statements of compliance with GLP standards and Quality Assurance were included.

C. Methods and Results:

1. Observations:

The animals were observed daily for signs of toxicity including changes in appearance and behavior. No individual animal data for clinical signs were given, except for a table of individual incidences of soft stool/diarrhea and individual animal results for physical examinations at pre-dosing, and 3, 6, and 12 months of treatment.

There was no mortality among treated animals. One control female (#1360) was sacrificed on day 70 due to protracted elevated body temperature, anorexia, and deteriorating physical condition. Female #1365, from the same shipment of animals, replaced control female #1360 on study day 70.

Incidences of soft stool/diarrhea were observed but the frequencies or number of occurrences did not appear to be dose-related. The authors reported also incidences of emesis (2 at the high dose, 5 at the mid dose and 2 in controls), but the listing of incidences was not supported by a table for individual animals.

Examination of the individual physical examination forms indicated that for females at 12 months, 2/4 at the HDT were slightly obese, 2/4 at the LDT were slightly obese or obese and 0/4 controls were obese.

2. Body weight:

The animals were weighed at weeks -1 and -2, weekly during the first 6 months and every two weeks thereafter. Individual animal weights were reported and group mean weights were calculated.

Table 5 shows selected group mean body weights during treatment. No significant differences in body weights and body weight gains were found between treated and control dogs.

Table 5. Selected group mean body weights of dogs treated with HWG 1608. Data from pp. 19-20 of the Study Report.

Day	Group mean body weights + S.E. (Kg)					
	Males (n=4/group)			Females (n=4/group)		
	0	100 ppm	150 ppm	0 ppm	100 ppm	150 ppm
0	7.1±0.53	7.6±0.64	7.6±0.65	6.4±0.38	6.5±0.42	6.3±0.35
28	7.7±0.57	8.2±0.55	8.5±0.77	7.0±0.38	7.3±0.52	6.9±0.54
56	8 ±0.65	8.8±0.56	9.3±1.0	7.2±0.25	8.0±0.66	7.7±0.75
84	8. ±0.67	9.3±0.51	9.9±1.22	7.6±0.41	8.5±0.89	8.3±0.81
112	9.2±0.74	9.7±0.56	10.3±1.33	8.0±0.40	9.2±1.00	8.8±0.86
140	9.7±0.82	9.9±0.72	10.7±1.38	8.4±0.42	9.9±1.19	9.2±0.91
175	10.1±0.88	10.1±0.94	10.8±1.45	8.7±0.50	10.7±1.43	9.5±0.92
210	10.6±0.99	10.3±1.20	11.2±1.50	9.1±0.56	10.8±1.35	9.9±1.04
238	11.1±1.08	10.8±1.37	11.6±1.60	9.4±0.62	10.9±1.40	10.4±1.22
266	11.4±1.18	11.0±1.30	11.9±1.60	9.7±0.75	10.9±1.40	10.9±1.29
294	12.0±1.37	11.6±1.39	12.1±1.67	10.2±0.92	11.3±1.46	11.3±1.24
336	12.7±1.63	12.2±1.54	12.8±1.61	10.5±0.89	12.2±1.64	11.8±1.15
364	13.1±1.82	12.6±1.73	12.8±1.52	10.6±0.92	12.3±1.57	12.0±1.09
Ter[a]	13.4±1.88	12.8±1.77	13.1±1.58	10.8±0.95	12.6±1.75	12.3±1.17
Gain[b]	6.2±1.55	5.2±1.24	5.5±1.03	4.4±0.62	6.1±1.37	6.0±0.85

[a] Terminal sacrifice was done after days 369-370 of treatment
[b] Mean weight gain between days 0 and terminal sacrifice.

3. Food consumption and compound intake:

Test diet consumption was recorded daily and statistically analyzed weekly during the first 6 months and every two weeks thereafter. Individual and group mean data were reported weekly for the first six months and for every two weeks thereafter.
No statistically significant differences in diet consumption were found.

