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DATA EVALUATION RECORD

STUDY TYPE: Mouse oncogenicity (21 mos) (EPA Guideline 83-2) TOX. CHEM. NO: 463P

ACCESSION NUMBER: MRID NO.: 407009-41

TEST MATERIAL: HWG 1608 technical a.i.; 1-(4-chlorophenyl-4,4-dimethyl-3-(1,2,4-triazole-1-yl-methyl)-pentane-3-ol; CAS 80-443-41-0

SYNONYMS: Terbuconazole

STUDY NUMBER(S): Report no. 16376; Lab. proj. id report no. 96709

TESTING FACILITY: BAYER AG, Toxicology Division, FRG

TITLE OF REPORT: HWG 1608, Study for cancerogenicity in NMRI mice (administration in diet for up to twenty-one months)

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

REPORT ISSUED: January 25, 1988

CONCLUSIONS: Terbuconazole administered in the diet (0, 20, 60, 180 pm) for 21 months produced a slight depression of body weight in male but not female mice at the HDT during the first third of the study. The major target organ is the liver in both sexes with elevations in bilirubin and liver weights in the mid and high groups associated with slight centrilobular and periportal vacuolation and lipid deposition. Mid and high dose females also had increased minimal medullary hemopoiesis and sinusoidal cellularity. In males there was an increase in adrenal cortical cell size and hyperplasia (MDT, HDT); both sexes had an elevation in stomach gastritis (HDT) while females were reported with an increase in pancreatic interstitial edema (mid, high doses). Based on these findings it appears that the HDT (180 ppm) was not high enough to approximate the MTD. A slight apparent elevation in male benign but not malignant liver tumors was reported; the combined incidences of these tumors are within the historical control range submitted from 6 studies. It is concluded that terbuconazole is not oncogenic in NMRI mice under the conditions of this bioassay.

CLASSIFICATION: CORE SUPPLEMENTARY

A. Materials: (a photocopy of the methods is appended)

1. Test compound: HWG 1608, Description: colorless crystals, Batch # mixed, Fl.no. 132, Purity approx. 95 %, contaminants: not listed

2. Test animals: Species: mouse, Strain: Bor: NMRI (SPF Han), Age: 5-6 weeks, Weight: males, 29 gm (24-34 gm); females, 24 gm (18-31 gm), Source: Winklemann, Borchen. animals

B. Study Design:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test group	Dose in diet(ppm)	Main study 21 mos male	Main study 21 mos female	Interim sacrifice 12 mos male	Interim sacrifice 12 mos female
1 control	0	50	50	10	10
2 low(LDT)	20	50	50	10	10
3 mid(MDT)	60	50	50	10	10
4 high(HDT)	180	50	50	10	10

2. Diet preparation

Diet was prepared weekly and method of storage not stated--presumably at room temperature. Samples of treated food were analyzed for stability, concentration and homogeneity.

Results-

Test substance concentration (from Table 1, p. 77)

month/year	nominal conc. (mg/kg) 20	60	180
12/84	20.6	53	173
3/85	20.8	50	175
6/85	22.4	52	160
9/85	22.0	53	171
12/85	21.4	55	194
3/86	22.6	54	185
6/86	23.2	56	191
9/86	19.6	49	153
mean (rel. S.D.,%)	21.6(6)	53(4)	175(7)
mean % nominal	108	88	97

Average per cent of nominal for 20, 60 and 180 mg/kg ranged from 88 to 108% which is within acceptable variabilty for test substance concentrations.

Homogeneity (from Table 2, p. 78)

	nominal conc. (mg/g)	
sample no. (random nos.)	20	180
1	23.8	---
2	23.4	169
3	---	164
4	21.2	---
5	---	160
mean	22.8	164
Maximum deviation (%) relative to mean	7	3
rel. S.D. (%)	6	3
mean in % nominal	114	91

Stability (from Table 3, p. 79)

	nominal conc. (mg/kg)	
storage period (days)	20	180
0	18.2	164
7	19.0	---
14*)	19.6	178
active ingredient conc. in % nominal relative to storage period marked*)	98	99

Five samples of 50 to 100 gm of the food mix were taken from a rectangular bowl from various sites (e.g., front left, front right, etc.) for 20 and 180 mg/kg nominal concentrations. As shown in the table above, the mean per cent of nominal were 114 and 91, respectively. Stability was not affected at either nominal concentration based on per cent of nominal at 14 days of storage (98, 99%, respectively). The storage was presumably at room temperature.

