SECTION HEAD 2

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

009462

APR 27 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: HWG 1608 (Tebuconazole) technical. Teratogenicity data review.
Tox Chem No. 463
HED Project No. 2-1198
MRID No. 421750-01
Barcode No. D170624
Submission No. S406118

From: Alberto Protzel, Ph.D. 4/21/92
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

To: Mr. Benjamin Chambliss/Ms. Susan Lewis (PM-21)
Fungicide-Herbicide Branch
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Thru: James N. Rowe, Ph.D., Head 4/21/92
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D., Chief 4/23/92
Toxicology Branch II
Health Effects Division (H7509C)

ACTION: Review of the following studies on the chemical HWG 1608 (Tebuconazole) Technical submitted by Mobay Corporation:

1. Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Mouse (Dermal Application). [MRID 420103-01].

2. Supplementary study to: "Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Mouse (Dermal Application)". This supplementary study was imbedded in the main study, it was not presented as a separate document. [MRID 420103-01].

CONCLUSIONS:

1. Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Mouse (Dermal Application).

Dermal administration of tebuconazole in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day during days 6-15 of gestation in the NMRI/KFM/HAN mouse did not produce any evidence of maternal toxicity, as determined by mortality, clinical observations, mean body weights, mean body weight gains (corrected and uncorrected), food consumption and gross pathology findings. A supplementary study (See below), done to assess the maternal toxicity of tebuconazole, indicated a maternal toxicity LOEL of 300 mg/kg/day and a NOEL of 100 mg/kg/day. Although palatoschisis and exencephaly were observed, these were not statistically significantly elevated vs controls.

Examination of the skeletal findings revealed statistically significant ($p \leq 0.05$) increases vs controls in the HDT fetal incidences of bipartite sternebra (11 vs 3.8%), supernumerary ribs (72 vs 48%), and non-ossification of phalanxes in the forelimbs (e.g. 12.4 vs 6.2%), in addition to up to two-fold increases in their litter incidences. These statistically significant increases in fetal incidences of skeletal variations, coupled to marked increases in their litter incidences (e.g. bipartite sternebrae 20% controls up to 40% at the HDT) are suggestive of an incipient treatment-related developmental effect at the HDT. Thus, this study defines a LOEL of 1000 mg/kg/day and a NOEL of 300 mg/kg/day for developmental toxicity.

The study was classified as CORE: Minimum

2. Supplementary study to: "Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Mouse (Dermal Application)". This supplementary study was imbedded in the main study, it was not presented as a separate document.

In this supplementary study with NMRI/KFM/HAN mice, dermal application of tebuconazole followed the same protocol as in the main study (tebuconazole in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day during days 6-15 of gestation). It is tentatively concluded that maternal toxicity /physiological alterations occurred at the MDT and the HDT. Liver Microsomal enzymes (cytochrome P-450, N- and O-demethylase) were significantly elevated (37-100%, $p \leq 0.01$) at the MDT and the HDT. Periportal fatty deposition in the liver was observed at at the MDT and the HDT. Alanine aminotransferase activity in plasma (ALT/GPT) increased in dose-dependent fashion (up to 37% at the HDT) and reached statistical significance at the HDT. All of these changes are consistent with a toxic effect on liver at the MDT. A dermal maternal toxicity LOEL of 300 mg/kg/day is set based on the induction of microsomal enzymes and periportal fatty deposition in liver. The maternal toxicity NOEL is set at 100 mg/kg/day.

The study was classified as: Acceptable.

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GUIDELINE: 83-3

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

4/21/92

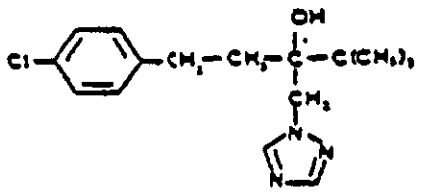
4/21/92

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity (Dermal application)
Species: Mouse
EPA Guideline: 83-3

EPA Identification No.s: EPA MRID No. 420103-01
Caswell No. 463P
HED Project No. 2-0329
DP Barcode No. D170624
Submission No. S406118

Test Material: HWG 1608 (Technical) 98.1% a.i., Batch No. 16002/85 (Main study).



Synonyms: Tebuconazole; α-[2-(4-Chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol.

Sponsor: BAYER AG; Institut fur Toxicologie Landwirtschaft; Wuppertal 1; Federal Republic of Germany.

Study Number: 224256

Testing Facility: RCC, Research and Consulting Company AG. P.O. Box CH 4452. Itingen/Switzerland.

Title of Report: Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Mouse (Dermal Application).

Author(s): H. Becker et al.

Report Issued: July 16, 1990

Conclusions:

Dermal administration of tebuconazole in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day, 6h/day, during days 6-15 of gestation in the NMRI/KFM/HAN mouse did not produce any evidence of maternal toxicity. A supplementary study (MRID 420103-01, submitted in the same volume with the present study)

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with NMRI/KFM/HAN mice dosed according to the same protocol indicates a maternal toxicity dermal NOEL of 100 mg/kg/day and a maternal toxicity dermal LOEL of 300 mg/kg/day based on histological observation of dose-dependent fatty changes in periportal areas of the liver, statistically significant elevation of plasma (ALT/GPT) at the HDT, and induction of liver microsomal enzymes at the MDT and the HDT.

The fetal incidence of palatoschisis was somewhat higher at the HDT (12/285, 4.2%) than in concurrent controls (8/301, 2.7%), but it was not statistically significant. Litter incidence was 7/25 litters (28%) in both HDT and concurrent controls. Historical control incidence of palatoschisis (1 study) was 5/307 fetuses (1.6%) and 5/24 litters (20.8%).

The fetal incidence of exencephaly was somewhat higher at the HDT (2/285, 0.7%) than in concurrent controls (1/301, 0.3%), but it was not statistically significant. Litter incidence was 1/25 litters (4%) in both HDT and concurrent controls. Historical control incidence of exencephaly was 5/307 fetuses (0.3%) and 1/24 litters (4.2%).

