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Section I, Toxicology-Herbicide, Fungicide, Antimicrobial
Support Branch (T.H.F.A.S.B.) (TS-769C)
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Section I, T.H.F.A.S.B./HED(TS-769C)

DATA EVALUATION RECORD

STUDY TYPE: Rat chronic; EPA Guideline 83-1 TOX. CHEM. NO: 463P

ACCESSION NUMBER: MRID NO.: 407009-39

TEST MATERIAL: HWG 1608; 1-(4-chlorophenyl)-3-(1,2,4-triazol-1-yl-methyl)-4,4-dimethyl-pentane-3-ol

SYNONYMS: Terbuconazole; Folicur®

STUDY NUMBER(S): BAYER report no. 16375; Lab Proj. ID 96711

TESTING FACILITY: BAYER AG, Toxicology Division, FRG

TITLE OF REPORT: HWG 1608, Study for chronic toxicity and cancerogenicity in Wistar rats (Administration in diet for two years)

AUTHOR(S): Dr. E. Bomhard, Dr. W. Ramm

REPORT ISSUED: January 25, 1988

CONCLUSIONS: Dietary administration of terbuconazole (0, 100, 300, 1000 ppm) for 2 years produced a slight but statistically significant depression in MDT and HDT female body weights. Hematological alterations were noted in MDT and HDT females (depressions in hemoglobin, hematocrit, MCHC, MCV) associated with apparent enhanced clearance of RBCs in the spleen (HDT, increased incidence of hemosiderosis). Dose-related depressions in female adrenal weights were noted at all dose levels in association with dose-related decrease in adrenal cortical hemorrhagic degeneration. Also noted in females were statistically significantly elevations in liver microsomal enzyme at all dose levels as compared to controls. In males there was a statistically significant elevation in the combined incidences of thyroid C-cell adenoma, carcinoma and hyperplasia but not of adenoma or carcinoma alone. Based upon parafollicular tumors from eleven studies, the findings in treated animals were within the historical range and this is not considered an oncogenic response. Systemic LOEL, NOEL = 300, 100 ppm, resp.

CLASSIFICATION: MINIMUM

A. Materials: (a photocopy of methods is attached)

1. Test compound:HWG 1608, solid/light yellow crystals; mixed Batch/Fl. no. 132, Purity approx. 95%

2. Test animals: Species: rat, Strain: Bor:WISW(SPF Cpb), Age: 5-6 weeks, Weight: males, 97 g(80-112); females, 90 g (71-111), Source: Winkelmann, Borchen.

B. Study Design:

1. Animal assignment

Animals were assigned randomly (using random number lists generated by computer program from Scientific Subroutine Package, IBM, Institute of Biometrics, Bayer, AG) to the following test groups:

Test group	Dose in diet(ppm)	Main study 24 mos		Interim sacrifice 12 mos	
		male	female	male	female
1 control	0	50	50	10	10
2 low(LDT)	100	50	50	10	10
3 mid(MDT)	300	50	50	10	10
4 high(HDT)	1000	50	50	10	10

2. Diet preparation

Diet was prepared weekly and stored (temperature not stated). Reserve samples of dietary mix with test substance were taken for possible reanalyses and kept for a minimum of six weeks under refrigeration and then destroyed. The test substance content was checked at approximately 3 month intervals. Homogeneity and stability (period of seven days) of dietary test mixture were determined from sample mixes analyzed prior to study initiation.

Results-

Summary tables of percent nominal, homogeneity and stability analyses are presented below.

Analysis of samples of dietary test mixture indicated that the average per cent of nominal concentrations were within 15% of target concentrations (88-91% for the three dose levels). Homogeneity and stability analyses were within exceptable values with mean % nominal concentrations of 50 and 5000 ppm being 92 and 104% for homogeneity, respectively; stability at 7 days of storage (presumably at room temperature) was 92 and 96% of nominal values of 50 and 3000 ppm, respectively.

Nominal concentrations (from p. 3 90 of report)

Month/year	nominal conc. (mg/kg) 100	300	1000
10/84	93	267	900
1/85	86	267	900
4/85	88	273	980
7/85	94	276	890
10/85	91	270	880
1/86	90	282	850
4/86	87	279	890
7/86	82	267	950
10/86	83	270	950
mean	88	272	910
rel S.D.(%)	5	2	5
mean % (nominal)	88	91	91

Homogeneity was determined for five samples (50-100 gm) of food mix taken from a rectangular plastic bowl from front left(sample 1), front right(sample 2), middle (sample 3), back left (sample 4) and back right (sample 5).