3. Animals received food (acclimatization: Altromin(R) 1324 pellets; study period: Altromin(R) 1321 meal, manufacturer Altromin GmbH, Lage) and water ad libitum.

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

Arithmetic group means and standard deviations were calculated from individual results and for organ weights and some of medical laboratory examinations the upper and lower confidence limits were determined. Collective data were compared with control using the Mann and Whitney U Test or by Wilcoxon's method. Incidence data (mortality, clinical signs, etc.) were analyzed by Fisher's exact test.

5. Statements of data confidentiality(none claimed), adherence to GLPs and Quality Assurance inspections with signatures were included.

C. Methods and Results:

1. Observations

Animals were inspected twice daily (once on weekends and public holidays) for signs of toxicity and mortality.

Summary mortality data are presented below:

Cumulative mortality data (from Table 1, p. 37)

Dose(ppm)		0	20	60	180	0	20	60	180
sex		m	m	m	m	f	f	f	f
n		50	50	50	50	50	50	50	50
weeks:									
1-13		1	0	0	0	0	1	0	0
	%	2	0	0	0	0	2	0	0
1-26		1	0	2	0	1	2	1	0
	%	2	0	4	0	2	4	2	0
1-52		1	0	4	0	5	4	3	4
	%	2	0	8	0	10	8	6	8
1-78		5	10	13	12	18	18	13	23
	%	10	20	26	24	36	36	26	46
1-91		12	22	21	22	33	28	27	32
	%	24	44	42	44	66	56	54	64
1-93		12	22	21	22	33	29	27	32
	%	24	44	42	44	66	58	54	64

Cumulative mortality was lower in male controls for time periods beyond 52 weeks than in all dose groups receiving terbuconazole. This was stated by the authors as being statistically significant ($p<0.05$). No general differences in cumulative mortality were apparent in any of the female dose groups as compared to controls. The finding in male mice is biologically questionable since mortality among the controls is lower than expected and there is no dose-relationship.

A summary of selected clinical findings of possible toxicity are presented below. No unusual clinical findings were noted in the male or female interim dose groups (not shown in table). Findings of rough coat and poor general condition appeared to be elevated among all male dose-groups as compared to the controls but not among compound-treated females. The loss of hair appeared to be a somewhat common occurrence among all dose groups of both sexes.

Clinical findings (from pp. 124-127 of report):

Dose(ppm)	0	20	60	180	0	20	60	180
sex	m	m	m	m	f	f	f	f
n	50	50	50	50	50	50	50	50
Rough coat	12	25	20	23	23	23	21	25
Loss of hair	7	8	9	9	14	16	12	20
Poor general condition	3	16	10	17	22	22	21	21

2. Body weight

Animals were weighed before study initiation, weekly up to and including week 13, and at two-weekly intervals from week 15 until week 89. Extra body weights for calculating relative organ weights were recorded immediatedly before planned sacrifices in weeks 52 and 91/92.

A summary table of mean body weights (gm) is presented below (taken from report, pp. 137-144):

Body weights: mean(S.D.)

MALES Dose: (ppm)	wk0	wk5	wk13	wk53	wk79	wk91/92
0	29(2)	37(3)	41(4)	49(5)	48(4)	46(3)
20	29(2)	35(4)**	40(5)	49(6)	48(5)	47(4)
60	29(2)	36(3)**	40(4)	48(6)	48(5)	46(6)
180	29(2)	35(3)**	39(4)**	48(5)	47(5)	44(4)
FEMALES						
0	24(2)	26(2)	30(3)	37(4)	38(5)	39(5)
20	24(2)	27(2)	30(3)	39(4)*	40(4)	40(4)
60	24(2)	28(2)**	31(3)	38(5)	40(5)	39(4)
180	25(2)	26(2)	31(2)*	38(4)	39(3)	41(4)

There was a minimal (statistically significant in 10 of first 31 weeks on test) depression in mean body weights observed in males (primarily at the HDT) treated with the test compound as compared to the control group. No compound-related effects were apparent in females treated with terbuconazole.

3. Food consumption and compound intake

Weekly consumption was determined and mean daily diet consumption was calculated. Compound intake was calculated from the consumption and body weight gain data.