Examination of the skeletal findings revealed statistically significant increases vs controls in the HDT fetal incidences of bipartite sternebra (11 vs 3.8%), supernumerary ribs (72 vs 48%), and non-ossification of phalanxes in the forelimbs (e.g. 12.4 vs 6.2%), in addition of up to two-fold increases in their litter incidences. These statistically significant increases in fetal incidences of skeletal variations, coupled to marked increases in their litter incidences (e.g. bipartite sternebrae 20% controls up to 40% at the HDT) are suggestive of an incipient treatment-related effect at the HDT. Thus, this study defines a tentative LOEL of 1000 mg/kg/day and a NOEL of 300 mg/day for developmental toxicity.

D. Study Deficiencies:

No significant study deficiencies were noted.

E. Core Classification: Core minimum

Maternal NOEL = 100 mg/kg/day
Maternal LOEL = 300/mg/kg/day
Developmental Toxicity NOEL = 300 mg/kg/day
Developmental Toxicity LOEL = 1000 mg/kg/day

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A. Materials

A copy of the "Materials and Methods" section from the report is appended.

Test Compound: Purity: 98.1% (Main study)
Description: Colorless crystals
Lot No.: 16002/85 (Main study)
Contaminants: A certificate of analysis was included.

Vehicle(s): Aqueous 4.0% (w/v) carboxymethylcellulose, CMC (Fluka AG).

Test Animal(s): Species: Mouse
Strain: NMRI KFM-HAN (Outbred, SPF quality)
Source: KFM, Kleintierfarm Madorin AG, Switzerland
Age: 8 weeks at mating
Weight: 22-38 g

B. Study Design

This study was designed to assess the effects of HWG Technical on embryonic and fetal development in the mouse when applied dermally on days 6-15 of gestation.

Mating:

Mating took place overnight, one male was placed with three females. The day in which a vaginal plug was found was designated as day 0 of gestation (day 0 post-coitum).

Group Arrangement:

Animals were randomized using a computer generated algorithm. Dose levels are shown in Table 1.

Table 1. Dose levels used in testing

Test Group	Dose Level (mg/kg)	Number Assigned
Control	0 (Vehicle Control)	35 (1-34)
Low dose (LDT)	100	30 (35-64)
Middle dose (MDT)	300	34 (65-98)
High dose (HDT)	1000	30 (99-128)

Dosing:

All doses were administered by the dermal route in a volume of 2.5 ml/kg of body weight/day in aqueous 4% CMC during the dosing period. The dosing solutions were applied evenly to the shaved skin of the back (approx. 10% of the body surface) once daily on days 6 through 15 of gestation. The area of application was covered with an occlusive bandage; the bandage was removed after six hours of contact. It was not stated if the skin was washed after

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removal of the bandages. The dosing volume (2.5 ml/kg/day) was adjusted daily for changes in body weight.

Dosing suspensions were prepared daily. The suspensions were reportedly analyzed for concentration, homogeneity, and stability on five occasions during the dosing period and for concentration and homogeneity once during the dosing period. Samples analyzed on 12/28/88, 1/10/89, and 3/1/89 ranged from 88.1-92.0% of nominal. A sample analyzed on 2/27/89 had a range of 68.1-79.3% of nominal. Data for one analysis indicated that an HWG-1608 suspension was stable for at least 6 hours after preparation. Analytical data for all the six occasions in which analyses were reportedly done were not available for review. The four reported dates of analysis 12/28/88, 1/10/89, 2/27/89, 3/1/89 make it unclear whether the dosing was done with one or two batches of animals (i.e 12/28/88-1/10/89 and 2/27/89-3/1/89). No explanation was offered by the authors.

Table 2. Day 0 of gestation at the various dosage groups.

Control		LDT		MDT		HDT	
No.[a] Dams	Day 0 of Gestation	No. Dams	Day 0 of Gestation	No. Dams	Day 0 of Gestation	No. Dams	Day 0 of Gestation
16(1)	12/29-1/2	20(0)	12/29-1/2	16(3)	12/29-1/2	20(0)	12/29-1/2
9(5)	1/12-1/15	5(3)	1/12-1/15	9(7)	1/12-1/14	5(2)	1/12-1/15
9(2)	2/13	5(2)	2/11-2/13	9(0)	2/13	5(1)	2/11-2/13

[a] Number of mated dams. Numbers in parenthesis indicate number of non-pregnant dams.

Observations:

The animals were checked for mortality and systemic symptoms twice each day of the entire study. Skin reaction was assessed by the Draize scoring system. Body weights were recorded daily from day 0 of gestation through day 18 of gestation. The dams were sacrificed at day 18 of gestation.

Examinations at sacrifice consisted of: examination of gross lesions, counting of corpora lutea, determination of the number, distribution, and viability of any fetuses present. The uteri (and contents) of all females with live fetuses were weighed to determine corrected body weight gains. If no implantation sites were evident, the uterus was placed in aqueous ammonium sulfide for visualizing possible implantation sites.

The fetuses were examined in the following manner: the fetuses were weighed, sexed and examined for external alterations. One half of the live fetuses were examined by Wilson's slicing technique for examination of the viscera and brain. The remaining fetuses were cleared in potassium hydroxide and stained

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with alizarin red S for evaluation of skeletal malformations.

Historical control data were provided to allow comparison with concurrent controls.

Statistical analysis

The following statistical analysis methods were employed:

Dunnett's test (many-one t-test) was used to compare treated groups with controls if the variables followed a normal distribution; if the variables were not normally distributed, the Steel-test (many-one rank test was used. Fisher's exact test was applied if the variables could be dicotomized without loss of information.

Compliance:

A signed Statement of No Confidentiality Claim was provided.

A signed and dated Statement of compliance with EPA GLP's was provided.

A signed and dated Quality Assurance Statement was provided.

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Results:

1. Maternal Toxicity

Mortality:

No deaths were observed during the course of the study.

Clinical Observations:

No abnormal clinical signs were observed. One dam in the HDT (dam #102) delivered spontaneously on day 17 of gestation (7 fetuses were found dead in the morning of day 17 of gestation) and was sacrificed: necropsy revealed 7 empty implantation sites and one dead fetus in the left uterine horn and 6 live fetuses in the right uterine horn.

Reportedly there were no local skin reactions, the Draize scores, however, were not reported.

