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

15 SEP 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Carcinogenicity Peer Review of Tebuconazole (1st)

FROM: Alberto Protzel, Ph.D. 9/9/93
Review Section III
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and

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TO: Mr. Benjamin Chambliss/Ms. Susan Lewis
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THROUGH: Penelope A. Fenner-Crisp 9/14/93
Penelope Fenner-Crisp, Ph.D.
Director, Health Effects Division (H7509C)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on May 26, 1993, to discuss and evaluate the weight-of-the-evidence on Tebuconazole with particular reference to its carcinogenic potential. The CPRC concluded that Tebuconazole should be classified as Group C - possible human carcinogen and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk.

This decision was based on the statistically significant increase in the incidence of hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas in both sexes of NMRI mice both by positive trend and pairwise comparison at the HDT, and the structural correlation with at least six other related triazole pesticides that produce liver tumors.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Reto Engler

William L. Burnam

Marcia Van Gemert

Kerry Dearfield

Elizabeth Doyle

Hugh Pettigrew

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Alberto Protzel[1] 9/9/93

James Rowe

Lori Brunsman

for Michael Stedham[2] (PAI/Clement)

3. Other Attendees:

Diane Mandell (Clement)

[1]Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

[2]Signature indicates concurrence with pathology report.

B. Material Reviewed:

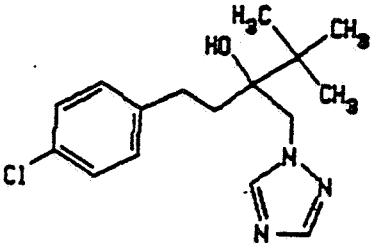
The material available for review consisted of DERs and other data summaries prepared by Alberto Protzel, a memorandum upgrading the original mouse carcinogenicity study, and statistical analyses prepared by Lori Brunsman. The material reviewed is attached to the file copy of this report. The data reviewed are based on studies submitted to the Agency by BAYER AG and Miles, Inc.

C. Background Information

Tebuconazole [α-[2-(4-chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1H -1,2,4-triazole-1-ethanol] is a systemic fungicide used for cereals, peanuts, oilseed rape, grapes, bananas, stonefruit, and pome fruit. It is produced by Miles Inc., Kansas City, MO. Tebuconazole Technical is a crystalline material of 95-98.3% purity. The compound has a high octanol/water partition coefficient (~ 5000, MRID 410685-04) and is soluble in organic solvents (e.g. ethanol).

The Caswell (or Tox Chem) Number of Tebuconazole is 463P. The Chemical Abstract Registry Number (CAS No.) is 107534-96-3.

The structure of Tebuconazole is presented below:



D. Evaluation of Carcinogenicity Data

1. NMRI Mouse Carcinogenicity Study (Low-Dose)

Reference: Chronic toxicity/carcinogenicity study in NMRI mice. (Administration in the diet for up to twenty-one months.) MRID No. 407009-41. Report No. 96709. Unpublished study conducted by BAYER AG, Toxicology Division, Federal Republic of Germany. Report dated January 25, 1988.

This study was followed by a second carcinogenicity study in mice at higher doses which is discussed in Section D.2. of this document. The present low-dose study plus the higher-dose mouse study (see next section) together with Supplementary data submitted by the Registrant have been classified as Core Minimum.

a. Experimental Design

Groups of Bor:NMRI(SPF Han) mice (50/sex/dose) received HWG 1608 (95% purity) in the diet at dose levels of 0, 20, 60, and

180 ppm for 21 months. A satellite group consisting of 10 mice/sex/dose was sacrificed at 12 months. Doses were selected based on two prior 4- and 8-week pilot feeding studies conducted in mice of the same strain at doses of 125 ppm to 2000 ppm.

b. Discussion of Tumor Data

Statistical analysis of tumor data indicated no significant compound-related hepatocellular tumor rates in either males (Table 1) or females (Table 2). The combined incidences of adenomas/carcinomas in either males or females (up to 12%) were within the historical control range (6-18%) reported by the Registrant for combined benign plus malignant liver tumors from 6 studies with NMRI mice performed from 1980 to 1984.

Pulmonary adenomas and adenocarcinomas were observed, but the effect was not dose-related.

Table 1. Tebuconazole - Winkelmann Bor:NMRI(SPF-Han) Mouse

Low-Dose Study

Male Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors:	0	20	60	180
Adenomas	2/49	2/48	5[a]/46	6/49
(%)	(4)	(4)	(11)	(12)
p =	0.056	0.684	0.192	0.134
Carcinomas	1/49	0/48	0/46	1[b]/49
(%)	(2)	(0)	(0)	(2)
p =	0.446	0.505[n]	0.516[n]	0.753
Combined	3/49	2/48	5/46	6/49
(%)	(6)	(4)	(11)	(12)
p =	0.093	0.510[n]	0.322	0.243

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[n]Negative change from control.

[a]First adenoma observed at week 71, dose 60 ppm.

[b]First carcinoma observed at week 77, dose 180 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Tebuconazole - Winkelmann Bor:NMRI(SPF-Han) Mouse

Low-Dose Study

Female Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors:	0	20	60	180
Adenomas	1[a]/44	0/46	0/47	0/45
(%)	(2)	(0)	(0)	(0)
p =	0.242[n]	0.489[n]	0.484[n]	0.494[n]
Carcinomas	0/44	0/46	0/47	1[b]/45
(%)	(0)	(0)	(0)	(2)
p =	0.247	1.000	1.000	0.506
Combined	1/44	0/46	0/47	1/45
(%)	(2)	(0)	(0)	(2)
p =	0.434	0.489[n]	0.484[n]	0.747

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[n]Negative trend or negative change from control.

[a]First adenoma observed at week 92, dose 0 ppm.

[b]First carcinoma observed at week 90, dose 180 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

c. Non-neoplastic lesions and other findings

Statistical analysis of mortality data indicated no significant trends in mortality with increasing doses in either sex. However, pair-wise comparisons indicated a significant total higher mortality ($p < 0.05$) in high-dose males (24/52) vs. controls (13/51).

Body weight and body weight gain were slightly but significantly decreased 4.9% and 7% from control, respectively, in males at the highest dose tested (HDT). No alteration in female body weight was noted.

There were no consistent, compound-related changes in hematology. Clinical chemistry values were altered in females but not in males. Bilirubin values were statistically significantly elevated in a dose-related fashion at all doses relative to controls, and cholesterol levels were decreased in 180 ppm females at 53 weeks and in 60 ppm females at termination.