Food consumption/compound intake

No apparent alterations (statistically significant) in mean food consumption (g/kg b. wt/day or g/animal/day) were noted in any dose group for either sex as compared to the respective controls.

Food consumption(from pp.101-104)

Dose: (ppm)	wk1	wk5	wk13	wk53	wk79	wk91
0						
MALES	405[a]	379	320	235	258	275
	13.0[b]	14.1	13.2	11.4	12.4	12.8
FEMALES	531	598	503	373	398	492
	13.0	15.6	14.9	13.7	15.3	19.4
20						
MALES	420	397	342	250	287	277
	13.2	13.8	13.7	12.2	13.6	12.9
FEMALES	538	577	503	382	398	372
	13.3	15.3	15.3	14.7	15.9	14.9
60						
MALES	428	380	343	252	292	284
	13.5	13.5	13.7	12.2	14.0	13.3
FEMALES	537	542	472	367	385	371
	13.2	15.0	14.6	14.0	15.3	14.4
180						
MALES	436	373	355	247	261	270
	13.5	13.1	13.8	11.8	12.3	12.3
FEMALES	551	570	498	419	408	393
	13.5	14.9	15.3	15.8	15.8	15.9

a g/kg body weight/day; b g/animal/day

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

-males: 5.9, 18.2, 53.1 for 20, 60 and 180 ppm, respectively
-females: 9.0, 26.1, 80.5 for 20, 60 and 180 ppm, respectively

4. Opthalmological examinations

No eye examinations were performed (not required).

5. a. Hematology

Blood was collected at 12 and 21 months for hematology and clinical analysis from 10 animals/dose group of the interim sacrifice and from 10 animals/dose group randomly selected from the main study groups. 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* (thrombocyte)	x	mean corpuscular volume (MCV)
	blood clotting measurements -thromboplastin time -clotting time -prothrombin time	x	reticulocyte count

* required for subchronic and chronic studies

Hematology summary table(Table 4, pp. 48,49 of report)

Dose(ppm) (week 51)	RBC 10E12/L	HB G/L	HCT L/L	THRO 10E9/L	RETI %	SEGM %	LYM %
MALES							
0	8.30	137	0.46	1585	19	16.3	83.4
20	8.57	140	0.48	1350*	17	20.7	78.6
60	8.41	136	0.47	1351*	18	21.1	77.7
180	8.73*	140	0.49	1277**	15**	17.7	81.3
FEMALES							
0	8.30	142	0.47	840	22	13.7	84.7
20	8.07	140	0.46	838	23	10.9	88.3
60	8.42	141	0.47	854	18	13.6	84.2
180	7.88*	133**	0.45*	921	20	11.7	87.4
(week 90)							
MALES							
0	8.20	144	0.428	1478	18	20.3	77.7
20	8.55	154	0.432	1432	20	22.9	76.0
60	8.15	145	0.426	1451	18	23.9	73.6
180	7.65**	139	0.410	1445	12	35.1*	61.6*
FEMALES							
0	7.87	143	0.409	975	23	28.9	67.0
20	7.26*	135	0.390	975	21	24.8	70.1
60	7.13	131	0.393	1145	23	31.6	63.4
180	7.56	141	0.392	998	25	18.1	79.7*

Selected hematology values are presented above. There were no consistent blood changes of a compound-related nature. In males, RBCs were statistically significantly elevated at the HDT at the 51 week sampling period but significantly lower at 90 weeks. Females had statistically significantly lower RBCs, Hb and hematocrit at 51 weeks but not at 90 weeks sampling in the HDT.

In treated males, there was a statistically significant depression at all dose levels for thrombocytes as compared to controls at 51 weeks but not at 90 weeks on study. Inconsistent findings were observed for HDT males for reticulocytes, segmented neutrophils and lymphocytes at 51 or 90 weeks; HDT females had elevated lymphocyte counts at 90 weeks.

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

Electrolytes:	Other:
calcium*	albumin*
chloride*	x blood creatinine*
magnesium*	x blood urea nitrogen*
phosphorus*	x cholesterol*
potassium*	globulins
sodium*	glucose*
Enzymes	x total bilirubin*
x alkaline phosphatase	xtotal serum protein*
cholinesterase#	triglycerides
creatinine phospho-kinase*@	serum protein electrophoresis
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.