Homogeneity (from p. 91 of report)

sample no.(random)	nominal conc. (mg/kg) 50	5000
1	45	5100
3	48	5150
4	44	5300
mean	46	5183
max. deviation(%) relative to mean	4	2
relative S.D.(%)	5	2
mean(%) nominal	92	104

Stability (from p. 92 of report)

storage period(days)	nominal conc. (mg/kg) 50	3000
0	46	2880
7	--	2670
14*	43	2520
active ingredient conc. in % nominal relative to storage period*	86	84

3. Animals receive food (fixed formula standard diet: acclimatization period, Altromin@ 1324 pellets, and study period, Altromin@ 1321 meal, manufacturer Altromin GmbH, Lage) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data:

a) for clinical/hematology examinations, animal weights, food intake data and organ weights the arithmetic group means, standard deviations and 95 and 99 conficence limits (organ weights only) were determined. Collective numbers were compared against the controls with H.B. Mann and D.R. Whitney's signficance test (U test) or by F. Wilcoxon's method using signficance of $p<0.05$ or $p<0.01$, two-tailed.

b) for incidence data (mortality, clinical signs, etc.) was processed with Fisher's exact test, $p<0.05$ or $p<0.01$, two-tailed.

5. Statements of Data Confidentiality, GLP declarations and Quality Assurance were included with dated signatures.

C. Methods and Results:

1. Observations

Animals were inspected twice daily for signs of toxicity and mortality (once on weekends and public holidays). Detailed individual examinations were performed once a week.

Toxicity/mortality (survival)

No compound-related increase in mortality was noted in the main or satellite groups. Male survival at 102 weeks was 82, 86, 84 and 94 % in 0, 100, 300 and 1000 ppm, respectively, suggesting a slight enhancement in male survival rate.

Clinical signs of toxicity were not apparently treatment-related. Lens opacities (p. 400 of report) were a common finding across all dose groups of both sexes, i.e., Males: 9/50, 12/50, 10/50, 12/50; Females: 4/50, 4/50, 5/50, 6/50, in respective dose groups noted under mortality discussion).

2. Body weight

Each animal was weighed prior to study initiation and then weekly up to and including week 12 and thereafter at biweekly intervals from week 15 to study termination. Extra body weights were recorded immediatedly before planned sacrifices for relative organ weight determinations.

Selected mean body weights (gm) are presented below.

Mean body weights were not statistically significantly different in treated males versus controls over the period of compound administration, although initially lower in the HDT prior to study initiation. There was a consistent but small depression in HDT and MDT females mean body weights (7-9%/HDT, 4-5%/MDT) observed by week one of compound administration in the HDT (data not shown) and by week 15 for the MDT. These decreases (statistically significant) are noted throughout the period of compound administration, and are considered compound-related, since they are not accounted for by significant changes in mean food consumption (g/kg b. wt./day)

MEAN BODY WTS

Dose (ppm)	Week 0	15	27	55	81	101
MALES						
0	99(7)[a]	339(21)	374(24)	404(31)	420(33)	403(31)
100	99(7)	345(26)	383(31)	413(34)	431(37)	412(38)
300	96(7)	333(25)	371(29)	410(38)	422(42)	411(44)
1000	95(7)**	327(25)*	369(29)	399(34)	416(35)	398(36)
FEMALES						
0	91(7)	201(17)	222(19)	243(23)	262(27)	261(30)
100	90(7)	201(15)	220(16)	241(21)	258(26)	262(28)
300	89(6)	195(12)*	212(14)**	232(16)*	248(19)*	254(19)
1000	90(6)	187(14)**	202(16)**	223(20)**	237(24)**	241(26)**

a = mean (standard deviation)
*, ** = statistically significant difference from respective controls at $p<0.05$, 0.01, respectively

3. Food consumption and compound intake

Consumption was determined and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Food consumption/food efficiency/compound intake

Selected food intakes (g/kg body weight/day, g/animal/day) are presented below (pp. 114-118):

Dose (ppm)	Week 1	15	27	55	81	101
MALES						
0	64	53	40	43	58	47
	9.1	17.9	15.1	17.5	24.3	19.0
100	110	49	42	45	51	50
	15.6	16.9	16.1	18.6	22.2	20.6
300	105	54	41	44	46	48
	14.5	17.8	15.3	18.0	19.3	19.8
1000	94	54	42	47	52	48
	12.2	17.6	15.6	18.7	21.8	19.2

FEMALES (food consumption summary data tables continued)

0	54	74	72	75	67	85
	6.2	14.8	16.0	18.3	17.4	22.1
100	136	70	61	71	70	81
	15.3	14.1	13.4	17.1	18.2	21.3
300	113	75	63	73	76	87
	12.4	14.6	13.3	16.9	18.9	22.1
1000	116	83	69	91	88	87
	12.2	15.5	13.9	20.3	20.7	21.0

Mean food intake (g/kg body wt./day) over the course of the study was as follows: Males, 54.6, 52.8, 53.1, 55.0; Females, 74.8, 73.7, 76.1, 86.3, respectively.