Body Weights

There were no apparent effects on mean body weights (Table 3) or on mean body weight gains (Table 4). An instance of statistically significant ($p<0.05$) increased body weight in the LDT at 12 days (38 g vs 36 g in controls) is regarded as incidental, not dose-related, and not treatment related.

Table 3. Mean body weights (From pp. 43-50 of the Study Report).

Test Group	Body Weights, g(s.d.)					
	Day 0	Day 6[a]	Day 12	Day 15[b]	Day 16	Day 18[c]
Control	28 (2.6)	32 (3.1)	36 (3.1)	42 (3.9)	45 (4.6)	53 (6.3)
LDT	29 (2.2)	32 (2.5)	38 (2.8)*	44 (3.3)	47 (3.7)	56 (5.1)
MDT	28 (1.7)	31 (1.2)	36 (2.2)	43 (2.7)	46 (3.0)	56 (4.0)
HDT	28 (2.7)	32 (2.7)	36 (3.3)	42 (4.3)	44 (5.0)	53 (6.7)

[a] First day of dosing.
[b] Last day of dosing.
[c] Day of sacrifice.
* Statistically significant at the 5% level, with respect to controls.

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Table 4. Mean body weight gains (From pp. 51-55 of the Study Report)

Test Group	Body Weight Gains, g(%)			
	Day 0-6	Day 6-16[a]	Day 16-18	Corrected body weight gain, days 6-18[b]
Control	4 (+14.3)	13 (+40.6)	8 (+17.8)	3.5 (+11.5)
LDT	3 (+10.3)	15 (+46.9)	9 (+19.1)	3.5 (+11.0)
MDT	3 (+10.7)	15 (+48.4)	10 (+21.7)	4.1 (+13.1)
HDT	4 (+14.3)	12 (+37.5)	9 (+20.5)	3.9 (+12.6)

[a] Dosing was done on days 6 through 15 gestation; the animals were sacrificed on day 18 of gestation.
[b] Corrected body weight: (body weight at sacrifice) - (b.w. on day 6) - (weight of gravid uterus at cesarean section).

Food Consumption

There were no apparent effects on food consumption (Table 5). An instance of statistically significant ($p<0.05$) increased food consumption in the LDT at days 16-18 (12.5 g vs 11.5 g in controls) is regarded as incidental, not dose-dependent, and not treatment related.

Table 5. Mean Food Consumption (From pp. 36-41 of the Study Report).

Test Group	Food Consumption, g (% of control) at Days:				
	0-6	6-11[a]	11-16	6-16[b]	16-18
Control	6.4	7.1	8.6	7.9	11.5
LDT	6.4 (+0.0)	7.3 (+2.8)	8.8 (+2.3)	8.1 (+2.5)	12.5 (+8.7)*
MDT	6.5 (+1.6)	7.3 (+2.8)	8.9 (+3.5)	8.1 (+2.5)	11.9 (+3.5)
HDT	6.4 (+0.0)	7.0 (-1.4)	8.8 (+2.3)	7.9 (+0.0)	12.4 (+7.8)

[a] Day 6 = first day of dosing.
[b] Day 16 = last day of dosing.
[c] Day 18 = day of sacrifice.
* Statistically significant at the 5% level with respect to controls.

Gross Pathological Observations

No abnormal findings were observed.

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Cesarean Section Observations

Pregnancy rates ranged from 76.4% in controls and the MDT to 90% in the HDT (Table. 6). No treatment related effects were reported for the total and average (i.e. per dam) number of corpora lutea, implantations, resorptions (early and late), mean number of dead and live fetuses, fetal weights, and sex ratio.

Although the number of total and early resorptions in the treated mice was not significantly different from controls, the number of affected litters at the LDT (14, $p<0.01$) and the MDT (13, $p<0.05$) was significantly higher than in controls (5 affected). Although the percent of post-implantation loss was somewhat elevated at the LDT (8.0%) and the MDT (6.4%) vs controls (5.0%), the effect was not statistically significant, the number of affected litters at the LDT (19, $p<0.01$) and the MDT (16, $p<0.05$) was significantly higher than in controls (8 affected).

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Table 6: Cesarean Section Observations for Dams with Live Fetuses (From pp. 25, 56-57, 58-61, 70-97 and pp. 99-102 of the Study Report).

Parameter	Control	LDT	MDT	HDT
#Animals Assigned	34	30	34	30
#Animals Mated/Inseminated	34	30	34	30
Pregnancy Rate (%)	26(76.4)	25(83.3)	26(76.4)	27(90)
Dams with Live Fetuses	25[1]	25	24[2]	25[3]
Maternal Wastage				
#Died	0	0	0	0
#Died/pregnant	0	0	0	0
#Non pregnant	8	5	8	3
#Aborted	0	0	0	0
#Premature Delivery	0	0	0	1
Total Corpora Lutea	359	386	381	342
Corpora Lutea/Dam	14.4	13.4	15.90	13.7
Preimplantation Loss [Tot(%)]	42(11.7)	25(6.5)	21(5.5)	39(11.4)
Mean (per dam)	1.7	1.0	0.9	1.6
# Dams affected	20	14	14	17
Total Implantations	317	361	360	303
Implantations/Dam	12.7	14.4	15.0	12.1
Postimplantation Loss[Tot(%)]	16(5.0)	29(8.0)	23(6.4)	18(5.9)
Mean (per dam)	0.6	1.2*	1.0	0.7
# Dams affected	8	19**	16*	12
Total Live Fetuses	301	332	337	285
Live Fetuses/Dam[4]	12.04	13.3	14.0	11.4
Total Resorptions	16	29	23	18
Early ("Embryonic")	12	20	16	14
No. Dams affected	5	14**	13**	9
Late ("Fetal")	4	9	7	4
No. Dams affected	3	7	7	3
Resorptions/Dam	0.64	1.2	0.96	0.72
Total Dead Fetuses	0	0	0	0
Dead Fetuses/Dam	0	0	0	0
Mean Fetal Weight (gm)	1.2	1.2	1.1	1.2
Sex Ratio (% Males/litter)	51.2	50.0	55.2	51.9

[1] One female (No. 16) had two implantation sites only).
[2] Two females (Nos. 69 and 80), had 6 and 9 implantation sites only.
[3] One female (No. 108) had 2 embryonic resorptions only; another female (No. 102) delivered prematurely on day 17 of gestation and was necropsied.
[4] Counting only dams with live fetuses (e.g. 25 in controls).