Mean compound intake over the course of the study (mg/kg b.wt./day) was proportionally increased in both sexes as follows:

- Males: 2.96 and 4.39 for the 100, and 150 ppm treatment groups, respectively. (From p. 12 of the Study Report).

- Females: 2.94 and 4.45 for the 100, and 150 ppm treatment groups, respectively. (From p. 12 of the Study Report).

Table 6. Selected food consumption values of dogs treated with HWG 1608. Data from pp. 21-22 and 65-76 of the Study Report.

Week	Mean food consumption values (g/kg body weight/day)					
	Males (n=4)			Females (n=4)		
	0	100 ppm	150 ppm	0 ppm	100 ppm	150 ppm
1	210.0±0.00	210.0±0.00	210.0±0.00	210.0±0.00	210.0±0.00	210.0±0.00
4	210.0±0.00	210.0±0.00	210.0±0.00	210.0±0.00	210.0±0.00	210.0±0.00
17	210.0±0.00	210.0±0.00	209.3±0.73	210.0±0.07	210.0±0.07	210.0±0.07
29	210.0±0.00	200.8±9.20	204.4±5.56	210.0±0.07	198.7±11.28	210.0±0.07
35	210.0±0.07	202.9±7.12	195.6±14.37	210.0±0.07	188.9±12.27	206.3±3.74
41	210.0±0.19	208.4±1.59	205.4±4.58	210.0±0.00	204.3±3.32	200.8±5.46
47	210.0±0.07	203.7±3.92	190.6±11.54	181.8±24.29	204.6±3.11	192.6±6.70
52	150.0±0.00	135.4±8.92	140.6±6.25	175.5±4.51	171.9±8.10	177.7±2.33

4. Ophthalmological examinations:

Ophthalmological examinations were performed by a veterinarian on all dogs before treatment (9 days before day 0 of dosing), and at 3, 6 and 12 months after the beginning of treatment. The individual examination forms indicated that the lens, cornea, iris, sclera, conjunctiva and fundus of both eyes were examined. No instances of corneal or lenticular opacities were reported. No treatment-related effects were observed.

5. a. Hematology:

Hematology parameters were determined for all dogs on 3 "pretreatment occasions" (actual dates or time span before dosing were not specified), and at 15, 26, and 52 weeks of treatment. Blood samples were obtained by jugular puncture. The checked (x) parameters were examined:

- x Hematocrit (HCT)*
- x Hemoglobin (HGB)*
- x Erythrocyte count*
- x Leucocyte count (WBC)*
- x Platelet count *
- Blood clotting measurements
- x -Partial thromboplastin time
- -Clotting time
- x -Prothrombin time
- x Leucocyte differential count*
- x Mean corpuscular HGB (MCH)
- x Mean corpuscular HCB conc. (MCHC)
- x Mean corpuscular volume (MCV)
- x Reticulocyte count
- x Blood sedimentation rate (BSG)
- x Erythrocyte appearance

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* Required for subchronic and chronic studies

There were no apparent changes in the above-listed hematological parameters when means for dosed groups (MRID 425372-01, Supplemental submission to the Study report, EPA MRID 420306-01) were compared with untreated controls.

In all groups (controls and treated) mean values for HGB and HCT almost always were higher at 26 or 52 weeks than before treatment. This effect was also seen sporadically for MCH and MCV (MRID 425372-01, Supplemental submission to EPA MRID 420306-01).

Blood cell aberrations for the period prior to dosing and for the 52-week examination were not significantly different in number or intensity; they are summarized in Table 7:

Table 7. Summary of RBC aberrations for the pretreatment period and at 52 weeks. (Compiled by the reviewer from individual animal data in pages 81-132 of the Study Report).