At termination of the study there was a consistent elevation in absolute and relative liver weight at the HDT for both sexes, but statistical significance was reached only for relative weights in the HDT males. Terminal sacrifice histopathology also indicated the liver as the major target for toxicity, although minimal effects were noted in some other organs. In males, the most frequent hepatic alterations (in 50 mice/dose) were minimal to marked centrilobular fine vacuolation (0/control vs. 1/LDT, 4/MDT, 13/HDT)[3]; minimal focal periportal vacuolation (0/control vs. 0/LDT, 1/MDT, and 8/HDT); various degrees of centrilobular and periportal lipid deposition (3/controls vs. 1/LDT, 4/MDT, and 19/HDT); minimal focal centrilobular fine vacuolation (0/controls vs. 2/LDT, 5/MDT, and 2/HDT).

In females, the most frequent hepatic alterations (in 50 mice/dose) were 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 for MDT and HDT); increased sinusoidal cellularity (1/control vs. 5/HDT); various degrees of lipid deposition (3/control vs. 6/MDT, 12/HDT).

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The initial Agency reviewer concluded that the high-dose treatment (180 ppm) was not high enough to assess the carcinogenic potential of the chemical and classified this study as Supplementary. This classification was based on a decrease in body weight of only 7% in HDT males, elevations in bilirubin in HDT females only, and an increase in relative liver weight only in HDT males, even though microscopic pathology liver findings occurred at the mid- and high-doses (both sexes), and a significant pairwise increase in mortality was seen in the HDT male group compared to control.

This conclusion was ratified by the HED RfD/Peer Review Committee following a meeting held on March 5, 1991 (Memorandum from G.Z. Ghali, SACB, to S. Lewis, FHB, dated July 11, 1991), and it was concluded that the chemical should have been tested at a higher dose. Following this, the Registrant submitted a second carcinogenicity study in mice at higher doses. That study is summarized below.

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[3]LDT=low-dose treatment group; MDT=mid-dose treatment group; HDT=high-dose treatment group

2. NMRI Mouse Carcinogenicity Study (High-Dose)

Reference: Toxic dose-range carcinogenicity study in NMRI mice. (Supplement to Chronic toxicity/carcinogenicity study in NMRI mice; Administration in the diet for up to twenty-one months.) MRID No. 421750-01. Report No. 96709-3. Unpublished study conducted by BAYER AG, Toxicology Division, Federal Republic of Germany. Report dated December 12, 1991.

This study, together with the Supplementary data in the Memorandum dated April 26, 1993, regarding the upgrade of Tebuconazole carcinogenicity study from A. Protzel to B. Chambliss/S. Lewis, have been classified as Core Minimum.

a. Experimental Design

Groups of Bor:NMRI(SPF Han) mice (60/sex/dose) received HWG 1608 (96.2% purity) in the diet at dose levels of 0, 500, or 1500 ppm for up to 91 weeks. A group consisting of 10 mice/sex/dose was interim-sacrificed at 52 weeks, the remaining animals were terminally sacrificed at 91 weeks. Doses were selected based on the first mouse carcinogenicity study and in two prior 4- and 8-week pilot feeding studies conducted in mice of the same strain.

b. Discussion of Tumor Data

Statistical analysis of tumor data indicated that male mice had statistically significant, dose-related increasing trends in hepatocellular adenomas, carcinomas and combined adenomas and/or carcinomas (Table 3). There were also statistically significant differences in the pair-wise comparisons of the controls with the 1500 ppm dose group for hepatocellular adenomas (29% vs. 5% controls), hepatocellular carcinomas (21% vs. 0% controls) and combined adenomas and/or carcinomas (47% vs. 5% controls). No statistically significant differences were found in paired comparisons for the 500 ppm group vs. controls.

Table 3. Tebuconazole - Winkelmann Bor:NMRI(SPF-Han) Mouse

High-Dose Study

Male Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)		
Tumors:	0	500	1500
Adenomas	3/56	2[a]/53	17/58
(%)	(5)	(4)	(29)
p =	0.000**	0.526[n]	0.001**
Carcinomas	0/46	0/43	10[b]/47
(%)	(0)	(0)	(21)
p =	0.000**	1.000	0.001**
Combined	3/56	2/53	27/58
(%)	(5)	(4)	(47)
p =	0.000**	0.526[n]	0.000**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 51 for adenomas and combined and before week 54 for carcinomas.

[n]Negative change from control.

[a]First adenoma observed at week 51, dose 500 ppm.

[b]First carcinoma observed at week 78, dose 1500 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Female mice had statistically significant, dose-related increasing trends in hepatocellular carcinomas and combined adenomas and/or carcinomas (Table 4). There were also statistically significant differences in the pair-wise comparisons of the controls with the 1500 ppm dose group for hepatocellular carcinomas (12/44 vs. 1/42 controls) and combined adenomas and/or carcinomas (14/44 vs. 1/42 controls). No statistically significant differences were found in paired comparisons for the 500 ppm group vs. controls.

Table 4. Tebuconazole - Winkelmann Bor:NMRI(SPF-Han) Mouse

High-Dose Study

Female Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)		
Tumors:	0	500	1500
Adenomas (%)	0/42 (0)	0/40 (0)	2[a]/44 (5)
p =	0.120	1.000	0.259
Carcinomas (%)	1/42 (2)	0/40 (0)	12[b]/44 (27)
p =	0.000**	0.512[n]	0.001**
Combined (%)	1/42 (2)	0/40 (0)	14/44 (32)
p =	0.000**	0.512[n]	0.000**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[n]Negative change from control.

[a]First adenoma observed at week 89, dose 1500 ppm.

[b]First carcinoma observed at week 72, dose 1500 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

The incidence of hepatocellular tumors in males from this study (hepatocellular adenomas 29%, hepatocellular carcinomas

21%) exceeds the upper end of the historical control range for these tumor types (Table 5). In historical control males the incidence of hepatocellular adenomas ranged from 0 to 12% (mean incidence of adenomas 4%) and hepatocellular carcinomas ranged from 1 to 10% (mean incidence of carcinomas 3%). Historical control data is shown in Table 5.

The incidence of hepatocellular tumors in females from this study (hepatocellular adenomas 5%, hepatocellular carcinomas 27%) exceeds the upper end of the historical control range for these tumor types (Table 5). In historical control females the incidence for both hepatocellular adenomas and carcinomas ranged from 0 to 4% (means were <1%).