Mean compound intake (mg/kg body weight/day) over the course of the study are as follows: Males, 5.3, 15.9, 55.0 and Females, 7.4, 22.8, 86.3 in 100, 300 and 1000 ppm, respectively. The relatively higher female mean compound intake at 1000 ppm was due to the consistently higher food consumption observed in the HDT females. The reason for this increased food consumption is not apparent although it is of interest to note that HDT females (primarily) had depressed mean body weight gains over the course of the study.

4. Opthalmological examinations

Performed before study initiation, at 52 weeks and terminal sacrifice on ten animals/sex of control and 1000 ppm dose groups.

Findings at terminal sacrifice (ten animals/group) are presented below (p. 439 of report):

Findings	Males (0 ppm)	Females	Males (HDT)	Females
-no pupil reflex (both sides)	3	1	0	0
-fundus badly or not appraisable (one, both sides)	6	3	7	1
-total to almost total lens opac.	3	1	2	1
-slight to moderate opacity	---	1	4	1
-corneal dystrophy/damage	5	3	2	2
-focal opacity (one, both)	1	1	---	1
-rt. inclusion in vitreous body	---	1	---	1

There was no evidence of dose-related eye changes at 52 weeks in either treated sex as compared with controls. Various eye alterations (lack of pupillary reflex, fundus not appraisable, lenticular opacities, corneal dystrophy/damage) were observed in both control and HDT animals at similar incidences. Examination of the summary histopathology table at terminal kill indicate widespread evidence of progressive retinal atrophy in all dose groups of both sexes (i.e., males: 45/49, 44/48, 46/49, 43/50 at respective doses; female: 47/50, 43/48, 42/47, 42/48, in respective dose groups).

5. a. Hematology

Blood was collected after 6, 12, 18 and 24 months for hematology and clinical analysis from 10 animals per dose group. The checked (X) parameters were examined:

X		X	
X	hematocrit (HCT)*	X	leukocyte differential count *
X	hemoglobin (HGB)*	X	mean corpuscular HGB (MCH)
X	leukocyte count(WBC)*	X	mean corpuscular HGB conc. (MCHC)
X	platelet count*	X	mean corpuscular volume (MCV)
	blood clotting measurements	X	reticulocyte count
X	-thromboplastin time	X	-RBC count
	-clotting time	X	(RBC morphology)
	-prothrombin time		

* required for subchronic and chronic studies

Selected values are presented below:

There are generally no consistent hematology changes noted in treated males. In treated females, there are small, consistent, but generally statistically significant depressions in hemoglobin, hematocrit values associated with lowered mean corpuscular volumes and concentrations. These effects are most evident by 79 and 104 weeks of compound adminstration with statistically significant decreases in both the MDT and HDT females for Hb, Hct, MCV and MCH (e.g., Hb: 145/MDT, 144/HDT vs 149/con). These small alterations are still evident, although not statistically significant (except for MCH), in the mid and high dose groups at 104 week analyses.

(HEMATOLOGY SUMMARY): (from Table 4, p. 47)