Aberration[a]	Control		100 ppm		150 ppm	
	Prior	52-Week	Prior	52-Week	Prior	52-Week
Males						
Polychromasia	1[b]	2	1	1	1	3
Hypochromasia	4	3	4	3	4	2
Poikilocytosis	0	3	1	0	1	2
Anisocytosis	4	3	4	3	4	1
Females						
Polychromasia	4	4	3	2	1	3
Hypochromasia	4	0	4	1	3	3
Poikilocytosis	0	2	1	0	0	1
Anisocytosis	4	4	4	4	4	4

[a] Aberrations were ranked in three categories of increasing severity: 1, 2, and 3. Only categories 1 (slight) and 2 (moderate) were seen, and they have been lumped together to obtain the values in this table.
[b] Numbers indicate incidence/group of 4 dogs.

5b. Clinical Chemistry.

Clinical chemistry parameters were determined for all dogs on 3 "pretreatment occasions" (actual dates or time span before dosing were not specified), and at 15, 26, and 52 weeks of treatment. Blood samples were obtained by jugular puncture. The checked (x) parameters were examined:

Electrolytes:
x Calcium*
x Chloride*
Magnesium*
x Inorganic Phosphate*
x Potassium*
x Sodium*

Enzymes:
x Alkaline phosphatase
x Aspartate aminotransferase (SGOT)*
x Alanine aminotransferase (SGPT)*
x Gamma-glutamyl transpeptidase (GGTP)
Glutamate dehydrogenase
Cholinesterase'
Creatine phosphokinase

Other:
x Albumin*
x Creatinine*
x Blood urea nitrogen*
x Cholesterol*
x Globulin*
x Albumin/globulin
x Total serum protein*
x Total bilirubin
x Glucose*
x Triglycerides (serum)
x Triglycerides (liver)

Microsomal Enzymes:
x Cytochrome P-450
x N-demethylase
x O-demethylase

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* Required for subchronic and chronic studies
' Should be required for OP's.
• Not required for sub-chronic studies.

No significant differences between treated animals and controls were observed in clinical chemistry values. Alkaline phosphatase activities decreased (e.g. 198 U/l at pre-treatment and 114 U/l at 52 weeks in male controls), and blood urea nitrogen increased (e.g. 9.5 mg/dl at pre-treatment and 15.7 at 52 weeks in male controls) during the treatment period (Table 8).

Liver triglyceride levels and microsomal enzyme activities at sacrifice are shown in Table 9. O-demethylase was statistically significantly increased in mid-dose females but the effect was not dose-related. N-demethylase activity was decreased in a dose-related fashion in females; in the absence of histopathological correlates, the effect is not likely to be toxicologically significant.

6. Urinalysis.

Samples for urinalysis were obtained for all dogs on 3 "pretreatment occasions" (actual dates or time span before dosing were not specified), and at 15, 26, and

52 weeks of treatment. The checked (x) parameters were examined:

Appearance*	x Glucose*
x Volume*	x Ketones*
x Specific gravity	x Bilirubin*
x pH	x Blood*
x Sediment (microscopic)*	x Urobilinogen
x Protein*	x Chloride
x Potassium	x Sodium

* Required for chronic studies.

No treatment-related effects on urinalysis were observed.

Table 8. Summary of selected clinical chemistry values in dogs treated with HWG 1608. Data abstracted from pp. 13, 14, 16, 22, 23, 25, of the Supplemental Submission (MRID 425372-01) to the Study Report.