Table 5. Historical Controls: Incidence of Spontaneous Hepatocellular Adenomas and Carcinomas in NMRI mice[a]

Experiment Number	Males		Females	
	Adenoma (%)	Carcinoma (%)	Adenoma (%)	Carcinoma (%)
1	0/48 (0)	5/48 (10)	0/49 (0)	0/49 (0)
2	0/47 (0)	0/47 (0)	0/47 (0)	0/47 (0)
3	6/50 (12)	1/50 (2)	0/49 (0)	0/49 (0)
4	2/50 (4)	3/50 (6)	0/48 (0)	0/48 (0)
5	2/45 (4)	2/45 (4)	0/46 (0)	0/46 (0)
6	1/50 (2)	5/50 (10)	0/50 (0)	2/50 (4)
7	1/49 (2)	1/49 (2)	1/49 (2)	0/49 (0)
8	2/50 (4)	0/50 (0)	0/48 (0)	0/48 (0)
9	1/49 (2)	0/49 (0)	0/50 (0)	0/50 (0)
10	5/44 (11)	4/44 (9)	0/45 (0)	1/45 (2)
11	2/48 (4)	1/48 (2)	0/47 (0)	1/47 (2)
12	1/50 (2)	2/50 (4)	0/50 (0)	0/50 (0)
13	3/50 (6)	1/50 (2)	2/50 (4)	0/50 (0)
14	1/49 (2)	0/49 (0)	1/48 (2)	0/48 (0)
15	2/50 (4)	1/50 (2)	1/49 (2)	0/49 (0)
16	3/50 (6)	0/50 (0)	0/48 (0)	0/48 (0)
17	2/47 (4)	1/47 (2)	1/48 (2)	0/48 (0)
18	3/47 (6)	0/47 (0)	0/47 (0)	1/47 (2)
Total (average)	37/873 (4)	27/873 (3)	6/868 (<1)	5/868 (<1)

[a] Historical data were obtained from 18 chronic/carcinogenicity studies with NMRI mice started at Bayer between 7/81 and 8/88. All studies were 21 months in duration (except for Nos. 8 and 5, which lasted 20 and 24 months, respectively). The registrant indicated [Miles Report 96709-4; EPA MRID 424693-01] that no data are available for studies started after 10/85 because chronic/carcinogenicity studies at the Bayer facility after 1985-86 were performed with B6C3F1 mice, except for the high-dose mouse tebuconazole study (No. 18), which used NMRI mice.

The incidence of histiocytic sarcomas in high-dose males (6%) shown in Table 6 exceeded the range for histiocytic sarcomas in controls (0-4%). Analysis of tumor data indicated that there were no statistically significant dose-related trends or pair-wise differences between controls and treated animals for the incidences of histiocytic sarcomas in either males (Table 6) or females (Table 7). Thus, it appears somewhat dose-related but is

not statistically significant by pairwise comparison. It is noted, however that the historical controls cover the period of 3/82-10/85 and not the period of 8/88-5/90 in which the subject high-dose study in mice was performed. As noted above, the registrant indicated that no data are available for studies started after 10/85 because chronic/carcinogenicity studies at Bayer Fachbereich Toxicology after 1985-86 were performed with B6C3F1 mice, except for the subject high-dose mouse study, which used NMRI mice.

The incidence of histiocytic sarcomas in high-dose females (Table 7) is within the range of historical controls (Table 8): 1/50-5/50 in 9 studies performed between 3/82 and 10/85 at Bayer Fachbereich Toxicology. This represents a period prior to the one in which the current study was performed, for which historical control data are unavailable.

Table 6. Tebuconazole - Winkelmann Bor:NMRI(SPF-Han) Mouse

High-Dose Study

Male Histiocytic Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)		
Tumor:	0	500	1500
Sarcomas (%)	1/49 (2)	2/45 (4)	3[a]/47 (6)
p =	0.199	0.468	0.293

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First sarcoma observed at week 78, dose 1500 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 7. Tebuconazole - Winkelmann Bor:NMRI(SPF-Han) Mouse

High-Dose Study

Female Histiocytic Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)		
Tumor:	0	500	1500
Sarcomas (%)	1/59 (2)	3[a]/59 (5)	5/59 (8)
p =	0.069	0.309	0.103

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 18.

[a]First sarcoma observed at week 18, dose 500 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 8. Historical Controls: Incidence of Histiocytic Sarcoma in NMRI Mice[a,b]

Study Number	Males (n=50/study)	Females (n=50/study)
T6011121	2	5
T5016332	1	1
T5016954	1	2
T4016962	0	3
T9017407	1	3
T2018454	1	1
T6018953	0	2
T9019388	1	3
T4021010	0	2

[a] Extracted from MRID 424693-01, p. 21.
[b] Historical data were obtained from 9 studies with NMRI mice started at Bayer Fachbereich Toxicology between 3/82 and 10/85. All studies were 21 months in duration. The submitted historical data do not encompass the period (8/22/88 - 5/25/90) in which the subject high-dose, carcinogenicity study of Tebuconazole in mice was performed. The Registrant indicated that no data are available for studies started after 10/85 because chronic/carcinogenicity studies at Bayer Fachbereich Toxicology after 1985-1986 were performed with B6C3F1 mice, except for the subject high-dose mouse study, which used NMRI mice.

c. Non-neoplastic Lesions and Other Findings

Statistical analysis of mortality data indicated no significant trends in mortality with increasing doses in either sex. Body weight in both sexes was depressed in a dose-related fashion; effects were seen at 500 ppm.in the first half of the study (-6.3% in males, sporadic in females) and 1500 ppm throughout the study in both males (-9% to -11%) and females (-7.6% to -8.5%). Body weight gain was decreased in a dose-related fashion in both sexes. For weeks 0-24, body weight gain averaged 8% and 10.4% below control levels in both sexes of the 500 and 1500 ppm groups, respectively. Statistically significantly increased food consumption at 500 ppm in males and at 1500 ppm in both sexes was reported, consistent with decreased food efficiency in these groups.

Statistically significant changes in blood parameters were observed at the high dose in both sexes, mainly in males. At sacrifice, the statistically significant changes included leucocytosis, and changes consistent with anemia (decreased erythrocytes, hemoglobin, MCHC, and hematocrit values). In addition, high-dose males had statistically significantly increased platelet counts and decreased thromboplastin times. In the case of high-dose females, a reduced hematocrit and leucocytosis were observed at 51 weeks, and only an increased platelet count at terminal sacrifice.

Clinical chemistry data revealed dose-dependent and statistically significant increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) for both sexes in the interim and final sacrifices. Alkaline phosphatase (AP) increased with dose in both sexes and reached statistical significance at 1500 ppm. These changes correlated with dose-dependent and statistically significant histopathological findings in liver. Cholesterol was statistically significantly decreased vs. controls in both sexes at 500 and 1500 ppm for the interim sacrifice, and at 500 ppm for the final sacrifice.