DOSE(PPM) Week 27:		HB (g/L)	HCT (L/L)	MCV (fL)	MCH (pg)	THROMBOPLASTIN TIME seconds
0	M	157	0.442	54	19.2	32.6
100		156	0.447	54	18.7	31.3
300		158	0.445	53	18.7	32.3
1000		160	0.458	53	18.4**	32.3
0	F	158	0.457	58	20.0	28.8
100		156	0.457	59	20.1	29.6
300		156	0.454	57	19.7	29.1
1000		155	0.450	56*	19.4*	28.6
Week 52:						
0	M	151	0.474	55	18.2	35.3
100		147*	0.459*	55	18.1	33.1
300		151	0.470	54	17.9	32.4
1000		149	0.475	55	17.6	33.4
0	F	141	0.438	61	20.2	29.6
100		143	0.427	59	20.3	28.9
300		141	0.423	59	20.0	28.8
1000		146	0.418*	57**	20.5	29.6
Week 79:						
0	M	157	0.496	59	18.5	31.2
100		153	0.482	59	18.5	30.2
300		153	0.482	57	18.2	28.0
1000		153	0.482	57	18.0	32.4
0	F	149	0.466	65	20.5	31.0
100		148	0.460	63	19.9	28.0**
300		145**	0.452**	61**	19.5*	28.1**
1000		144*	0.453*	60**	19.1**	28.9
Week 104:						
0	M	147	0.459	58	18.6	33.4
100		152	0.472	58	18.6	31.1*
300		146	0.460	58	18.3	32.4
1000		151	0.478	57	17.9	28.9
0	F	146	0.454	63	20.3	31.4
100		148	0.453	60	19.4	31.4
300		143	0.441	59	19.1*	31.2
1000		143	0.446	59	19.1**	31.2

*, ** statistically significant difference from controls at $p<0.05$, 0.01, respectively

5.b. Clinical Chemistry (x indicates analyzed for)

Electrolytes:	Other:
x calcium*	x albumin*
x chloride*	x blood creatinine*
magnesium*	x blood urea nitrogen*
x phosphorus*	x cholesterol*
x potassium*	globulins
x sodium*	x glucose*
Enzymes	x total bilirubin*
x alkaline phosphatase	xtotal serum protein*
cholinesterase#	xtriglycerides
x creatinine phospho-	serum protein electrophoresis
kinase*@	x (iron)
x lactic acid dehydrogenase	
x serum alanine aminotransferase (also SGPT)*	
x serum aspartate aminotransferase (also SGOT)*	
gamma glutamyl transferase (GGTP)	
glutamate dehydrogenase	

* required for subchronic and chronic studies
# should be required for OP: plasma, erthrocyte ChE conducted 2X prior to study initiation, 3 and 6 mos. and prior to terminal sacrifice
@ not required for subchronic studies

Selected clinical chemistry values are presented below:

Although statistically significant alterations (both increases and decreases) in ASAT, ALAT, LDH, CK and triglycerides are noted they are inconsistent, sporadic findings which are not dose-related, sex-related and often are in opposite directions.

CLINICAL CHEMISTRIES (Table 5, p. 51 of report)

DOSE(PPM)	ASAT(GOT) U/L	ALAT(GPT) U/L	LDH U/L	CK U/L	TRIG MMOL/L
Week 27:					
0 M	45.1	28.8	86	68	0.59
100	41.2	26.4	82	89	0.63
300	39.1*	27.4	84	92	0.76
1000	43.6	30.5	69	87	0.57
0 F	42.9	26.4	169	91	0.40
100	39.7	22.5	127*	58*	0.37
300	40.3	22.3	96**	39**	0.35
1000	39.5	24.4	65**	35**	0.31*
Week 52:					
0 M	35.2	27.9	88	49	0.95
100	37.4	29.1	101	47	0.78
300	39.6*	30.6	117	59	1.04
1000	64.3**	38.2*	1093**	226	0.70*
0 F	36.9	26.9	126	45	0.59
100	46.9	29.5	250	70	0.64
300	42.1	30.3	157	52	0.45*
1000	41.2	28.2	105	38	0.43**
Week 79:					
0 M	37.4	49.8	184	66	1.88
100	40.0	45.2	174	58	2.00
300	37.5	51.6	162	46	2.04
1000	40.5	52.9	169	52	2.02
0 F	54.5	50.8	447	124	1.33
100	77.0	52.8	1281**	282*	1.71
300	67.6	56.0	804	262*	1.32
1000	68.7*	65.0**	706**	286**	1.16
Week 104:					
0 M	39.6	46.5	176	148	2.49
100	33.8	47.9	168	81	3.17
300	38.8	52.9	117**	68	2.09
1000	42.4	58.6*	706**	70	1.88
0 F	36.9	42.2	108	63	1.45
100	46.0	49.8*	115	52	2.03
300	37.0	41.5	95	63	1.42
1000	38.8	47.3	102	110*	1.07

*, ** statistically significant difference from controls at $p<0.05$, 0.01, respectively

6. Urinalysis

Urine was collected from fasted animals at 6, 12, 18 and 24 months. The Checked (X) parameters were examined.