There was a generally consistent compound-related effect upon bilirubin in mid and/or high dose females. At week 53 bilirubin values in HDT females were significantly increased ($p<0.01$) and were also increased at all dose levels ($p<0.01$) as compared to the respective controls at the 92 week analysis. Cholesterol values were significantly depressed ($p<0.01$) in HDT females at 53 weeks and in the mid dose at 92 weeks ($p<0.01$) as compared to controls. Creatine values were significantly elevated at the mid and high dose levels at 92 weeks in females but not at 53 weeks. Treated males had no apparent clinical chemistry changes.

Dose(ppm)	ALAT	AP	BILI	UREA	CHOL	CREAT
(week 53)	(SGOT)U/L	U/L	umol/L	mmol/L	mmol/L	umol/L
MALES						
0	35.4	93	3.9	10.56	4.66	41
20	30.3	95	3.8	11.13	4.38	35
60	36.4	84	3.8	9.65	4.36	36
180	45.8	107	3.9	9.75	3.61*	34
FEMALES						
0	59.1	196	2.7	8.98	3.86	39
20	32.48**	260	3.2	9.40	4.32	40
60	44.0	180	3.3	9.52	3.43	41
180	53.3	186	3.7**	9.90	2.44**	42
(week 92)						
MALES						
0	74.3	152	3.3	8.43	4.31	29
20	56.6	141	3.2	7.76	3.93	36
60	49.4	131	3.3	8.14	3.93	32
180	83.4	153	3.4	8.01	3.27	36
FEMALES						
0	72.9	168	2.2	9.45	3.57	26
20	66.0	393*	2.6*	8.35	3.53	26
60	73.8	201	3.4**	8.82	2.97*	32*
180	101.4	227	3.6**	8.77	3.46	36**

6. Urinalysis

Urines were not collected.

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.

X	X
Digestive system	Cardiovascular/hematopoietic
x-tongue	x-aorta*
x-salivary glands*	x-heart*
x-esophagus*	x-bone marrow*(femur,sternum)
x-stomach*	x-lymph nodes*(mandibular, mesenteric)
x-duodenum*	x-spleen*
x-jejunum*	x-thymus*(if present)
x-ileum*	Urogenital
x-cecum*	x-kidneys*1(both)
x-colon*	x-urinary bladder*[ureter,urethra]
x-rectum*	x-testes*1(both)
x-liver*1	x-epididymides
x-gall bladder*@	x-prostate
x-pancreas*	x-seminal vesicle
Respiratory	x-ovaries*1(with oviduct)
x-trachea*	-uterus*
x-lung*	Neurologic
-nose#	x-brain*1
-pharynx#	x-peripheral nerves*@(n.ischiadicus)
[larynx#]	x-spinal cord (3 levels)*@
	x-pituitary*
	x-eyes [optic n.]*@
Glandular	[eyelids]
x-adrenals*(both)	x-extraorbital glands/Harder's gl.
-lacrimal gland*@	[head, rest]
x-mammary gland*@	x-perianal glands
-parathyroids*2	x-sternum
x-thyroids*2	x-vagina/cervix
Other	
x-bone*@ (femur)	
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
[ ] kept for possible future reference
___ underlined organs were weighed at interim or terminal sacrif.

Ovary weights were not determined as recommended by EPA test guidelines.

a. Organ Weight

A summary of mean male/female organ weights (mg) is presented below (from Table 6, p. 55 of report):

WEEK 53 Dose (ppm)	BRAIN	HEART	LUNGS	LIVER	SPLEEN	KID-NEYS	ADREN-NALS	TESTES
0	501/	308/	284/	2421/	163/	853/	7/	276/
	502	209	233	1817	202	504	16	---
20	478/	253**/	289/	2148/	172/	753*/	8/	258/
	507	186	218	1665	219	489	14	---
60	487/	297/	266*/	2332/	147/	843/	6/	267/
	510	204	230	1900	201	524	16	---
180	498/	269/	267/	2461/	180/	803/	9/	257/
	497	219	262	1980	212	482	17	---
WEEK 92/93 Dose (ppm)								
0	495/	288/	299/	2294/	167/	865/	9/	239/
	504	206	250	2255	250	533	13	---
20	513/	292/	296/	2281/	167/	839/	13/	221/
	504	214	286	2131	285	548	14	---
60	500/	277/	290/	2325/	178/	829/	9/	237/
	504	211	293	2284	249	539	12	---
180	500/	287/	289/	2423/	142/	858/	9/	225/
	509	221	273	2822	269	574	14	---