Non-neoplastic histopathology at interim sacrifice (52 weeks) revealed hepatocellular abnormalities in both sexes (Table 9). In males, dose-dependent increases in individual hepatocyte necrosis, panacinar fatty vacuolation, pigment laden Kupfer cells and ORO stained panacinar fat which were statistically significant ($p < 0.05$-0.001) at 500 and 1500 ppm. Incidences of these effects at 1500 ppm ranged from 5/10 (periportal fibrosis) to 10/10 (panacinar fine fatty vacuolation) vs. 0/10 in controls. In addition, the incidence of bile duct hyperplasia at the HDT (8/10) was statistically significantly elevated vs. controls (0/10).

In females, panacinar fine fatty vacuolation was seen in 100% of both 500 and 1500 ppm females and was statistically significantly elevated ($p < 0.001$) vs. controls which had no incidence of this effect. There were also dose-related increases

in individual hepatocyte necrosis, bile duct hyperplasia, chronic inflammatory cells in the portal area, extramedullary hemopoiesis, all of which reached statistical significance at the high-dose ($p < 0.05$-0.001). Incidences of these effects at 1500 ppm ranged from 5/10 (extramedulary hemopoiesis) to 9/10 (hepatocyte necrosis) vs. 0/10 in controls.

Non-neoplastic histopathology at terminal sacrifice (91 weeks) revealed hepatocellular abnormalities in both sexes (Table 10). In males, dose-related and statistically significant increases in hepatic panacinar fine fatty vacuolation at 500 (14/48) and 1500 (25/48) ppm vs. 0/47 in controls and statistically significant increases in focal hyperplasia of hepatocytes (23/48) and oval cell proliferation (23/48) at 1500 ppm vs. 0/47 in controls.

In females, dose-related increases in hepatic panacinar fine fatty vacuolation (19/46) which was statistically significant at 1500 ppm. In addition, at 1500 ppm there were increases in periacinar hepatocyte hypertrophy (13/46), oval cell proliferation (17/46), and eosinophilic foci of hepatocyte alteration (7/46) which were statistically significant vs. controls (0/47).

Table 9. Selected statistically significant non-neoplastic histopathology findings at interim sacrifice (52 weeks).

Finding	Incidence of non-neoplastic findings 0 ppm	500 ppm	1500 ppm
	Males		
Liver (Examined)	10	9	10
Necrosis of individual hepatocytes (Minim.-Moderate)	0	5*	8***
Panacinar fine fatty vacuolat. Minimal-Moderate	0	8***	10***
Bile duct hyperplasia	0	1	8***
Periportal fibrosis	0	1	5*
Pigment laden Kupfer cells	0	4*	8***
ORO stain panacinar fat	0	6*	8**
	Females		
Liver (Examined)	10	10	10
Focal inflammation with hepatocytic degeneration	0	5*	2
Necrosis of individual hepatocytes (Minim.-Moderate)	0	2	9***
Panacinar fine fatty vacuolat. Minimal-Moderate	0	10***	10***
Centriacinar fatty vacuolation	0	9***	6*
Bile duct hyperplasia	0	2	6*
Chronic inflammatory cells in the portal area	0	4	8**
Extramedullary hemopoiesis	0	3	5*
Pigment laden Kupfer cells	0	0	8***
ORO stain periacinar fat	0	0	5*
Stomach (Examined)	10	10	10
Keratinized region: hyperkeratosis and acanthosis	2	6	8*

[a] Data extracted from the Study Report, pp. 344-348.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 10. Summary of statistically significant non-neoplastic histopathology findings at terminal sacrifice.

Finding	Incidence of non-neoplastic findings		
	0 ppm	500 ppm	1500 ppm
		Males	
Liver (Examined)	47[a]	48	48
Necrosis of individual hepatocytes	3	11*	2
Focal hyperplasia of hepatocytes	6	2	23***
Panacinar fine fatty vacuolat.	0	14***	25***
Oval cell proliferation	0	0	23***
Extramedullary hemopoiesis	0	2	7*
		Females	
Liver (Examined)	47	45	46
Focal hyperplasia of hepatocytes	1	0	12*
Panacinar fine fatty vacuolat.	1	4	19***
Centriacinar fatty vacuolation	3	13**	4
Periacinar hepatocyte hypertrophy	0	0	13***
Oval cell proliferation	0	0	17***
Eosinophilic focus/foci	0	0	7**
Pigment laden Kupfer cells	1	3	7*
Ovaries (Examined)	47	44	45
Bilateral: luteal cell hyperplasia	0	4	5*
Atrophy	7	17*	28***

[a] Includes animals killed at terminal sacrifice and those dead or sacrificed in extremis during treatment.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The CPRC concluded that the HDT may have been excessively toxic for assessing the carcinogenic potential of Tebuconazole based on the following changes in both sexes of mice: dose-related statistically significant decreases in body weight and decreased food efficiency were seen in mid- and high-dosed males and females; hematological changes (including anemia in males) and clinical chemistry changes were found in both sexes (such as increases in serum liver enzymes); dose-dependent increases in liver weight were found that correlated with adverse histopathological alterations in the liver; and significant ovarian atrophy at the HDT.

3. Carcinogenicity Study in Rats

Reference: Chronic toxicity/carcinogenicity study in Wistar rats (Administration in diet for two years.) MRID No. 407009-39. Study No. 96711, Report No. 16375. Unpublished study conducted by Bayer AG, Toxicology Division, Federal Republic of Germany. Report dated January 25, 1988.

This study has been classified as Core Minimum.

a. Experimental Design

Groups of Bor:WISW(SPF Cpb) rats (50/sex/dose) received HWG 1608 in the diet at dose levels of 0, 100, 300, or 1000 ppm for 24 months. A satellite group consisting of 10 rats/sex/dose was sacrificed at 12 months. Doses were selected based on a subchronic (13-week) dietary study using rats of the same strain administered dietary concentrations of 0, 100, 400 or 1600 ppm.

b. Discussion of Tumor Data

Thyroid follicular adenomas, C-cell thyroid adenomas and carcinomas were noted in treated males but not in controls (Tables 11, 12, and 13). There was an increasing statistical trend in thyroid follicular adenomas observed in male rats (Table 13); the statistical significance of this finding may be overstated due to increased survival at the HDT. The Fisher's Exact test was the only test applicable to the data for pairwise comparison because of the small number of thyroid tumors; this test may have exaggerated the significance of the results observed in the male rats because of the increasing trend in survival. There was no significant difference in the pair-wise comparisons of the dosed groups with the controls.

In females, C-cell adenomas were observed at the 300 ppm and 1000 ppm at the same frequency as in controls (1/50); C-cell carcinomas were not observed at any dose level (Table 12). Follicular cell adenomas were limited to the mid- (1/50) and high-dose groups (1/50) and were not seen in the low-dose group or in control animals (Table 13). There were no significant compound-related tumors observed in female rats.