X		X	
X	appearance*	X	glucos*
X	volume*	X	ketones*
X	specific gravity*	X	bilirubin*
X	pH	X	blood*
X	sediment (microscopic)		nitrate
X	protein*	X	urobilinogen

* required for chronic studies

DOSE(PPM)		PROT	PROT*VOL
Week 27:		g/L	mg
0	M	1.58	5.8
100		1.51	8.6
300		1.59	8.4
1000		1.49	5.3
0	F	0.39	2.4
100		0.33	2.1
300		0.31	1.5**
1000		0.30	1.5**
Week 52:			
0	M	1.72	7.8
100		2.46	12.2*
300		1.71	8.9
1000		1.86	8.5
0	F	0.33	1.6
100		0.34	1.7
300		0.21	1.2
1000		0.17*	1.0*
Week 79:			
0	M	4.32	11.6
100		4.73	18.0
300		2.82	7.9
1000		3.14	8.3
0	F	0.62	3.9
100		0.76	5.3
300		0.37	2.1
1000		0.21**	2.2

(URINALYSIS CONTINUED):

DOSE(PPM)		PROT	PROT*VOL
Week 104:			
0	M	2.28	16.1
100		4.46*	25.8*
300		2.97	17.7
1000		2.64	16.5
0	F	0.93	4.4
100		1.23	8.2
300		1.28	5.8
1000		0.31**	2.0*

*, ** statistically significant difference from controls at $p<0.05$, 0.01, respectively

Selected urinalysis values are presented above.

In HDT females, but not males, there was a generally consistent, often statistically significant, decrease in protein recovered in the urine at all time periods analyzed. This would suggest a possible compound-related effect upon kidney clearance, although no apparent histopathological changes were noted.

7. Sacrifice and pathology-
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organ in addition were weighed.

X	X
Digestive system	Cardiovascular/hematopoietic
x-tongue	x-aorta*
x-salivary glands*	xx-heart*
x-esophagus*	x-bone marrow*(femur,sternum)
x-stomach*	x-lymph nodes*(mandibular, mesenteric)
x-duodenum*	xx-spleen*
x-jejunum*	x-thymus*
x-ileum*	Urogenital
x-cecum*	xx-kidneys*1
x-colon*	x-urinary bladder*
x-rectum*	xx-testes*1
xxliver*1	x-epididymides
x-gall bladder*@	x-prostate
x-pancreas*	x-seminal vesicle
Respiratory	xx-ovaries*1(with oviduct)
x-trachea*	x-uterus*
xxlung*	Neurologic
-nose#	xx-brain*1 (n. ischiadicus)
-pharynx#	x-peripheral nerves*@(n. opticus)
x-larynx#	x-spinal cord (3 levels)*@(cervical,
	x-pituitary* thoracic, lumbar)
	x-eyes (optic n.)*@
Glandular	
xxadrenals*	x-extraorbital glands
-lacrimal gland*@	x-Harder's glands
x-mammary gland*@	x-ureter
-parathyroids*2	x-urethra
x-thyroids*2	x-head (rest)
Other	x-vagina
x-bone*@ (femur, sternum)	
x-skeletal muscle*@ (thigh)	
x-skin*@	
-all gross lesions and masses*	

* required for subchronic and chronic studies
# required for chronic inhalation studies
@ in subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
1 organ weights required in subchronic and chronic studies
2 organ weights required for non-rodent studies

a. organ weight

Selected absolute (mg)/relative weights (mg/100 gm b.wt.) are presented below for interim and final sacrifices:

INTERIM Dose(ppm)	B.wt.	lungs	liver	spleen	adrenals	testes/ ovaries
Males:						
0	418	1369/ 328	14437/ 3447	636/ 153	39/ 9	3896/ 932
100	423	1382/ 328	13856 3269	672/ 159	41/ 10	3726/ 884
300	398	1334/ 337	13126/ 3305	622/ 156	36/ 9	3551/ 896
1000	384*	1368/ 356	12881/ 3361	636/ 166	37/ 9	3576/ 932
Females:						
0	229	965/ 422	8638/ 3769	430/ 188	62/ 27	122/ 53
100	227	971/ 428	8140/ 3585	462/ 203*	62/ 27	123/ 54
300	233	970/ 416	8048/ 3454*	416/ 178	59/ 25	114/ 49
1000	232	1116*/ 482*	7812*/ 3365**	504**/ 217**	60/ 26	120/ 52