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RELATIVE LIVER WEIGHTS (mg/100 g)

	Males	Females
WEEK 53		
0 ppm	4987	4932
20 "	4736	4750
60 "	4809	4746
180 "	5123	5260
WEEK 92/93		
0 ppm	4943	5686
20 "	4908	5308
60 "	4970	5804
180 "	5287**	6902

There was a consistent elevation in absolute (mg) and relative liver weights (mg/100 gm b.wt.) for both HDT males and HDT females at week 92 (absolute) and both at 53 and 92 weeks (relative weights; statistically significant only for relative male liver weights at week 92/93) as compared to respective controls. This is consistent with terbuconzole's liver

microsomal enzyme-inducing ability observed in the range-finding study. The net effect of this would be to increase the liver weights. No other consistent changes were observed.

b. Gross pathology

A summary of selected gross pathology findings is presented below (from Table 1, 2 of pathology report, pp. 6-22):

INTERIM SACRIFICE

(males) PPM:	0	20	60	180
animal # examd	10	10	10	10
KIDNEYS				
-cyst(s)	0	0	1	2

DEAD(D)/TERMINATION(T)

PPM:	0		20		60		180	
Males:	D	T	D	T	D	T	D	T
animal # examd	12	38	20	30	21	29	22	28
LUNGS								
-nodule(s)	2	15	4	13	5	10	3	5
-discolored	4	1	3	1	5	0	9	1
LIVER								
-nodules	0	1	0	2	1	2	2	3
-enlarged	0	0	0	0	2	0	1	0
Females	D	T	D	T	D	T	D	T
animal # examd	33	17	29	21	27	23	31	19
LUNGS								
-nodules	0	2	4	11	6	6	4	3
-discolored	6	0	11	0	10	2	12	0
OVARIES								
-cyst(s)	1	2	4	0	2	0	5	2

In males and females at terminal sacrifice, there was a general, treatment-related but not dose-related increase in discoloration of the lungs (e.g., females: 6/control vs 11/LDT, 12/MDT, 12/HDT). The number of lung nodules grossly observed was also generally greater in treated than control females but not males (i.e., 2/control vs 15/LDT, 12/MDT, 7/HDT). There appeared to be a slight, dose-related elevation in male but not female liver nodules (1/control vs 2/LDT, 3/MDT, 5/HDT).

c. Microscopic pathology (from Table , pp. 334-346, Table 7, 8, pp. 361-385)

1) Non-neoplastic

INTERIM SACRIFICE
Dead(D)/Interim(I)

PPM:	0		20		60		180	
MALES	D	I	D	I	D	I	D	I
animal # examd	1	9	0	10	0	10	0	10
Heart								
-min.myocard. degen.(focal)	0	0	0	0	0	0	0	1
Liver								
-min.focal peri-portal vacuola.	0	0	0	0	0	0	0	4
Liver ORO								
-min.centrilob. lipid depos.(focal)	0	1	0	2	0	3	0	0
-min.centrilob. lipid depos.	0	4	0	3	0	5	0	8
-marked centrilob. lipid depos.	0	0	0	0	0	0	0	1
-min.periportal lipid depos.(focal)	0	0	0	0	0	2	0	3
-min. periportal lipid depos.	0	0	0	0	0	0	0	4
Kidney								
-occas. dil. tub-ules, eosinoph. material	0	0	0	0	0	2	0	1
Adrenals								
-subcapsular prolif. fibrobl.-like cells	0	1	0	6	0	1	0	3
Eyes								
-few periorbital inflammatory c.	0	0	0	3	0	2	0	4

FEMALES	D	I	D	I	D	I	D	I
animal # examd	1	9	0	10	1	9	1	9
Liver								
-min. focal centri-lob. vacuol.	0	0	0	0	0	1	0	2
-min. centrilob. fine vacuol.	0	0	0	0	0	1	0	2
-mod. periportal vacuol.	0	0	0	0	0	0	0	1
-min. focal peri-portal vacuol.	0	0	0	0	0	4	0	5
-min. periportal fine vacuol.	0	0	0	0	0	1	0	0

(INTERIM SACRIFICE, CONTINUED)

FEMALES	0		20		60		180	
	D	I	D	I	D	I	D	I
animal # examd	1	9	0	10	1	9	1	9
Liver ORO -various degrees of centrilob./ periportal lipid depos.	0	3	0	2	0	9	0	9
Adrenals -subcapsular prolif. fibrobl.-like cells	0	6	0	10	0	7	1	7

Selected non-neoplastic lesions from interim sacrifice are presented above.