Table 11. Tebuconazole - Winkelmann Bor:WISW(SPF-Cpb) Rat Study

Male Thyroid C-Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors:	0	100	300	1000
Adenomas	0/50	1/50	3[a]/50	2/50
(%)	(0)	(2)	(6)	(4)
p =	0.184	0.500	0.121	0.248
Carcinomas	0/50	1[b]/50	0/50	1/50
(%)	(0)	(2)	(0)	(2)
p =	0.313	0.500	1.000	0.500
Combined	0/50	2/50	3/50	3/50
(%)	(0)	(4)	(6)	(6)
p =	0.126	0.248	0.121	0.121

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First adenoma observed at week 104, dose 300 ppm.

[b]First carcinoma observed at week 105, dose 100 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 12. Tebuconazole - Winkelmann Bor:WISW(SPF-Cpb) Rat Study

Female Thyroid C-Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors:	0	100	300	1000
Adenomas (%)	1[a]/48 (2)	0/50 (0)	1/50 (2)	1/49 (2)
p =	0.393	0.490[n]	0.742	0.747

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[n]Negative change from control.

[a]First adenoma observed at week 105, dose 0 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 13. Tebuconazole - Winkelmann Bor:WISW(SPF-Cpb) Rat Study

Thyroid Follicular Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors:	0	100	300	1000
Male				
Adenomas	0/50	1/50	0/50	3[a]/50
(%)	(0)	(2)	(0)	(6)
p =	0.034*	0.500	1.000	0.121
Female				
Adenomas	0/48	0/50	1[b]/50	2/49
(%)	(0)	(0)	(2)	(4)
p =	0.062	1.000	0.510	0.253

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First male adenoma observed at week 104, dose 1000 ppm.

[b]First female adenoma observed at week 104, dose 300 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

An increased incidence, not dose-related or statistically significant, of atypical carcinoma of the uterus, described as highly malignant, was noted in the treated dose-groups (3/50, 2/50, 1/50, in the low-, mid- and high-dose groups) as compared to controls (0/50). There was no evidence of dose-related increases in hepatocellular adenoma or carcinoma.

The incidences of C-cell hyperplasia, C-cell adenomas, and C-cell carcinomas are within the historical control ranges for both sexes of Wistar rats (Table 14). Historical control data are found in Table 14.

Incidences of follicular cell adenomas in 1000 ppm males (3/50, 6%) marginally exceeded the upper end of the historical range for Bayer 81-87 (up to 3/58, 5.2%) and for Bayer 73-76 (up to 4/76, 5.3%). The upper end of the RITA historical control range (up to 8/99, 8.1%), which includes Wistar rat controls from studies performed at other facilities, is not exceeded.

Incidences of follicular cell adenomas in 1000 ppm females (2/49, 4.1%) only marginally exceeded the upper end of the historical control range for Bayer 81-87 (up to 2/50, 4%). The Bayer 71-76 historical range (up to 2/83, 2.4%) is exceeded, however it may be argued that these controls are not contemporary to the Bayer 81-87 set. The upper end of the RITA historical control range (up to 4/98, 4.1%) is not exceeded.

Table 14. Historical Controls: Incidence of Thyroid Tumors/Lesions in Wistar Rats[a]

	Incidence (%) of:			
	C-Cell (Parafollicular Cell)			Follicular Cell
	Hyperplasia	Adenomas	Carcinomas	Adenomas
MALES				
Bayer 81-87[b]	0/50-48/50 (0-96)	0/50-8/47 (0-17)	0/50-8/50 (0-16)	0/50-3/58 (0-5.2)
Bayer 73-76[c]	No data	0/68-15/83 (0-18)	0/89-5/76 (0-7)	0/89-4/76 (0-5.3)
RITA (24-26 Months)[d]	0/20-57/60 (0-95)	1/50-3/20 (2-15)	0/99-3/99 (0-3)	0/98-8/99 (0-8)
FEMALES				
Bayer 81-87[b]	0/50-47/50 (0-94)	0/50-7/49 (0-14)	0/50-2/47 (0-4)	0/50-2/50 (0-4)
Bayer 73-76[c]	No data	2/90-18/85 (2-21)	0/90-5/83 (0-6)	0/86-2/83 (0-2.4)
RITA (24-26 Months)[d]	1/50-57/60 (2-95)	0/50-17/98 (0-17)	0/100-4/98 (0-4)	0/100-4/98 (0-4.1)

[a] Historical data from Miles, Inc. Report No. 96711-3 (May 7, 1993).
[b] Bayer 81-87: Controls from 25 studies initiated in 6/81-9/87 (one of them, T 8018630, is the subject Tebuconazole study) at Bayer Pharma Research Center with BOR:WISW (SPF-CPB)Wistar rats from Winkelmann.
[c] Bayer 73-76: Controls from 11 studies initiated in 1973-1976 at Bayer Pharma Research Center with Wistar rats TNO/W.70 from Winkelmann, later renamed BOR:WISW (SPF-CPB).
[d] RITA: Registry of Industrial Toxicology Animals. Controls from 21 studies with Wistar rats (24-26 months duration) from various laboratories.

c. Non-neoplastic Lesions and Other Findings

No adverse clinical signs or decreased mortality was observed in treated rats. Male rats actually showed a statistically significant increasing trend in survival with increasing doses of Tebuconazole. Consistent and statistically significant decreases in body weights were reported for mid- (5.4%) and high-dose females (7% to 9.6%), but not in males. Body weight gain in HDT females had decrements of 13.1% for the

0-15 week period. A compound-related decrease in food efficiency was seen in mid- and high-dose females. Female rats in these dose groups also had statistically significant changes in hematology tests (decreases in Hb, HCT, MCV and MCH) throughout the test period. These changes were consistent with clearance of RBCs in the spleen. No treatment-related hematological effects were apparent in males. Clinical chemistry changes were inconsistent, sporadic, and were not dose- or sex-related.

Significantly decreased absolute and relative adrenal weight was noted in all female treatment groups at terminal sacrifice. A dose-related significant decrease in relative testes weights in the HDT males was also reported at the final sacrifice.

Gross pathology observation of animals dead or sacrificed moribund revealed an apparent increase in the incidences of cysts/cystic kidneys (4/50 HDT males vs. 0/49 in controls) and of reddened lymph nodes (6/50 HDT males vs. 1/49 in controls). The incidences of shrunken testes were increased at the mid (7/50) and high doses (6/50) vs. controls (3/49).