Time	Mean clinical chemistry values					
	Males			Females		
	0 ppm	100 ppm	150 ppm	0 ppm	100 ppm	150 ppm
Alkaline Phosphatase (U/l)						
Pre_3*	198.25	195.62	213.67	221.22	201.05	207.55
Pre_2	201.90	201.95	207.87	210.90	193.35	206.45
Pre_1	186.97	180.47	188.40	206.67	178.75	199.50
Week 15	182.65	142.87	156.72	189.67	169.75	195.22
Week 26	137.47	109.12	137.10	153.62	119.62	143.10
Term (Wk. 52)	114.0	90.27	81.10	104.07	95.70	106.17
Blood Urea Nitrogen (mg/dl)						
Pre_3	9.50	7.55	7.85	8.90	9.45	7.07
Pre_2	9.40	7.55	8.47	9.22	8.67	8.37
Pre_1	9.92	8.35	9.65	8.92	8.55	8.77
Week 15	15.40	12.17	14.30	14.70	15.10	13.80
Week 26	17.50	13.05*	17.65	16.60	16.00	16.80
Term (Wk. 52)	15.70	13.57	14.52	12.95	14.57	13.52
Inorganic Phosphate (mg/dl)						
Pre_3	7.49	7.01	7.85	8.12	7.89	7.45
Pre_2	7.09	6.86	7.36	7.15	7.00	6.74
Pre_1	6.65	6.62	6.73	6.67	6.76	6.42
Week 15	4.82	4.68	5.07	5.12	5.23	4.95
Week 26	4.07	4.12	4.87	4.23	4.62	4.52
Term (Wk. 52)	4.11	3.93	4.53*	4.36	3.98	4.07

* Actual dates or time span before dosing were not specified for Pre_1, Pre_2, and Pre_3.
* $p \leq 0.05$ vs controls; ** $p \leq 0.01$

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Table 9. Mean levels of hepatic triglycerides and microsomal enzymes (from p. 83 of the Study Report).

Parameter:	Level in:		
	Control	100 ppm	150 ppm
Males			
NDEM[a]	0.4517	0.5045	0.3380
ODEM[b]	0.434	0.550	0.556
CP450[c]	0.4652	0.4742	0.4735
TRIG[d]	1324	1560	1547
Females			
NDEM	0.5705	0.4545*	0.3450*
ODEM	0.5142	0.7025*	0.4860
CP450	0.4412	0.5182	0.3930
TRIG	1369	1335	1649

[a] NDEM: N-demethylase, µmol HCHO/mg protein.
[b] ODEM: O-demethylase, µmol p-nitrophenol/mg protein.
[c] CP450: Cytochrome P_{450}, µmol/mg protein.
[d] TRIG: Triglycerides, mg/dl.

7. Sacrifice and Pathology:

Except for a control female (No. 1360), which was sacrificed in extremis on day 68 of treatment, all animals were sacrificed after 369-370 days of treatment. All animals were subject to gross pathological examination and the CHECKED (X) tissues listed below were collected for histological examination. The DOUBLE-CHECKED (XX) organs, in addition, were weighed.

Digestive System		**Cardiovasc./Hemato.**		**Neurologic**	
-	Tongue	X	Aorta	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Periph. nerve (sciatic)*
X	Esophagus*	X	Bone marrow (rib)	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Eyes
X	Duodenum*	X	Spleen*+	X	Optic nerve
X	Jejunum*	X	Thymus*	**Glandular**	
X	Ileum*	**Urogenital**		XX	Adrenal gland*+
-*	Cecum*	XX	Kidneys*+	-	Lacrimal gland
X	Colon*	X	Urinary bladder*	X	Mammary gland*
X	Rectum*	XX	Testes*+	X	Parathyroid*b
		X	Seminal vesicles	X	Pituitary*
XX	Liver*+	X	Epididymides	X	Thyroid*
XX	Gall bladder*	X	Prostate	**Other**	
X	Pancreas*	X	Uterus*	X	Skeletal muscle (thigh)*
Respiratory		XX	Ovaries*	X	Skin*
X	Trachea*	-	Oviduct	X	All gross lesions and masses*
X	Lung*- (left, post.)	X	Vagina*	-	Harderian gland
-	Nose			-	Head with nasal cavities.
-	Pharynx	X	Ureter	X	Bone (costocondral)*
X	Larynx	X	Urethra	-	Eyelids
-	Nasal turbinates			-	Extraorbital glands
				-	Perianal glands
				-	Tooth
				-	Zymbal glands

* Required for carcinogenicity studies (EPA Guideline 83-2)
- Organ weights required in carcinogenicity studies (EPA Guideline 83-2).
* Not collected for microscopic examination.
b Parathyroids were examined only if present in thyroid section (an attempt was made to assure that parathyroids were present).

a. Organ weights

A summary of mean absolute and relative organ weights final sacrifice for males and females is presented below in Tables 10 and 11, respectively. No statistically significant differences between control and treated groups were observed.