TERMINAL KILL Dose(ppm)	B.wt.	lungs	liver	spleen	adrenals	testes/ ovaries
Males:						
0	400	1517/ 381	14760/ 3700	814/ 204	51/ 13	3880/ 980
100	403	1596/ 399	14549/ 3613	832/ 207	53/ 13	3807/ 952
300	407	1563/ 387	14448/ 3555	802/ 199	46/ 11	3619/ 887
1000	395	1469/ 375	14256/ 3620	783/ 200	47/ 12	3489/ 883*
Females:						
0	259	1156/ 451	9176/ 3567	548/ 215	78/ 31	142/ 55
100	260	1194/ 464	9248/ 3550	561/ 216	65*/ 25*	142/ 57
300	252	1134/ 454	8843/ 3504	549/ 220	64**/ 26*	138/ 55
1000	242**	1148/ 478	9108/ 3773*	562/ 233	57**/ 24**	137/ 57

*, ** statistically significantly different from controls at $p<0.05$, 0.01, respectively

Interim organ weights (absolute, relative) in males at 52 weeks were not affected by terbuconazole treatment. At terminal kill, the testes weights were depressed (statistically significant for relative weights, $p<0.05$).

A consistent, dose-related depression was noted in female absolute and relative adrenals weights which was statistically significant ($p<0.05$, 0.01) at all dose levels(e.g., absolute: 65/LDT, 64/MDT, 57/HDT vs 78 gm/control). Inconsistent liver and spleen weights were noted between the interim and terminal organ weights with depressed liver weights and elevated spleen weights noted at the HDT at interim kill but not at 2-years (relative liver weights were statistically higher; spleen weights were similar to controls).

b. Gross pathology

Selected findings are presented below:

Dose(ppm):	0		100		300		1000	
Sex:	M	F	M	F	M	F	M	F
# animals	49	50	49	50	50	50	50	50
KIDNEYS								
-cyst,cystic	0	0	0	1	1	1	4	0
LYMPH NODES								
-enlarged	3	0	3	0	2	0	6	0
-reddened	1	0	2	1	1	0	6	0
TESTES								
-shrunken	3	0	2	0	7	0	6	0
-flaccid consistency	2	0	3	0	1	0	0	0
UTERUS								
-thickened	0	8	0	7	0	5	0	8

In HDT males there was an apparent increase in the presence of kidney cyst/cystic kidneys (4/50, HDT vs 0/49, control) and in enlarged or reddened lymph nodes (e.g., reddened: 6/50, HDT vs 1/49, control). The number of testes of MDT and HDT males also appeared to somewhat more shrunken in appearance than control males (7/60, MDT, 6/50, HDT vs 3/49, controls). Thickening of the uterus was found across all dose groups.

c. Microscopic pathology

1) Non-neoplastic

ORGAN/LESION (male/female)	0 PPM T	TK	ID	100 PPM T	TK	ID	300 PPM T	TK	ID	1000 PPM T	TK	ID
ADRENALS	(49	41	8)	(49	41	8)	(50	42	8)	(49	46	3)[a]
	(50	39	11)	(50	38	12)	(50	39	11)	(50	41	9)
-hemorrhagic	3	3	0...4	3		1..4	4		0..1	0		1
degen.(cortex)	23	21	2..15@	12		3..13#	9		4..4**	4		0
LIVER	(49	41	8)	(49	41	8)	(50	42	8)	(50	47	3)[a]
	(49	39	11)	(50	38	12)	(50	39	11)	(50	41	9)
-pale cell	4	3	1...4	3		1..2	2		0..8	8		0
	0	0	0...0	0		0..1	1		0..1	1		0
-Kupffer cell	0	0	0...1	0		1..0	0		0..1	0		1
pigmentation	2	2	0...2	2		0..1	1		0..7	7		0
-single cell	0	0	0...3	1		2..5	5		0..2	2		0
necrosis	1	0	1...3	2		1..3	2		1..3	3		0
LUNG	(49	41	8)	(49	41	8)	(50	42	8)	50	47	3)[a]
	(50	39	11)	(50	38	12)	(50	39	11)	(50	41	9)
-interstitial	17	17	0..14	12		2..16	14		2..17	16		1
pneumonitis	10	8	2..26	21		5..20	17		3..13	12		1
-mineraliza-	21	19	2..29	27		2..33	31		2..22	22		0
tion(bld vessel walls)	20	18	2..23	18		5..24	20		4..21	19		2
LYMPH NODES	(49	41	8)	(49	41	8)	(50	42	8)	(50	47	3)[a]
	(50	39	11)	(50	38	12)	(50	39	11)	(50	41	9)
(MESENTERIC)												
-blood-filled	2	2	0.. 4	3		1.. 4	2		2..5	5		0
sinuses	0	0	0...0	0		0.. 2	2		0..3	2		1
SPLEEN	(49	41	8)	(49	41	8)	(50	42	8)	(50	47	3)[a]
	(50	39	11)	(50	38	12)	(50	39	11)	(50	41	9)
-hemosiderin	0	0	0...0	0		0...1	0		1.. 0	0		0
(increased)	2	0	2...3	2		1...3	0		3..19**	17		2
THYROID												
-C-cell hyperplasia...(see neoplastic lesions)												
URINARY BLADDER	(48	41	7)	(48	41	7)	(50	42	8)	(50	47	3)[a]
	(49	39	10)	(49	37	12)	(50	39	11)	(50	41	9)
-epithelial	2	2	0...1	0		1...3	1		2.. 2	2		0
hyperplasia	1	0	1...1	0		1...1	1		0.. 4	4		0
UTERUS	(50	39	11)	(50	38	12)	(50	39	11)	(50	41	9)
-squamous meta-	4	3	1...8	5		3...5	4		1..10	8		2
plasia												