Interim sacrifice indicates the liver as a primary toxicity site with an elevation in both sexes in mid and/or high dose groups of minimal or moderate focal centrilobular vacuolation, minimum focal periportal or minimum periportal fine vacuolation and various degrees of centrilobular/periportal lipid deposition.

Terminal sacrifice histopathology again implicates the liver as a major target site for toxicity as well as possibly the heart, adrenals, pancreas, stomach and uterus in either treated males or females usually at mid or high dose levels.

In males, the most frequent hepatic alterations of a test substance induced nature were minimal focal centrilobular fine vacuolation (0/control vs 2/LDT, 5/MDT, 2/HDT), minimal to marked centrilobular fine vacuolation (0/control vs 1/LDT, 4/MDT, 13/HDT), minimal focal periportal vacuolation (0/control vs 8/HDT), and various forms of lipid deposition (centrilobular, focal, periportal) (3/control vs 4/MDT, 18/HDT). Enlarged adrenal cortical cells or minimal adrenal cortical hyperplasia were also evident in mid and high dose groups as compared to controls. Minimal stomach gastritis was also elevated in the HDT (2/control vs 12/HDT). Myocardial scarring was increased in HDT males as compared to controls (4/control vs 9/HDT).

In female livers, there was an apparent increase in moderate centrilobular vacuolation (0/control vs 2/MDT, 2/HDT), minimal diffuse vacuolation (0/control vs 7/HDT), minimal extramedullary hemopoiesis (2/control vs 5/LDT, 6/MDT, 6/HDT), increased sinusoidal cellularity (1/control vs 5/HDT) and various degrees of lipid deposition (3/control vs 6/MDT, 12/HDT). In addition to hepatoxicity, the pancreas (minimal to moderate interstitial edema), uterus (minimal to moderate cystic hyperplasia of

TERMINAL SACRIFICE: NON-NEOPLASTIC (CONTINUED)

Dead(D)/Terminal(T)

PPM:	0		20		60		180	
MALES	D	T	D	T	D	T	D	T
animal # examd	12	38	20	30	21	29	22	28
Heart								
-myocardial scarring	0	4	0	1	0	2	3	6
Liver								
-necrosis	0	2	2	2	1	1	3	1
-single cell necrosis	0	0	0	0	1	0	1	0
-min. centrilob. hepat. degen./inflamm c.	0	0	0	0	1	0	0	1
-min. focal centrilob. fine vacuol.	0	0	0	2	1	4	1	1
-min. centrilob. fine vacuol.	0	0	0	1	0	3	0	8
-mod. centrilob. fine vacuol.	0	0	0	0	0	1	1	3
-marked centrilob. fine vacuol.	0	0	0	0	0	0	0	1
-min. focal centrilob. vacuol.	1	2	0	3	0	0	1	1
-min. centrilob. vacuol.	1	1	1	1	0	0	0	0
-moderate centrilob. vacuol.	0	0	0	0	1	0	0	0
-min. periportal fine vacuol.	0	0	0	0	0	0	0	1
-min. focal periportal vacuol.	0	0	0	0	1	0	3	5
-min. diffuse vacuol.	0	0	0	0	0	0	1	1
-inflamm. c./ degen. hepatoc.	0	1	0	7	0	3	3	2

endometrial glands) and stomach, also noted in males (minimal gastritis), were affected by terbuconazole at the mid and high dose levels compared to control responses.