Non-neoplastic histopathology indicated a statistically significant increase in hemosiderin deposition in the spleen of high dose females (19/50) vs. controls (2/50); these changes were consistent with the hematological findings and indicated increased clearance of RBC's in the spleen. The incidence of thyroid C-cell hyperplasia in males was somewhat elevated in the mid- and high-dose groups (7/50 and 6/50, respectively, vs. 1/50 in control animals); this elevation was statistically significant ($p < 0.05$) in the mid- but not in the high-dose group.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The CPRC agreed that the doses used in this study were adequate for assessing the carcinogenic potential of the chemical. This conclusion was based on statistically significant decreased body weight (5.4% at 300 ppm, 7.0 to 9.6% at 1000 ppm) and body weight gain (13.1% lower than controls for the 0-15 week period at the HDT) in females, and decreased food efficiency. Males had decreased testes weight at the HDT, and HDT females had histopathological changes in the spleen and hematological changes consistent with increased RBC clearance by the spleen.

E. Additional Toxicological Data on Tebuconazole .

1. Metabolism

Reference: (MRID Nos. 409959-11 and 409959-12).

This study was classified as acceptable (Core Minimum). The metabolism of ^{14}C-labeled Tebuconazole technical after oral dosing was studied in Wistar rats of both sexes. A single oral

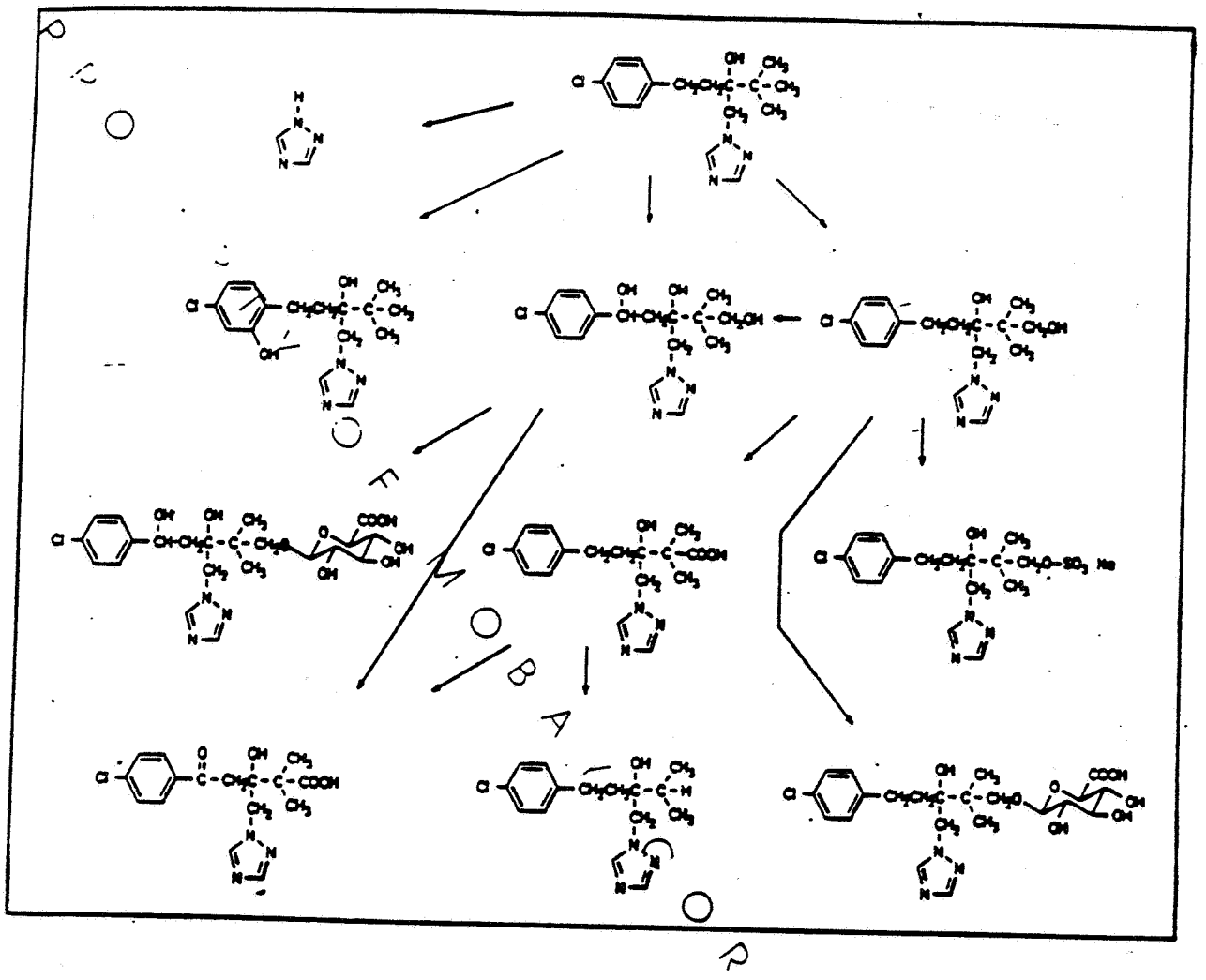
dose of 2 or 20 mg/kg of [phenyl-UL-^{14}C]-labeled Tebuconazole was administered to male and female Wistar rats.

Results of this study indicated that the compound was rapidly and extensively absorbed, extensively metabolized, and rapidly excreted. Over 98% of a single oral dose of [phenyl-UL-^{14}C]-labeled Tebuconazole (2 mg/kg) was absorbed from the gastrointestinal tract, based on [^{14}C] excretion in urine (7.4% of the dose) and in bile (90.68% of the dose), as determined in bile-fistulated male rats. In intact rats, over 86-98% of the administered radioactivity was excreted by 72 hours. In males, about 14-16% and 72-82% of the dose appeared in urine and feces; in females, about 28-32% and 62% of the dose appeared in urine and feces, respectively. Tissue concentrations were highest in liver at sacrifice, 72 hours after dosing.

Tebuconazole undergoes extensive metabolism in rats. A total of 10 metabolic products were identified in excreta, amounting to 51-58% of the dose in males and to 68-71% of the dose in females. The untransformed parent compound amounted to 0.5-2.2% of the dose. A large fraction of the identified metabolites corresponded to successive stages in the oxidation of one of the methyl groups in the t-butyl moiety of Tebuconazole.

The biotransformation of Tebuconazole in the rat is shown in Figure 1. The compound undergoes successive oxidation steps. At high doses, the ratio of carboxylic acid-to-diol compounds decreases, which suggests that the detoxification patterns changed. This implies that metabolic oxidation is saturated at these doses.