(NON-NEOPLASTIC LESION CONTINUED)

LIVER ENZYME INDUCTION				
FEMALES:	8/37	18/39*	14/40	27/43**

[a] number of male finding/number of female findings: T = total, TK = terminal kill, ID = interim death
*, ** stat. sign. difference from controls at p<0.05, 0.01, resp.
@, # p<.074, .03 (reviewer's statistical analysis, Fisher's exact test)

There was a dose-related, statistically significant decrease in the incidence of adrenal cortical hemorrhagic degeneration in the MDT and HDT females (LDT approached statistical significance) as compared to the controls. An increase in HDT males of liver pale cell (4/49, control vs 8/50, HDT) is suggested as well as increased Kupffer cell pigmentation (2/49, control vs 7/50) in HDT females. Furthermore, an overall treatment but not dose-related increase in male and females for single cell necrosis is suggested at all dose levels.

There was a statistically significant elevation in the finding of increased hemosiderin deposition in HDT females as compared to controls (2/50, control vs 19/50, p<0.01). This is consistent with hematological changes observed in HDT females. The incidence of uterine squamous metaplasia was increased in treated over controls (approaching statistical significance at the high dose level).

Histological changes related to liver microsomal enzyme induction were evident in all female but not male treatment groups as compared to controls--consistent with the known liver enzyme inducing ability of terbuconazole. These increases were statistically significant in the LDT and HDT dose groups (p<0.05, 0.01, respectively).

2) Neoplastic

Selected neoplastic findings are presented below.

There was no evidence of dose-related increases in hepatocellular adenoma or carcinoma and pituitary adenoma/adenocarcinoma. An increased incidence, not dose-related, in atypical carcinoma of the uterus, described as high malignant, was noted in the treated dose groups (0/50, controls vs 3/50, LDT, 2/50, MDT, 1/50, HDT) as compared to the controls.

In males, but not females, C-cell thyroid adenoma and carcinoma were noted in treated but not control groups. These were non-dose-related findings and were not statistically significant. The incidence of thyroid C-cell hyperplasia was somewhat elevated at the MDT and HDT (1/50, control vs 7/50, MDT, 6/50, HDT) being statistically significant (P<0.05 level) at the mid but not high

dose level. Combination hypeplasia/neoplasia increased the statistical significance of the thyroid findings.