(TERMINAL SACRIFICE, CONTINUED)

Dead(D)/Terminal(T)

PPM:	0		20		60		180	
MALES	D	T	D	T	D	T	D	T
animal # examd	12	38	20	30	21	29	22	28
Liver(continued)								
-min. focal portal fibrosis	0	0	0	0	0	0	1	0
-prominent mitosis	0	0	0	0	0	0	0	1
Liver ORO								
-min. centrilob. lipid depos.	0	3	0	1	0	4	0	9
-mod. centrilob. lipid depos.	0	0	0	0	0	0	0	3
-trace focal peri-portal lipid depos.	0	0	0	0	0	0	0	3
-min. focal peri-portal lipid depos.	0	0	0	0	0	0	0	4
Adrenals								
-min. cortical hyperplasia	0	0	0	0	2	5	2	3
-enlarged cortical cells	0	0	5	12	4	8	2	8
-min. brown degen.	0	2	2	4	2	0	3	5
Stomach								
-min. gastritis(g)	1	1	1	1	0	1	5	7
-mod. gastritis(g)	0	0	0	0	0	0	0	1
-mod. acanthosis limiting ridge(ng)	0	0	0	0	0	0	0	1
Eyes								
-partial retinal atrophy	0	0	5	2	0	4	0	2

Dead(D)/Terminal(T)

PPM:	0		20		60		180	
FEMALES	D	T	D	T	D	T	D	T
animal # examd	33	17	29	21	27	23	31	19
Heart								
-myocardial scarr.	0	0	2	0	0	2	1	1
-min. epicarditis	0	1	0	0	1	1	1	1
Liver								
-necrosis	3	0	3	3	3	1	2	0
-single cell necrosis	2	4	1	0	0	1	0	4
-min. centrilob. fine vacuol.	1	1	0	1	1	0	1	2
-min. centrilob. vacuol.	2	0	3	1	1	0	1	1
-mod. centrilob. vacuol.	0	0	0	0	2	0	2	0
-marked centrilob. vacuol.	0	0	0	0	1	0	0	0

TERMINAL SACRIFICE, FEMALES (CONTINUED)

Dead(D)/Terminal(T) PPM:	0		20		60		180	
FEMALES	D	T	D	T	D	T	D	T
animal # examd	33	17	29	21	27	23	31	19
Liver (continued)								
-min. periportal fine vacuol.	1	0	0	0	0	0	0	0
-min. focal peri-portal vacuol.	0	0	0	0	0	1	0	2
-min. periportal vacuol.	0	0	1	0	1	0	0	1
-mod. periportal vacuol.	0	0	0	0	1	0	1	0
-min. diffuse vacuol.	0	0	0	0	0	0	4	3
-min. pleomor-phism	1	4	0	1	0	2	4	5
-min. extramed. hemopoiesis	2	0	4	1	3	3	3	3
-increased sinu-soidal cellularity	1	0	1	0	2	0	1	4
Liver ORO								
-various degrees centrilob., peri-portal, focal, dif-fuse lipid depos.	0	3	0	2	0	6	0	12
Pancreas								
-min. intersti. edema	2	0	3	0	3	3	7	1
-mod. interst. edema	0	0	0	0	0	0	2	0
Kidneys								
-min. glomerulo-nephritis	4	6	8	9	7	8	12	6
-mod. glomerulo-nephritis	2	1	2	1	5	0	6	0
-marked glomerulo-nephritis	5	0	4	0	3	0	2	0
Uterus								
-min. focal cystic hyperpl. endometrial glands	0	0	1	0	0	0	2	3
-mod. focal cystic hyperpl. endometrial glands	1	4	0	3	2	5	5	6
Stomach								
-min. gastritis(g)	1	0	6	5	2	5	2	5
Skin								
-min. subcut. edema	1	0	2	0	3	0	5	0

2) Neoplastic (from Table 5, pp. 347-360)

Dead(D)/Terminal(T)

PPM:	0		20		60		180	
MALES	D	T	D	T	D	T	D	T
animal # examd	12	38	20	30	21	29	22	28
LYMPH NODES								
-deposit of squamous c. carcinoma	0	0	0	0	0	0	0	1
LIVER								
-benign liver c. tumor	0	2	0	2	3	1	2	4
-benign liver c. tumor (two)	0	0	0	0	0	1	0	0
-malignant liver c. tumor	0	1	0	0	0	0	1	0
Combined (%)	6		4		10		14	
ADRENALS								
-pheochromocytoma	0	0	0	0	0	0	0	1
LUNGS								
-pulmonary adenoma	2	8	1	5	4	3	1	6
-pulmonary adenomata (two)	0	2	0	4	0	4	0	0
-pulmonary adenocarci-noma	1	4	2	4	3	4	4	0
-pulmonary adenocarci-noma (two)	0	0	1	1	0	0	0	0