2. Developmental Toxicity

External examinations

As shown in Table 6, the incidence of palatoschisis at the HDT was 12/285 fetuses (4.2%) vs. 8/301 fetuses (2.7%) in controls. On the other hand, the litter incidence of palatoschisis (7/25, 28%) was identical in controls and in HDT mice. Although the fetal incidence of palatoschisis may be somewhat higher in the HDT, the effect was not statistically significant. The incidence of palatoschisis in historical controls (1 study, 5/87-7/87, with NMRI/HAN/ outbred SPF quality, Appendix 2) was 5/307 fetuses (1.6%) and 5/24 litters (20.8%). It is noted that in this study the incidence of palatoschisis in controls and at the HDT was somewhat higher than in the historical controls.

Exencephaly was observed in 2/285 fetuses (0.7%) at the HDT and in 1/301 (0.3%) fetuses in concurrent controls. The effect was not statistically significant. Litter incidences at the HDT and concurrent controls were identical 1/25 (4%). Historical controls were 0.3% fetuses and 4.2% litters.

One dam in the HDT (dam #102) delivered spontaneously on day 17 of gestation (7 fetuses were found dead in the morning of day 17 of gestation) and was sacrificed: necropsy revealed 7 empty implantation sites and one dead fetus in the left uterine horn and 6 live fetuses in the right uterine horn. No data on these fetuses from dam #102 were included.

Table 6. External examinations in cesarean-delivered pups. Data from pp. 62-63 and pp. 78-97 of the Study Report.

Observations	Control	LDT	MDT	HDT
# pups (litters) examined	301(25)	332(25)	337(24)	285(25)
# pups (litters) affected	9(8)	10(8)	6(6)	15(9)
Finding: pups(litters)				
Palatoschisis	8(7)	8(6)	4(4)	12(7)
Tail cranial-bended	1(1)	-	1(1)	-
Exencephaly	1(1)	1(1)	-	2(1)
Hind leg malposition:				
Right leg	1(1)	-	1(1)	-
Left leg	-	1(1)	-	2(2)

Visceral Examinations

Table 7 summarizes the visceral examination data, none of the findings reached statistical significance.

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Table 7. Visceral examinations in cesarean-delivered pups (Wilson technique). Data from p. 64 of the Study Report.

Observations	Control	LDT	MDT	HDT
# pups (litters) examined	142(25)	161(25)	162(24)	140(25)
# pups (litters) affected	5(4)	9(7)	3(3)	12(7)
Finding: pups(litters)				
Palatoschisis	5(4)	8(6)	3(3)	11(7)
Exencephaly	-	1(1)	-	2(2)

Skeletal Examinations

Skeletal findings are presented below in Table 8. At the HDT there was statistical significance vs control in the fetal incidence of several skeletal variations, in addition to increases of up to 2-fold in litter incidences:

- Bipartite sternebra 5: 16/145 fetuses (11.0%) vs 6/159 (3.8%) [($p \leq 0.05$)], and 10/25 litters (40%) vs 5/25 (20%).
- Supernumerary ribs, one, right: 105/145 fetuses (72%) vs 76/159 (48%) [($p \leq 0.01$)], and 25/25 litters (100%) vs 22/25 (88%).
- Left forelimb, non-ossified distal phalanx digit 2: 18/145 (12.4%) vs 10/159 (6.2%) [($p \leq 0.05$)], and 11/25 litters (44%) vs 8/25 (32%).
- Right forelimb, non-ossified distal phalanx, digit 4: 19/145 fetuses (13%) vs 9/159 (9.7%) [($p \leq 0.05$)], and 10/25 litters (40%) vs 7/25 (28%).

Examination of Table 8 also indicates that, in addition, there were statistically significant decreases at the HDT and/or LDT in the fetal incidence of non-ossified phalanxes of the hindlimbs. These effect, however, did not produce any marked effects in litter incidences.

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Table 8. Summary of skeletal observations in cesarean-delivered pups. Data from pp. 65-69 and 231-443 of the Study Report.

Observations	Control	LDT	MDT	HDT
# pups (litters) examined	159(25)	171(25)	175(24)	145(25)
SKULL				
Part of cranium missing, (externally, as exencephaly)	1(1)[a]	-	-	-
CERVICAL VERTEBRAE				
Vertebra 2 (Non-ossified)	19(9)	10*(6)	20(8)	14(8)
STERNUM				
Assymetric sternebrae (2-5) or (4 and 5)	3(3)	1(1)	1(1)	-
Assymetric and bipartite sternebrae (2-5)	-	-	-	1(1)
Assymetric sternebra (3 and 4)	-	-	-	1(1)
Incompletely ossified Sternebra 5	128(25)	134(25)	156*(24)	108(24)
Bipartite sternebra 5	6(5)	9(7)	2(1)	16*(10)
RIBS				
Supernumerary "flying rib" (No. 14), left	-	-	1(1)	-
Supernumerary, one, left	92(23)	106(25)	105(22)	107*(25)
Supernumerary, one, right	76(22)	100*(25)	91(22)	105**(25)
LEFT FORELIMB (Non-ossified)				
Digit 2, medial phalanx	139(25)	149(25)	150(24)	122(23)
Digit 2, distal phalanx	10(8)	9(7)	3*(3)	18*(11)
Digit 4, distal phalanx	10(8)	9(6)	3*(3)	17(10)
RIGHT FORELIMB (Non-ossified)				
Digit 2, medial phalanx	137(25)	143(25)	145(24)	122(23)
Digit 2, distal phalanx	9(7)	9(7)	5(4)	16(8)
Digit 4, distal phalanx	9(7)	11(7)	5(4)	19*(10)
LEFT HINDLIMB (Non-ossified)				
Toe 5, proximal phalanx	34(10)	17**(9)	29(11)	14**(8)
Toe 5, distal phalanx	32(10)	16**(7)	19*(9)	25(13)
RIGHT HINDLIMB (Non-ossified)				
Toe 5, proximal phalanx	32(9)	16*(9)	31(13)	15*(9)
Toe 5, distal phalanx	30(10)	15*(7)	19(10)	25(13)

[a] Fetal(litter) incidence.
* Significant at the 5% level. ** Significant at the 1% level.