Figure 1. Biotransformation of Tebuconazole in the Rat



2. Genotoxicity

Tebuconazole has been tested in several genotoxicity studies. The acceptable tests fulfill requirements for all three categories: gene mutations, structural chromosomal aberrations, and other genotoxic effects (e.g. DNA damage and repair).

a) Salmonella assay. Negative in 1 acceptable Salmonella reverse mutation assay with metabolic activation (MRID 407009-47 and 407009-48).

b) Mouse micronucleus test for structural chromosomal aberrations: Negative in 1 acceptable assay (MRID 407009-51).

c) Sister chromatid exchange (CHO cells). Negative in 1 acceptable assay (MRID 407009-52).

d) Unscheduled DNA synthesis for DNA damage. Negative in 1 acceptable UDS/primary mouse hepatocyte assay (MRID 408164-02).

Tebuconazole was negative in the following unacceptable assays: CHO/HGPRT forward mutation assay (MRID 407009-49), mouse dominant lethal test (MRID 407009-50), in vitro cytogenetics with human lymphocytes (MRID 407009-53), and E. coli DNA damage/repair (407009-55).

The weight of the evidence does not suggest a genotoxicity concern for Tebuconazole.

3. Subchronic and Chronic Toxicity

Reference: 13-Week Feeding study in Rats. (MRID No. 407009-30).

Administration of Tebuconazole in the feed at concentrations of 100, 400, or 1600 ppm for 13 weeks resulted in decreased mean body weight and mean body weight gain (-11% and -15% in male and female Wistar rats of the high-dose group). An increased incidence of vacuole formation in zona fasciculata cells in the adrenals of high-dose animals of both sexes was found (males: 6/10 vs. 4/10 in control animals; females: 9/10 vs. 0/10 in control animals), and in females fed 400 ppm (4/10 vs. 0/10 in control animals). Similarly, high dose males and females had increased incidences of hemosiderosis. Both lesions were reported by the study author to be treatment-related. Adverse compound effects appeared to be more intense in females than in males and were attributed to increased female food consumption. In males the LOEL was 1600 ppm, based on decreased body weights and body weight gain and histological changes; the NOEL was 400 ppm. In females the LOEL was 400 ppm and the NOEL was 100 ppm.

Reference: 13-Week Feeding study in Dogs. (MRID No. 407009-34).

Administration of Tebuconazole in the feed at concentrations of 200, 1000, or 5000 ppm for 13 weeks resulted in decreased mean body weight, body weight gains, and food consumption in beagle dogs of the mid- and high-dose groups. Other findings in high-dose animals included compound-induced lens opacity, anisocytosis, and increased siderosis of the liver and spleen. Effects on the liver included increased alkaline phosphatase, decreased albumin, increased cytochrome P-450 at the high dose and a dose-related increase in N-demethylase activity. Increased vacuolation in the adrenals of females was considered to be compound-related by the study authors. This study defines a LOEL of 1000 ppm, based on decreases in mean body weights, body weight gains, and food consumption and on increases in N-demethylase activity; the NOEL is 200 ppm.

Reference: 52-Week Feeding study in Dogs. (MRID No. 407009-40).

Tebuconazole was administered to beagle dogs of both sexes at dietary concentrations of 0, 40, 200 and 1000 (1-39 weeks)/2000 (40-52 weeks) ppm for 52 weeks. The treatment caused lenticular and corneal opacity in mid- and high-dose animals. The liver appeared to be a target organ, based on elevations in alkaline phosphatase (HDT both sexes), N-demethylase activity and triglycerides (HDT, both sexes), iron-containing pigments (MDT, HDT) in addition to gross changes in liver appearance (MDT, HDT). Other tissues/organs affected included blood (anisocytosis), adrenals (increased vacuolation in zona fasciculata), kidney and spleen (elevated weights) at mid- and/or high-dose levels. The systemic LOEL was set at 200 ppm, based upon ocular lesions and hepatic toxicity in either sex at the mid- and high-dose levels. The NOEL was set at 40 ppm. The current RfD (0.01 mg/kg/day) was based on this study and uses the NOEL of 40 ppm.

Currently the Agency is reviewing additional dog chronic data (MRIDs 420306-01 and 425372-01) submitted by the Registrant in support of an increase in the dog chronic NOEL from 40 ppm to 100 ppm.

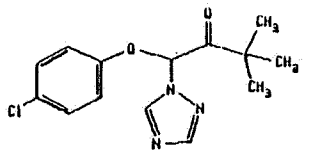
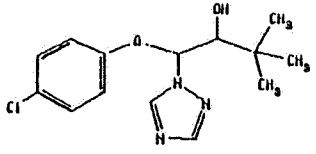
4. Structure-Activity Relationships

Tebuconazole is structurally related to other triazole pesticides (depicted in Table 13) [redacted]

[redacted]

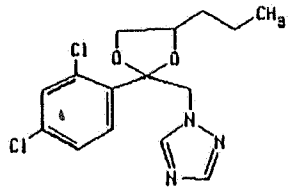
PENDING REGISTRATION INFORMATION IS NOT INCLUDED

Table 13. Structurally Related Triazole Pesticides.

Compound	Structure	Carcinogenic Effect	Carcinogen Class
Bayleton PC 109901 Tx.# 862AA		**NMRI Mouse** Doses 50, 300, 1800 ppm. Only hepatocellular adenoma, at 1800 ppm in (22%) ♂ & (18%) ♀, $p < 0.05$ for trend and paired comparisons. Historical Controls: 18.4% ♂, and 2.0% ♀. **Wistar rat** Doses 50, 500, 5000 ppm. Dose-related trend in TFC adenomas in ♂ and combined with cystic hyperplasia in ♂ & ♀. Pairwise comparisons not significant.	C, no Q_1^*
Baytan PC 127201 Tx.# 074A		**CF1-W74 mouse** Doses 2000 ppm. Hepatocellular adenomas and hyperplastic nodules ($p < 0.01$) in ♀. No increase in ♂. Adrenal adenomas noted in ♀ LDT and HDT but not in historical controls. No elevation in carcinomas.	C, no Q_1^* SAP 12/23/87

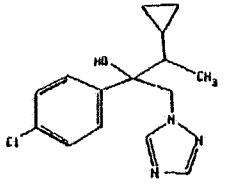
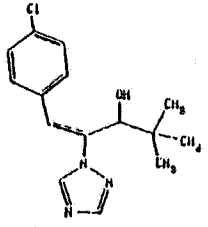
[redacted]

Table 13. Structurally Related Triazole Pesticides (Continued).

Propiconazole PC 122101 Tx.# 323EE		CD-1 mouse Doses 100, 500, 2500 ppm. Statistically significant trend and pairwise comparisons in liver adenomas and combined at 2500 ppm. For carcinomas only there were statistically significant trend and pairwise comparisons at the HDT for data from 2 of 3 pathologists; for the data from the third pathologist only the trend was significant ($p = 0.028$) (the pairwise comparison HDT vs. control had a $p = 0.050$).	C, no Q_1^*

[redacted]

Table 13. Structurally Related Triazole Pesticides (Continued).