Table 10. Mean absolute and relative organ weights in male dogs at final sacrifice. Data from pp. 23, 356 and 358 of the Study Report.

Organ	Mean Absolute (g)/Relative organ weight (g/kg b.w.)		
	0 ppm	100 ppm	150 ppm
Body weight (kg)	13.375	12.850	13.075
Adrenal	1.39/0.11	1.56/0.13	1.26/0.10
Brain	76.40/6.10	76.62/6.12	82.08/6.49
Heart	97.53/7.58	93.83/7.45	101.63/7.93
Kidney	62.26/4.74	62.99/5.00	66.18/5.04
Liver	363.7/27.4	323.1/25.7	318.0/24.3
Pituitary	0.084/0.007	0.093/0.007	0.082/0.007
Spleen	34.49/2.59	24.74/1.93	34.91/2.66
Thyroids	1.37/0.10	1.78/0.14	1.67/0.13
Thymus	3.38/0.27	2.87/0.22	3.64/0.27
Testis	18.08/1.36	18.16/1.47	18.27/1.41

* Values are means of 4 animals.

Table 11. Mean* absolute and relative organ weights in female dogs at final sacrifice. Data from pp. 24, 357 and 359 of the Study Report.

Organ	Mean Absolute (g)/Relative organ weight (g/kg b.w.)		
	0 ppm	100 ppm	150 ppm
Body weight (kg)	10.825	12.575	12.300
Adrenal	1.45/0.13	1.66/0.14	1.36/0.11
Brain	79.39/7.51	75.12/6.46	75.94/6.31
Heart	79.81/7.45	74.66/6.40	80.33/6.65
Kidney	51.41/4.82	57.79/4.72	55.02/4.55
Liver	284.1/26.2	338.3/27.7	318.4/26.1
Pituitary	0.072/0.007	0.075/0.006	0.072/0.006
Spleen	23.50/2.21	22.35/1.91	24.71/2.07
Thyroids	1.14/0.11	1.17/0.10	1.11/0.09
Thymus	4.32/0.39	4.99/0.41	2.61/0.21
Ovary	1.02/0.10	1.51/0.12	1.10/0.09

* Values are means of 4 animals.

b. Gross pathology

Gross pathology examination of the animals did not reveal any apparently treatment-related effects. One low-dose male (No. 1356) had a light yellow area (siderotic plaque) on the edge of the spleen. One high-dose male (No. 1339) had a loosely attached cyst on the cerebellum, and another high-dose male (No. 1350) had an enlarged prostate. A high-dose female (No. 1370) had a siderotic plaque on the spleen.

c. Microscopic pathology

Except for one control female (No. 1360), sacrificed in extremis on day 70 and replaced by female No. 1365, all animals survived until terminal sacrifice and were examined histopathologically.

1. Non neoplastic lesions

In males (Table 12), there was hypertrophy of zona fasciculata adrenal cells amounting to 4/4 at the HDT and to 0/4 at the LDT and in controls. Other adrenal findings included fatty changes in the zona glomerulosa (3/4) and lipid hyperplasia

in the cortex (2/4) at the HDT vs. 1/4 for both effects in LDT and control dogs.

In females (Table 13) there was hypertrophy of zona fasciculata cells of the adrenal amounting to 4/4 at the HDT and to 0/4 at the LDT and 1/4 in controls. Fatty changes in the zona glomerulosa of the adrenal amounted to 2/4 at the HDT and to 1/4 at the LDT and in controls.