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Discussion/Conclusions

a. Maternal Toxicity:

Dermal administration of tebuconazole in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day during days 6-15 of gestation in the NMRI/KFM/HAN mouse did not produce any evidence of maternal toxicity, as determined by mortality, clinical observations, mean body weights, mean body weight gains (corrected and uncorrected), food consumption and gross pathology findings. Thus, based on the data presented in the Main Part of this study the maternal toxicity NOEL and LOEL remain to be determined.

A supplementary study (MRID 420103-01, submitted in the same volume with the present study) with NMRI/KFM/HAN mice dermally dosed with aqueous 4% CMC tebuconazole at 0, 100, 300, and 1000 mg/kg/day during days 6-15 of gestation provides tentative values for the maternal NOEL and LOEL. This supplementary study indicates a dermal NOEL of 100 mg/kg/day and a dermal LOEL of 300 mg/kg/day based on histological observation of dose-dependent fatty changes in periportal areas of the liver, statistically significant elevation of plasma (ALT/GPT) at the HDT, and induction of liver microsomal enzymes at the MDT and the HDT.

It is noted that in a DER (dated 12/22/1988) of a supplementary study of maternal toxicity to NMRI/ORIG Kisslegg mice after oral administration of tebuconazole (10, 20, 30, and 100 mg/kg, MRID 408215-01, Addendum 1) in 0.5% aqueous Cremophor EL, the LOEL was set at 20 mg/kg/day based on hematological effects and the NOEL was set at 10 mg/kg/day. In the present study with NMRI/KFM/HAN mice, the LOEL and NOEL were 300 and 100 mg/kg/day, respectively. These values, higher than those obtained by the oral route, are suggestive of a decreased bioavailability of tebuconazole when administered dermally in an aqueous medium.

b. Developmental Toxicity:

Although the number of total and early resorptions in the treated mice was not significantly different from controls, the number of affected litters at the LDT (14, $p<0.01$) and the MDT (13, $p<0.05$) was significantly higher than in controls (5 affected). Although the percent of post-implantation loss was somewhat elevated at the LDT (8.0%) and the MDT (6.4%) vs controls (5.0%), the effect was not statistically significant, the number of affected litters at the LDT (19, $p<0.01$) and the MDT (16, $p<0.05$) was significantly higher than in controls (8 affected).

Although the fetal incidence of palatoschisis was somewhat higher at the HDT (12/285, 4.2%) than in concurrent controls (8/301, 2.7%), it was not statistically significant. Litter incidence was 7/25 litters (28%) in both HDT and concurrent controls. In the present study the incidence of palatoschisis in controls and in the HDT was somewhat higher than in the historical controls [Appendix 2], in which the incidence of palatoschisis was 5/307 fetuses (1.6%) and 5/24 litters (20.8%).

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Although the fetal incidence of exencephaly was somewhat higher at the HDT (2/285, 0.7%) than in concurrent controls (1/301, 0.3%), it was not statistically significant. Litter incidence was 1/25 litters (4%) in both HDT and concurrent controls. In the present study the incidence of exencephaly in the HDT was somewhat higher than in the historical controls, [Appendix 2], in which the incidence of exencephaly was 5/307 fetuses (0.3%) and 1/24 litters (4.2%), [Appendix 2].

Examination of the skeletal findings revealed statistically significant increases in the fetal incidences of bipartite sternebra, supernumerary ribs, and non-ossification of phalanxes in the forelimbs, in addition of up to two-fold increases in their litter incidences:

- Bipartite sternebra 5: 11.0% fetuses (HDT) vs 3.8% (controls) [($p \leq 0.05$)] and 40% litters (HDT) vs 20% (controls).
- Supernumerary ribs, one, right: 72% fetuses (HDT) vs 48% (controls [($p \leq 0.01$)], and 100 % litters (HDT) vs 88% (controls).
- Left forelimb, non-ossified distal phalanx digit 2: 12.4% fetuses (HDT) vs 6.2% (controls) [($p \leq 0.05$)], and 44% litters (HDT) vs 32% (controls).
- Right forelimb, non-ossified distal phalanx, digit 4: 13% fetuses (HDT) vs 9.7% (controls) [($p \leq 0.05$)], and 40% litters (HDT) vs 28% (controls).

The above statistically significant increases in fetal incidences of skeletal variations, coupled to marked increases in their litter incidences (e.g. bipartite sternebrae 20% controls up to 40% at the HDT) are suggestive of an incipient treatment-related effect at the HDT. Thus, this study defines a tentative LOEL of 1000 mg/kg/day and a NOEL of 300 mg/day for developmental toxicity.

D. Study Deficiencies:

No significant study deficiencies were noted.

E. Core Classification: Core minimum data.

Maternal NOEL = 100 mg/kg/day
Maternal LOEL = 300/mg/kg/day
Developmental Toxicity NOEL = 300 mg/kg/day
Developmental Toxicity LOEL = 1000 mg/kg/day

F. Risk Assessment:

Lowest-estimates of the Margin of Exposure (MOE) values for tebuconazole-containing pesticides have been determined using an oral mouse NOEL of 10 mg/kg/day [EPA/OPP/HED Memorandum from A. Protzel to B. Chambliss/S. Lewis, dated 9/6/1991]. The lowest-estimates of the MOE values for Elite 45-DF range from 8-50 (airblast applicators) and from 233-2326 (mixer/loaders). The lowest-estimates of the MOE values for Folicur 3.6 F range from 11-83 (groundboom applicators) ands from 36-288 (mixer/loaders). The MOE for aerial applicators of Folicur 3.6 is at least 20,000, under the conditions specified in the EUP application.

To assess the toxicologic significance of the above MOE values (using mouse oral data) it must be considered that rat dermal absorption paramenters were used in their estimation. The use of dermal absorption parameters obtained following application of the ai in ethanol to rats, constitutes a worst-case scenario for dermal absorption. Administration of the ai as a suspension in water would possibly result in very limited dermal penetration, leading to increased MOE estimates for the formulations.