Compound	Structure	Carcinogenic Effect	Carcinogen Class
[redacted]			
Cyproconazole PC 128993 Tx.# 272E		CD-1 mouse Doses 5, 15, 100, 200 ppm. Significant incidence of adenomas and carcinomas at the MDT and HDT in males and at the HDT in females.	B2
Uniconazole PC 128976 Tx.# 207H		Crl:CD-1(ICR)BR mouse Doses 10, 40, 200, 1500 ppm. Increased incidence of hepatocellular adenomas and carcinomas in 1500 ppm males only. Crl:CD-1(ICR)SD rat Doses 10, 40, 200, 1000 ppm. No increase in neoplastic findings.	C, no Q_1^*

5. Registrant's Rebuttal Concerning Carcinogenicity of Tebuconazole in Mice.

Reference: Position document entitled: "Discussion of the Toxicological Basis for Classification of Tebuconazole as an EPA Group E Non-Carcinogen" submitted by the registrant [Miles Report 103268; EPA MRID 424693-03].

Miles, Inc. has presented the following four arguments in support of the point of view that Tebuconazole should be classified as a Class E chemical (The complete presentation by Miles is included as an Attachment in the file copy of the peer review document):

Firstly, it was stated by the registrant that neoplastic changes were observed only at the highest dose. Neoplastic changes in the liver were observed in the second mouse carcinogenicity study, only at the highest dose tested (1500 ppm). This dose was 3-fold higher than the dose considered to be adequate (500 ppm). Thus, the tumor response at this dose level is due to factors which do not operate at or below the adequate dose level. No evidence was provided to discern these factors.

Second, there was no evidence of genotoxicity. Genotoxicity tests present no evidence that Tebuconazole is capable of interacting with or damaging genetic material. The liver tumor seen in the treated animals result from an epigenetic mechanism. The registrant stated that liver cell death followed by increased cell division may result in the development of tumors, and the data are consistent with a threshold effect.

Metabolism data for Tebuconazole provide evidence that the metabolic pathways were saturated at 1500 ppm (~ 225 mg/kg/day). In metabolism studies conducted with rats, at single dose levels of 2 and 20 mg/kg dose-dependent changes in metabolism ratios were observed. At the higher dose level (20 mg/kg) oxidative biotransformation is saturated.

Finally, the registrant stated that the dose levels at which liver tumors were observed in mice has no biological relevance to human exposure levels. In a chronic dietary exposure analysis submitted by Miles, Inc. (MRID 424693-03), exposure to Tebuconazole residues from its use in peanuts were estimated to range from 0.00008 to 0.000021 mg/kg/day. The high-dose in the mice study is >10 million times greater than the highest dietary exposure to Tebuconazole residue.

F. Weight of the Evidence Considerations

The Committee considered the following observations regarding the toxicology of Tebuconazole for a weight-of-the-evidence determination on its carcinogenic potential:

1. In mice of both sexes, 1500 ppm Tebuconazole induced an increase in the incidence of hepatocellular adenomas, carcinomas and combined adenomas/carcinomas. There was a statistically significant increase ($p < 0.01$) in tumor incidence by pairwise comparisons with concurrent controls, and a significantly increasing trend ($0 < 0.01$). In addition, at 1500 ppm Tebuconazole there was an increased incidence ($p < 0.001$ in males, $p < 0.05$ in females) of focal hyperplasia of hepatocytes vs. concurrent controls. The incidence of histiocytic sarcomas at 1500 ppm in males (6%), although not statistically significantly above controls, exceeded the historical control range of 0-4%. The HDT, 1500 ppm, was determined to be excessively toxic for assessing the carcinogenic potential of Tebuconazole based on statistically significant changes in both sexes; decreased body weight, decreased food efficiency, hematological and clinical chemistry changes, dose-dependent increases in liver weight that correlated with adverse liver histopathology (such as vacuolation, lipid deposition), and ovarian atrophy in females. Nevertheless, the high incidence of liver adenoma, carcinoma, and combined tumors in both sexes of mice in this study was concluded by the CPRC to be compound-related and biologically significant.

2. An increasing trend in thyroid follicular adenomas was seen in male Bor:WISW(SPF Cpb) rats fed up to 1000 ppm Tebuconazole. However, the statistical significance of this finding may have been exaggerated due to the statistical test used and the increased survival in the high dose group. The doses used in this study were determined to be adequate for carcinogenicity testing.

3. Tebuconazole has been tested in several acceptable genotoxicity studies. The results were negative. These studies covered the three categories: gene mutations, structural chromosomal aberrations, and other genotoxic effects (e.g. DNA damage and repair). Tebuconazole has been negative in a Salmonella assay, a mouse micronucleus test, a sister chromatid exchange (CHO cells), and an unscheduled DNA synthesis assay.

4. Dose-dependent changes in metabolite ratios (e.g. ratio of "acid" to "diol" was decreased at the higher dose) suggestive of changes in detoxication patterns were seen at the high dose in rats. These changes may result from saturation of metabolite oxidation in rats between the low dose (1 mg/kg) and the high dose (20 mg/kg).

5. Tebuconazole is structurally related to at least six other triazole pesticides known to induce hepatocellular adenomas and/or carcinomas in mice.

6. The Registrant, Miles Inc., submitted a document entitled "Discussion of the Toxicological Basis for Classification of Tebuconazole as an EPA Group E Non-Carcinogen" which was evaluated by the CPRC and which, in summary, states that Tebuconazole should be classified as a Group E due to the demonstrated non-genotoxic nature, induction of tumors only at the HDT in mice (a dose determined to be excessive), evidence for metabolic saturation at high doses, and estimate of low human exposure levels.

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the criteria contained in the EPA's "Guidelines for Carcinogenic Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

The Peer Review Committee agreed that the classification for Tebuconazole should be Group C - possible human carcinogen - and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk.

This decision was based on the statistically significant increase in the incidence of hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas in male and female Winkelmann Bor:NMRI(SPF-Han) mice by both trend and pairwise comparison at the HDT. Although dosing in this study was considered excessive for carcinogenicity testing, the CPRC considered the tumors to be compound-related and biologically significant. There was no evidence of carcinogenicity in rats, and no evidence of genotoxicity for Tebuconazole. However, the formation of benign and malignant hepatic tumors in both sexes of mice, and the structural correlation with at least six other related triazole pesticides that are proven liver tumorigens provided adequate evidence for the carcinogenic potential of Tebuconazole.