Hepatic findings in males (Table 12) included an apparently dose-related increase in lipofuscin granules (4/4) at the HDT, (3/4) at the LDT and 0/4 in controls; additionally, the degree of the effect seemed to increase with dose: minimal/mild at the LDT increased to mild/moderate at the HDT. In females (Table 13) the incidence of lipofuscin granules decreased (in frequency and degree) with increasing dose: 4/4 (controls), 3/4 (LDT) and 1/4 (HDT), suggesting that the pattern of lipofuscin granules in males is fortuitous and not treatment-related.

It is noted that the initial 1-year dog study [MRID 407009-40] reported Oil Red O (ORO)-positive staining Kupfer cells in 200 ppm (1/4) and 1000/2000 ppm (1/4) dogs vs none in 40 ppm or control animals. The present study did not include staining of liver sections with Oil Red O (ORO) thus it is not possible to ascertain if the effect is present at the dose levels used in this study.

2. Neoplastic lesions

No neoplasms were found in this study.

Table 12. Histologic findings in treated male dogs (Compiled by the reviewer from individual animal data in pages 314-343 of the Study Report).

Finding	Control				100 ppm (LDT)				150 ppm (HDT)				Totals[b]		
	42[a]	43	45	55	40	48	56	57	39	41	47	50	Cont.	LDT	HDT
ADRENALS															
Accessory cortical tissue	-	-	-	-	-	-	(2)[c]		-	-	-	-	0	1	0
Infilt. lympho. cortex	-	-	-	-	-	-	-	-	-	-	-	<2>	0	0	1
Fatty change, zona glomerulosa	-	-	-	<1>	<1>	-	-	-	<1>	(1)	-	<1>	1	1	3
Lipid hyperplasia, cortex	-	<2>	-	-	-	(1)	-	-	-	<1>	-	<1>	1	1	2
Hypertrophy, z. fascic. cells	-	-	-	-	-	-	-	-	<1>	<2>	<1>	<2>	0	0	4
LIVER															
Hepatitis, subacute/chronic	[2]	[2]	[2]	[1]	[1]	[2]	-	-	(2)	[1]	[1]	[1]	4	2	4
Lipofuscin, hepatocyte	-	-	-	-	[2]	[1]	-	[1]	[2]	[2]	[2]	[3]	0	3	4
Vacuolar change, glycogenic	-	[2]	-	-	-	-	-	-	-	-	-	-	1	0	0
Inflammation, portal tract	-	-	(1)	-	(2)	-	-	-	-	-	-	-	1	1	0
Vacuolar change, hydropic, hepat.	-	[2]	-	[1]	[1]	-	-	-	-	[2]	-	[2]	2	1	2
Fibroplasia, portal triad	-	-	-	-	-	(2)	-	-	-	-	-	-	0	1	0

[a] The identification number for each animal was shortened by the reviewer for tabulation purposes: No. 42 corresponds to animal No. 1342, No. 43 corresponds to animal No. 1343 etc.
[b] "Totals" equals the number of dogs at the indicated dose level that show the effect.
[c] Numbers in (), [], or <> indicate degree of effect: 1 = minimal, 2 = mild, 3 = moderate. Symbols represent the following: () = focal/unilateral, [] = locally extensive/diffuse, <> = bilateral, for paired organs.

Table 13. Histological findings in treated female dogs (Compiled by the reviewer from individual animal data in pages 314-343 of the Study Report).