Further consideration of the significance of the above MOE values and of the developmental toxicity potential of tebuconazole awaits consideration in a future HED developmental toxicity Peer Review.

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TEBUCONAZOLE

Page _____ is not included in this copy.

Pages 18 through 25 are not included in this copy.

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_____ Identity of product inert ingredients.

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GUIDELINE: 83-3

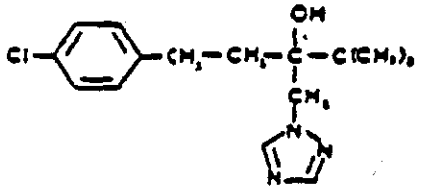
Reviewed by: Alberto Protzel, Ph.D. 4/21/92
Review Section III, Toxicology Branch II/HED (H7509C)
Secondary Review by: James N. Rowe, Ph.D. James N. Rowe 4/21/92
Section Head, Review Section III, Toxicology Branch II/HED (H7509C)

DATA EVALUATION RECORD

Study Type: Supplementary Study: Maternal Toxicity (Dermal application)
Species: Mouse
EPA Guideline: N/A

EPA Identification Nos: EPA MRID No. 420103-01 (Supplementary Study)
Caswell No. 463P
HED Project No. 2-0329
DP Barcode No. D170624
Submission No. S406118

Test Material: HWG 1608 (Technical) 96.0% a.i., Batch No. 816896061 (Supplementary study).



Synonyms: Tebuconazole; α-[2-(4-Chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol.

Sponsor: BAYER AG; Institut fur Toxicologie Landwirtschaft; Wuppertal 1; Federal Republic of Germany.

Study Number: 224256

Testing Facility: RCC, Research and Consulting Company AG. P.O. Box CH 4452. Itingen/Switzerland.

Title of Report: Supplementary study to: "Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Mouse (Dermal Application)". This supplementary study was imbedded in the main study, it was not presented as a separate document.

Author(s): H. Becker et al.

Report Issued: Date unspecified. Date of last necropsy: August 9, 1989.

Conclusions: In this supplementary study with NMRI/KFM/HAN mice, dermal application of tebuconazole followed the same protocol as in the main study (tebuconazole in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day during days

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6-15 of gestation). It is tentatively concluded that maternal toxicity /physiological alterations occurred at the MDT and the HDT. Liver Microsomal enzymes (cytochrome P-450, N- and O-demethylase) were significantly elevated (37-100%, $p \leq 0.01$) at the MDT and the HDT. Periportal fatty deposition in the liver was observed at at the MDT and the HDT. Alanine aminotransferase activity in plasma (ALT/GPT) increased in dose-dependent fashion (up to 37% at the HDT) and reached statistical significance at the HDT. All of these changes are consistent with a toxic effect on liver at the MDT. A dermal maternal toxicity LOEL of 300 mg/kg/day is set based on the induction of microsomal enzymes and periportal fatty deposition in liver. The maternal toxicity NOEL is set at 100 mg/kg/day.

Core Classification: ACCEPTABLE.

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A. Materials

A copy of the "Materials and Methods" section from the report is appended.

Test Compound: Purity: 96.0 %
Description: Colorless crystals
Lot No.: 816896061
Contaminants: A certificate of analysis was included.

Vehicle(s): Aqueous 4.0% (w/v) carboxymethylcellulose, CMC (Fluka AG).

Test Animal(s): Species: Mouse
Strain: NMRI KFM-HAN (Outbred, SPF quality)
Source: KFM, Kleintierfarm Madorin AG, Switzerland
Age: 8 weeks at mating
Weight: 22-38 g

B. Study Design

Due to the absence of maternal toxic effects in the main study, a supplementary study was initiated to determine the maternal toxic dose level by histological examination or clinical laboratory examination of the treated animals. In this study test material was applied dermally to the mice on days 6-15 of gestation.

Mating:

No details were given. In the main study, mating took place overnight, one male was placed with three females. The day in which a vaginal plug was found was designated as day 0 of gestation (day 0 post-coitum).

Group Arrangement:

Details of animal randomization were not given. In the main study, animals were randomized using a computer generated algorithm. The animals were divided into two series: Series A (for histological examination) and Series B (for clinical laboratory investigation). Dose Levels were are shown in Table 1.

Table 1. Dose levels used in testing

Test Group	Dose Level (mg/kg)	Number Assigned	
		Series A[a]	Series B
Control	0 (Vehicle Control)	10 (1-10)	10 (41-50)
Low dose (LDT)	100	10 (11-20)	10 (51-60)
Middle dose (MDT)	300	10 (21-30)	10 (61-70)
High dose (HDT)	1000	10 (31-40)	10 (71-80)

[a] Series A (for histological examination) and Series B (for clinical laboratory investigation).

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Dosing:

Dosing was done as described for the main study. All doses were administered by the dermal route in a volume of 2.5 ml/kg of body weight/day in aqueous 4% CMC during the dosing period. The dosing solutions were applied evenly to the shaved skin of the back (approx. 10% of the body surface) once daily on days 6 through 15 of gestation. The area of application was covered with an occlusive bandage; the bandage was removed after six hours of contact. It was not stated if the skin was washed after removal of the bandages. The dosing volume (2.5 ml/kg/day) was adjusted daily for changes in body weight.

Dosing suspensions were prepared daily. The suspensions were reportedly analyzed for concentration, homogeneity, and stability. Results for one analysis indicated 84.9% and 90.1% of target for the LDT and the MDT, respectively, and 74.5% of target for the HDT.

Observations:

Frequency of checking for mortality and systemic symptoms was not specified; presumably it was done at least once daily (based on daily clinical observations for one dam). Body weights were recorded daily from day 0 of gestation through day 16 of gestation. The dams were sacrificed at day 16 of gestation.

Examinations at sacrifice consisted of:

- Series A: Gross necropsy, examination of pregnancy status, and weighing of the liver and adrenals, followed by fixing and histopathology examination.
- Series B: Blood sampling prior to necropsy, gross necropsy, examination of pregnancy status, and removal of liver for in vitro assay of microsomal enzymes.

Examinations included recording of the number of living embryos, dead embryos (early and late stage), and total number of implantations.