ORGAN/LESION (male/female)	0 PPM T	TK	ID	100 PPM T	TK	ID	300 PPM T	TK	ID	1000 PPM T	TK	ID
LIVER	(49	41	8)	(49	41	8)	(50	42	8)	(50	47	3)[a]
	(49	39	10)	(50	38	12)	(50	39	11)	(50	41	9)
-hepatocellular adenoma	0	0	0...0	0		0..0	0		0..0	0		0
	0	0	0...1	1		0..3	3		0..0	0		0
-hepatocellular carcinoma	1	0	1...1	1		0..0	0		0..0	0		0
	1	1	0...0	0		0..0	0		0..0	0		0
THYROID	(50	41	9)	(50	41	9)	(50	42	8)	(50	47	3)[a]
	(49	39	10)	(50	38	12)	(50	39	11)	(50	41	9)
-follicular adenoma	0	0	0...1	1		0..0	0		0..3	3		0
	0	0	0...0	0		0..1	1		0..1	1		0
-C-cell adenoma	0	0	0...1	1		0..3	3		0..2	2		0
	1	1	0...0	0		0..1	1		0..1	1		0
-C-cell carcinoma	0	0	0...1	1		0..0	0		0..1	1		0
	0	0	0...0	0		0..0	0		0..0	0		0
-C-cell hyperplasia	1	1	0...3	3		0..7@	5		2..6#	6		0
	1	1	0...2	2		0..3	3		0..0	0		0
-combined hyperpl./neopl. (C-cell)	1	1	0...5	5		0..10**	8		2..9*	9		0
	2	2	0...2	2		0.. 4	4		0..1	1		0
PITUITARY	(50	41	9)	(50	41	9)	(50	42	8)	(50	47	3)[a]
	(50	39	11)	(50	38	12)	(50	39	10)	(50	41	9)
-adenocarcinoma	1	0	1...0	0		0..0	0		0..0	0		0
	0	0	0...0	0		0..2	0		2..1	0		1
-adenoma	6	5	1...3	3		0..6	5		1..6	6		0
	13	12	1..14	10		4..14	13		1.11	9		2
UTERUS	(50	39	11)	(50	38	12)	(50	39	11)	(50	41	9)
-atypical carcinoma (highly malignant)	0	0	0...3	0		3..2	0		2..1	0		1

[a] number of male finding/number of female findings: T = total, TK = terminal kill, ID = interim death

*, ** stat. sign. difference from controls at $p<0.05$, 0.01, resp.

@,# $p<0.03$, 0.06-reviewer's statistical analysis by Fisher's exact test

D. Discussion

Technical terbuconazole was orally administered (diet) for periods up to 24 months at 0, 100, 300 and 1000 ppm. There was no evidence of compound-related increases in mortality, rather the male but not female HDT dose group appeared to have a slight enhancement in survival rate. Minimal but statistically significant depressions in female body weights (MDT, HDT) were noted thoughout the study and were not accounted for by food consumption patterns.

In females, but not males, there was a small but consistent depressions in hemoglobin, hematocrit and altered mean corpuscular concentrations and volumes at 79 and 104 weeks of analyses which correlated with an increased deposition of splenic hemosiderin in HDT females. Dose-related depressions in female absolute and relative adrenal weights (statistically significant at all dose levels) were associated with a dose-related decrease in the incidence of adrenal cortical hemorrhagic degeneration (statistically significant at MDT and HDT). There was also a dose-related increase in liver microsomal enzyme induction at all dose levels tested. This is based upon histological examination not enzymatic analyses.

In HDT males, gross pathology suggested an increase in the presence of kidney cyst/cystic kidneys and an increase in reddened lymph nodes. Histological examination of the lymph nodes indicated a possible elevation of blood-filled sinuses of the mesenteric lymph nodes in HDT males.

In males, but not females, C-cell thyroid adenoma and carcinoma were noted in treated but not control groups. These were non-dose-related findings and were not statistically significant. The incidence of thyroid C-cell hyperplasia was somewhat elevated at the MDT and HDT (1/50, control vs 7/50, MDT, 6/50, HDT) being statistically significant ($P<0.05$ level) at the mid but not high dose level. The pathology report, p. 465, noted that thyroid C-cell neoplasia and hyperplasia can be combined since the differentiation is arbitrary depending mainly on size of the lesions. Combination of hyperplasia and neoplasia increased the statistical significance of the hyperplastic findings which resulted in the following respective incidences(%): 2, 10, 20 and 18%. The authors submitted historical control data (Bomhard et al., 1986: J.E.P.T.O, 7(1/1), 35-52) from the Bayer laboratories for spontaneous tumors in Wistar TNO/W.70 rats from eleven studies initiated between 1973-1976. The range of thyroid parafollicular tumors (which included interstitial or C-cell adenomas) was 0 to 19.3% with an average of 7.4%. Thus the individual and combined C-cell tumors from the present study were essentially within the historical parafollicular control range.

Atypical carcinoma of the uterus (a highly metastasising, malignant tumor of the uterine ligament) was noted in all treated animals in small frequencies (6%, 6%, 2% of respective treated groups) but not controls. This was not a dose-related tumor nor statistically signficantly different from concurrent controls. Historical control data provided by the registrant in Wistar (Han) rats indicates the occurrence of a large number of spontaneous, metastatic uterine adenocarcinomas (39% of 305 females) from Wistar rats used in a longevity study (Deerberg et al., 1981, Vet. Pathol., 18, 707-713). Therefore, it is unlikely that this is a compound-induced tumor.