Finding	Control				100 ppm (LDT)				150 ppm (HDT)				Totals[b]		
	61[a]	65	67	76	62	68	69	75	58	66	70	73	Cont.	HDT	HDT
ADRENALS															
Accessory cortical tissue	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0
Infilt. lympho. cortex	(2)[c]		-	-	-	-	(2)	-	-	-	-	(2)	1	1	1
Fatty change, zona glomerulosa	-	-	(1)	-	-	-	<2>	-	-	-	<3>	<2>	1	1	2
Lipid hyperplasia, cortex	-	<2>	-	-	<2>	-	(1)	-	-	<1>	-	<2>	1	2	2
Hypertrophy, z. fascic. cells	-	<1>	-	-	-	-	-	-	<1>	<2>	<2>	<2>	1	0	4
LIVER															
Hepatitis, subacute/chronic	[1]	[1]	[2]	[2]	(2)	[2]	[1]	[1]	-	(1)	[1]	-	4	4	2
Lipofuscin, hepatocyte	[2]	[2]	[3]	[1]	-	[2]	[2]	[1]	-	[2]	-	-	4	3	1
Vacuolar change, glycogenic	-	-	-	-	[3]	-	-	[2]	-	-	-	-	0	2	0
Inflammation, portal tract	-	-	-	(2)	-	-	-	-	(2)	(2)	-	-	1	0	2
Vacuolar change, hydropic, hepat.	-	[2]	-	[2]	-	[1]	-	-	-	-	-	[2]	2	1	1

[a] The identification number for each animal was shortened by the reviewer for tabulation purposes: No. 61 corresponds to animal No. 1361, No. 65 corresponds to animal No. 1365, etc.
[b] "Totals" equals the number of dogs at the indicated dose level that show the effect.
[c] Numbers in (), [], or <> indicate degree of effect: 1 = minimal, 2 = mild, 3 = moderate. Symbols represent the following: () = focal/unilateral; [] = locally extensive/diffuse; <> = bilateral, for paired organs.

D. Discussion:

The present report is a follow-up of an initial 12-month dog oral study (Mobay Report 95690, EPA MRID 407009-40) reviewed on 1/3/89. The initial dog study (at dietary levels of 0, 40, 200 and 1000/2000 ppm) defined a systemic LOEL of 200 ppm (based on ocular lesions and hepatic toxicity in either sex) and a systemic NOEL of 40 ppm. The present study was done at lower dose levels to further define the NOEL for tebuconazole (HWG 1608).

HWG 1608 was administered to beagle dogs of both sexes for a period of 12 months in the diet at levels of 0, 100 ppm (LDT), and 150 ppm (HDT) resulting in mean, respective, compound intakes of 0, 2.96, and 4.39 mg/kg body weight/day (males) and 0, 2.94, and 4.45 mg/kg body weight/day (females).

No apparent compound-related effects upon mortality, adverse clinical signs, body weight gain or food consumption were noted.

In contrast to the results observed at higher doses in the initial study (MRID 407009-40), ophthalmological examination revealed no treatment-related eye effects; no instances of corneal or lenticular opacities in the eyes were reported at any time.

Gross pathology did not reveal any treatment-related effects. Microscopic examination of tissues revealed effects to the adrenal gland limited to the HDT in both sexes:

- In males (Table 12) there was hypertrophy of zona fasciculata cells amounting to 4/4 at the HDT and to 0/4 at the LDT and in controls. Other adrenal findings at the HDT included fatty changes in the zona glomerulosa (3/4) and lipid hyperplasia in the cortex (2/4) vs. 1/4 for both effects in LDT and control dogs.

- In females (Table 13) there was hypertrophy of zona fasciculata cells of the adrenal amounting to 4/4 at the HDT and to 0/4 at the LDT and 1/4 in controls. Fatty changes in the zona glomerulosa of the adrenal amounted to 2/4 at the HDT and to 1/4 at the LDT and in controls.

It is noted that the initial 1-year dog study [MRID 407009-40] reported Oil Red O (ORO)-positive staining Kupfer cells in 200 ppm (1/4) and 1000/2000 ppm (1/4) dogs vs none in 40 ppm or control animals. The present study did not include staining of liver sections with Oil Red O (ORO) thus it is not possible to ascertain if the effect is present at the dose levels used in this study.

Attachment 1

Experimental procedure (Copied from pages 6-10 of the Study Report, Miles Report 99673, EPA MRID 420306-01).

TEBUCONAZOLE

TOX R 010471

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