Statistical analysis

The following statistical analysis methods were employed:

Dunnett's test (many-one t-test) was used to compare treated groups with controls if the variables followed a normal distribution; if the variables were not normally distributed, the Steel-test (many-one rank test was used. Fisher's exact test was applied if the variables could be dicotomized without loss of information.

Compliance:

Statements of EPA GLP compliance and Quality Assurance, clearly pertained to the Main Study, it is assumed (though unclear) that these statements apply also to the Supplementary Study, which was imbedded in the Main Study.

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C. Results:

Mortality:

No deaths were observed during the course of the study.

Clinical Observations:

No abnormal clinical signs were observed in Controls, MDT and HDT mice. One dam in the LDT had vaginal bleeding on days 13-14 of gestation. No other signs were observed. No local skin reaction was observed at any dose level.

Body Weights

There were no apparent effects on mean body weights (Table 2) or on mean body weight gains (Table 3).

Table 2. Mean body weights (From pp. 165-168 and 181-184 of the Study Rept.)

Test Group	Body Weights, g					
	Series A			Series B		
	Day 6[a]	Day 11	Day 16[b]	Day 6	Day 11	Day 16
Control	31	33	44	31	33	43
LDT	30	33	44	30	33	43
MDT	30	32	43	31	33	42
HDT	32	35	47	30	32	42

[a] First day of dosing.
[b] Day of sacrifice. Last day of dosing was day 15.

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Table 4. Mean body weight gains (From pp. 169 and 185 of the Study Report).

Test Group	Mean Body Weight Gains, g(%)			
	Series A		Series B	
	Day 6-11[a]	Day 6-16	Day 6-11	Day 6-16
Control	2 (+6.5)	13 (+41.9)	2 (+6.5)	12 (+38.7)
LDT	3 (+10.0)	14 (+46.7)	3 (+10.0)	13 (+43.3)
MDT	2 (+6.7)	13 (+43.3)	2 (+6.5)	11 (+35.5)
HDT	3 (+9.4)	15 (+46.9)	2 (+6.7)	12 (+40.0)

[a] Dosing was done on days 6 through 15 gestation; the animals were sacrificed on day 16 of gestation.

Food Consumption

There were no apparent effects on food consumption (Table 4).

Table 4. Mean body food consumption (From pp. 163 and 179 of the Study Report).

Test Group	Mean food consumption, g/animal/day (% vs control)			
	Series A		Series B	
	Day 6-11[a]	Day 6-16	Day 6-11	Day 6-16
Control	6.2	7.3	7.1	8.2
LDT	6.5 (+4.8)	7.8 (+6.8)	7.2 (+1.4)	8.6 (+4.9)
MDT	6.4 (+3.2)	7.5 (+2.7)	7.6 (+7.0)	8.8 (+7.3)
HDT	6.8 (+9.7)	8.2 (+12.3)	7.5 (+5.6)	8.4 (+2.4)

[a] Dosing was done on days 6 through 15 gestation; the animals were sacrificed on day 16 of gestation.

Reproduction Values.
As summarized in Table 5, no significant differences among groups were found in No. of pregnancies, No. of dead or living embryos/dam, and the total number of implantations/dam.

Necropsy and Organ Weights.
No significant effects were observed for absolute or relative liver weights between treated groups and controls. The mean absolute weights for the adrenals were significantly reduced vs controls in all treated groups; the relative weights decreased in a dose-dependent fashion and reached statistical significance at the HDT.

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Table 5. Reproduction values (From pp. 171-172 and 194-195 of the Study Report).

Test Group	Reproduction values					
	Total animals	No. pregnant	No. living embryos / dam	No. Dead/dam embryos		Total No. implantations/ dam
				Early	Late	
Series A:						
Controls	10	9	12.4	0.3	0.1	12.9
LDT	10	8	11.3	1.3	0.3	12.8
MDT	10	9	11.6	0.4	0	12.0
HDT	10	10	13.9	0.6	0	14.5
Series B:						
Controls	10	-[b]	11.9	0.2	0.6	12.7
LDT	10	8	12.8	0.8	0.4	13.9
MDT	10	8	9.8	0.8	1.3	11.8
HDT	10	7	10.6	0.6	0.1	11.9

[a] Dosing was done on days 6 through 15 gestation; the animals were sacrificed on day 16 of gestation.
[b] One dam (#43) was found dead in the morning of day 7 after mating, it was too early to determine pregnancy status. If dam #43 was not pregnant the total number of pregnancies is 9.

Table 6. Absolute and relative organ weights in treated dams (From pp. 188-193 of the Study Report)

	Mean absolute and relative organ weights				
	Body weight (g)	Liver		Adrenals	
		Absolute (g)	Relative (%)	Absolute (g)	Relative (%)
Controls	42.6	2.39	5.60	0.017	0.040
LDT	39.7	2.25	5.63	0.012*	0.033
MDT	41.9	2.38	5.67	0.011**	0.029
HDT	47.4	2.73	5.75	0.012*	0.025*

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Plasma and liver microsomal enzyme activities

As summarized in Table 7, there was a slight dose-dependent increase in the activities of AST (GOT) and ALT (GPT) in plasma (up to 37% at the HDT); this increase reached statistical significance only for ALT at the HDT. Glutamate dehydrogenase, although increased with respect to controls at all treatment groups, did not reached statistical significance vs controls at any level. Liver microsomal enzyme activities (cytochrome P-450, N- and O-demethylase) were significantly ($p \leq 0.01$) elevated (37-100%) at the MDT and the HDT. These effects on microsomal enzymes are consistent with the known effects of tebuconazole as a microsomal enzyme inducer.

Table 7. Mean plasma and liver microsomal enzyme activities of treated dams (from pp 154-158 of the Study Report).

Finding	0 ppm	100 ppm	300 ppm	1000 ppm
Plasma Activities:				
Aspartate Aminotransferase (AST/GOT) µkat/l	1.72	2.25	2.28	2.36
Alanine Aminotransferase (ALT/GPT) µkat/l	0.80	0.88	0.96	1.10*
Glutamate dehydrogenase (GLDH) µkat/l	220.5	277.8	476.2	407.9
Alkaline phosphatase (ALP) µkat/l	1.99	2.02	2.67	1.99
Microsomal Activities:				
Cytochrome P-450 (nmol/g)	30.0	45.1	74.2**	73.6**
N-Demethylase (nmol/min/g)	331.0	394.5	691.9**	640.5**
O-Demethylase (nmol/min/g)	32.27	31.40	43.78**	41.09**

* $p \leq 0.05$; ** $p \leq 0.01$.