PPM:	0		20		60		180	
FEMALES	D	T	D	T	D	T	D	T
animal # examd	33	17	29	21	27	23	31	19
LIVER								
-benign liver c. tumor	0	1	0	0	0	0	0	0
-malignant liver c. tumor	0	0	0	0	0	0	1	0
ADRENALS								
-pheochromocytoma	0	0	0	0	0	0	1	0
LUNGS								
-pulmonary adenoma	3	1	3	7	4	2	2	4
-pulmonary adenomata (two)	0	0	1	2	1	0	1	0
-pulmonary adenocarci-noma	0	0	2	3	1	2	0	1
-pulmonary adenocarci-noma (two)	0	0	0	0	0	3	1	0

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Historical control ranges(from Table 11, p. 65; 1980-84)

Study no.	1	2	3	4	5	6
# animals	50	50	50	45	46	48
Benign+	7	3	9	5	1	6
malignant*(%)	(14)	(6)	(18)	(11)	(2)	(12)

(*combined since different assessment criteria applied by study pathologists)

Selected neoplastic observations are presented in tabular form above along with submitted historical control data from the registrant.

The incidence (%) of male but not female benign liver tumors was somewhat higher in the mid and high dose groups as compared to the controls or low dose groups (4%/control, 4%/low, 8%/mid, 12%/high). Malignant liver cell tumors were not elevated in treated vs control males (2%/control vs 2%/high). Combined benign + malignant liver cell tumors in control and treated groups were within the range reported by the registrant for combined historical control data from 6 studies (6-18%).

Pulmonary adenomas (one, two per animal) and adenocarcinomas were generally present in all dose groups of both sexes but there is no evidence of a compound- or dose-related effect. These and other reported tumors are considered of a incidental or age-related nature.

D. Discussion

Terbuconazole was administered to NMRI mice (both sexes) for a period of up to twenty-one months in the diet at dose levels of 0, 20, 60 and 180 ppm. There was no dose-related increase in cumulative mortality in either sex or unusual clinical signs reported. A minimal but statistically significant depression for several weeks in male, but not female, mean body weights was observed during the first third of the dosing period. No apparent compound-related changes were observed in either sex for food consumption.

Bilirubin values in mid and/or high dose females were significantly increased at 53 and 92 weeks. Both absolute and relative liver weights of both sexes were elevated at 53 and/or 92/93 weeks reflective of terbuconazole's ability to induce microsomal enzymes (P-450, N- and O-demethylase). Gross pathology suggested a general increase in male liver enlargement and the presence of liver nodules.

Interim and both terminal sacrifice non-neoplastic histopathology indicate the liver as a primary target organ, usually at the mid and high dose levels in both sexes. In males the most frequent liver lesions are vacuolation (centrilobular, periportal) and lipid deposition (centrilobular, focal, periportal); in females, hepatic vacuolation (centrilobular, minimal diffuse), minimal extramedullary hemopoiesis, sinusoidal cellularity and increased lipid depostion were noted. In males, the adrenals were affected at the MDT and HDT with an increased enlargement and hyperplasia of cortical cells and there was an

increase in minimal stomach gastritis in the high dose group. Females also had apparent elevations in the pancreatic interstitial edema and stomach gastritis at the mid or high dose levels.

Although these findings indicate that the HDT resulted in some toxicity in liver and other organs, the nature and severity of such toxicity suggest that the HDT was not high enough and thus the MTD was not achieved in this study.

While in males, but not females, there was an apparent slight elevation in benign but not malignant liver tumors at 60 and 180 ppm (4%/control vs 8%/MDT, 12%/HDT) comparison to combined benign plus malignant liver tumors from 6 studies (1980-1984) indicated that the combined incidences were within the historical control range (6-18%). A breakdown of the historical control data into benign and malignant liver tumors for NMRI male mice was not provided by the registrant, the reason being that different criteria for pathological assessment of the liver lesion were used in the 6 studies. A breakdown of the histopathology would not provide any unexpected biological relevance since combining hepatocellular adenomas and carcinomas are acceptable and the combined data are not significantly different from the historical controls.

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