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As shown in Table 8, a dose dependent increase in the incidence and severity of fatty changes (stainable lipid deposition) was observed in liver. In particular, these fatty areas were limited to single cells in control and LDT mice and became extended to the periportal areas at the MDT and HDT. The severity of deposition increased in going from MDT (grades 1-2) to HDT (grades 1-3). No other apparently treatment-related effects were observed in liver or adrenals.

Table 8. Microscopic findings in treated dams (From pp 113-147 of the Study Report)

Finding	0 ppm	100 ppm	300 ppm	1000 ppm
Liver				
Number Examined:	10	10	10	10
Fatty changes				
Periportal (Total)	0	0	8	10
Grade 1	0	0	7	4
Grade 2	0	0	1	5
Grade 3	0	0	0	1
Single cell	10	10	2	0
Single cell necrosis	2	1	3	2
Hepatocytic vacuolation	1	1	1	1
Adrenals				
Number Examined:	10	10	10	10
Lipogenic pigment	9	8	9	10
Cortical vacuolization	2	0	2	2
A-cell hyperplasia	6	6	6	9
Monuclear infiltrate	0	0	1	1

Discussion/Conclusions

Due to the absence of maternal toxic effects in the main study (dermal administration of tebuconazole in aqueous 4% CMC at 0, 100, 300, and 10(mg/kg/day during days 6-15 of gestation in the NMRI/KFM/HAN mouse), a supplementary study was initiated to determine the maternal toxic dose l

In this supplementary study also with NMRI/KFM/HAN mice, dermal applicat tebuconazole followed the same protocol as in the main study (tebuconazc aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day during days 6-15 of gestation). The animals were sacrificed on day 16 of gestation for histological examination of liver and adrenals and assay of plasma and l microsomal enzyme activities.

No significant effects on mortality, body weight gains, food consumption reproduction values were observed on treated animals vs controls. No ef was observed on absolute or relative liver weights; relative adrenal wei decreased in a dose-dependent fashion and reached statistical significan the HDT.

Histopathology and enzyme activity studies revealed some effects on the at the HDT. Liver microsomal enzymes (cytochrome P-450, N- and O-demeth were significantly elevated (37-100%, $p \leq 0.01$) at the MDT and the HDT. effects on microsomal enzymes are consistent with the microsomal enzyme-inducing property of tebuconazole. Alanine aminotransferase activity in plasma (ALT/GPT) increased in a dose-dependent fashion (up to 37% at the and reached statistical significance at the HDT. Histopathology of the revealed a dose-dependent increase in the incidence and severity of fatt changes (stainable fatty deposition) in the liver. These changes consis transition from stainable fat in individual cells (controls and LDT) to stainable fat in periportal areas of increasing severity at the MDT (up degree 2) and the HDT (up to degree 3).

Together, the above evidence supports the idea that a pharmacologic/toxi effect was reached at the MDT and HDT.

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U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/SACB
TOX ONELINERS

TOXCHEM NO. 463P: HWG 1608 (Tebuconazole) FILE LAST PRINTED: 4/21/92 CURRENT DATE 2/20/92

CITATION	MATERIAL	ACCESSION/ MRID. NO.	RESULTS	TOX CAT	CORE GRADE/ DOCUMENT #
Teratogenicity (Dermal) 83-3. Species: NMRI KFM-HAN (Outbred, SPF) Mouse RCC, Research and Consulting Company AG. P.O. Box CH 4452. Itingen/Switzerland. 224256 12/12/91	HWG 1608 (Tebuconazole Technical). Batch 16002/85. Purity: 98.1%.	420103-01	Tebuconazole was administered dermally in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day, 6 hrs/day, during days 6-15 of gestation to NMRI/KFM/HAN mice, without evidence of maternal toxicity. A Supplementary study (same strain and dosing protocol) revealed a maternal toxicity LOEL of 300 mg/kg/day and a NOEL of 100 mg/kg/day based on liver histopathology and induction of microsomal enzymes. Examination of the skeletal findings in the Main study revealed statistically significant increases vs controls in the HDT fetal incidences of bipartite sternebrae (11 vs 3.8%), supernumerary ribs (72 vs 48%), and non-ossification of phalanxes in the forelimbs (e.g. 12.4 vs 6.2%), in addition to up to two-fold increases in their litter incidences. These statistically significant increases in fetal incidences of skeletal variations, coupled to marked increases in their litter incidences (e.g. bipartite sternebrae 20% controls up to 40% at the HDT) are suggestive of an incipient treatment-related effect at the HDT. Thus, this study defines a tentative LOEL of 1000 mg/kg/day and a NOEL of 300 mg/day for developmental toxicity.		Minimum
Teratogenicity (Oral). Supplementary study for Maternal Toxicity. Species: NMRI KFM-HAN (Outbred, SPF) Mouse RCC, Research and Consulting Company AG. P.O. Box CH 4452. Itingen/Switzerland. 224256 Date unspecified. (Last necropsy :9/9/89)	HWG 1608 (Tebuconazole Technical). Batch 816896061. Purity: 96.0%.	420103-01	Tebuconazole was administered dermally in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day, 6 hrs/day, during days 6-15 of gestation to NMRI/KFM/HAN mice. Liver microsomal enzymes (cytochrome P-450, N- and O-demethylase) were significantly elevated (37-100%, $p \leq 0.01$) at the HDT and the HDT. Periportal fatty deposition in the liver was observed at at the HDT and the HDT. Alanine aminotransferase activity in plasma (ALT/GPT) increased in dose-dependent fashion (up to 37% at the HDT) and reached statistical significance at the HDT. A dermal maternal toxicity LOEL of 300 mg/kg/day is set based on the induction of microsomal enzymes and periportal fatty deposition in liver. The maternal toxicity NOEL is set at 100 mg/kg/day.		Acceptable