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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

DEC 04 1996

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Bayleton (2nd) (Triadimefon)

FROM: Paul Chin, Ph.D.
Review Section 2
Toxicology Branch I
Health Effects Division (7509C)

and

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Manager, Carcinogenicity Peer Review Committee
Science Analysis Branch
Health Effects Division (7509C)

THROUGH: Stephanie R. Irene Ph.D.
Deputy Director, Health Effects Division (7509C)

TO: James Stone
Product Manager #22
Fungicide/Herbicide Branch
Registration Division (7505C)
and
Mark Wilhite
Special Review and Reregistration Division (7508W)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on April 24,1996 to discuss and evaluate the weight-of-the-evidence on bayleton with particular reference to its carcinogenic potential. The CPRC concluded that Bayleton 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 quantitation of human risk. This was based on a borderline statistically significant increase in thyroid adenomas in male Wistar rats and statistically significant increases in hepatocellular adenomas in both sexes of the NMRI mouse.

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SUMMARY

Bayleton (also known as triadimefon) was previously evaluated by the CPRC as a Group C with an RfD approach (Memo, dated September 26, 1990). This was based on statistically significant increases in hepatocellular adenomas in both sexes of the NMRI mouse and structural similarity to other triazole pesticides. At that time, 2 studies in the mouse (NMRI and CF1-W74 strains) and a Wistar rat study were available for review. The CPRC requested histopathological re-evaluation of the liver slides from the CF1 mice and determined that the Wistar rat study was unacceptable. The classification of Group C (RfD) was considered to be tentative by the CPRC, pending submission of another rat study and re-evaluation of the slides from the CF1 mouse study.

The registrant has now submitted a new rat study which was reviewed at the present meeting; since only 13 slides were re-evaluated from the CF-1 mouse study, these were not considered by the CPRC.

Administration of Bayleton in the diet to Wistar rats at doses up to 1800 ppm resulted in an increase in thyroid follicular cell adenomas in male rats only, which was borderline statistically significant at the highest dose and for which there was a statistically significant positive trend. There were no apparent increases in carcinomas or in any tumors in female rats. The incidence of adenomas was outside the range reported for historical controls. The dosing was considered to be adequate in male rats, based on body weight gain decrements of 12% and only marginal clinical pathology. The dosing in female rats was considered to be adequate; blood parameter effects and increases in liver size and weight were not considered to be excessive. The CPRC did not see signs of excessive toxicity in either sex; survival in both sexes was comparable with that of controls. The registrant did not provide data to support a mode of action for the thyroid tumors.

The study in the NMRI mouse was re-visited. Administration of Bayleton to NMRI mice at doses up to 1800 ppm resulted in statistically significant increases in hepatocellular adenomas in both sexes at the highest dose, with statistically significant positive trends. The incidences of the tumors in female mice exceeded that of historical controls; in males the incidence was within the upper range, but exceeded that of the mean. The dosing was considered to be adequate in both sexes, based on decreases in body weight gain >15%, but without clinical signs of excessive toxicity and with comparable survival to that of controls.

There are no apparent concerns for mutagenicity for Bayleton. Bayleton is structurally related to other triazole pesticides, most of which are associated with hepatocellular tumors in mice.

The classification of Group C was based on the borderline

statistically significant increase in thyroid adenomas in male Wistar rats and the increases in liver adenomas in both sexes of the NMRI mouse, statistically significant by both pair-wise and trend analysis - at doses that were adequate. There was no apparent genotoxicity concern, and the tumors were benign only; therefore, the CPRC recommended the RfD approach for quantification of carcinogenic risk.

A. Individuals in Attendance at the meetings:

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

Stephanie Irene

William Burnam

Karl Baetcke

Marion Copley

Kerry Dearfield

Elizabeth Doyle

Yiannakis Ioannou

Hugh Pettigrew

Esther Rinde

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

Paul Chin[1]

Joycelyn Stewart

Lori Brunsman

Lucas Brennecke[2]
(PAI/ORNL)

3. Other Attendees:

Yung Yang and Bernice Fisher (HED)

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[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 DER's, one-liners, data from the literature and other data summaries prepared and/or supplied by Dr. Chin, and tables and statistical analyses were reviewed by Lori Brunsman. The material reviewed is attached to the file copy of this report.

C. Background

The HED carcinogenicity Peer Review Committee previously classified Bayleton as group C, possible human carcinogen (Peer Review of Bayleton; Memo, Ghali to S. Lewis: September 26, 1990), at which time only a rat study and two mouse studies, summarized below, had been submitted. Quantification of potential human risk, using a linear low dose extrapolation model (Q*), was not recommended. This conclusion was based upon a statistically significant increase in hepatocellular adenomas in male and female NMRI mice in the high-dose group (1800 ppm). The increase was statistically significant ($p < 0.05$, Fisher exact test). Trend analysis using the Peto method indicated a significant positive trend in males ($p = 0.037$) and females ($p < 0.001$). The incidences were outside the historical control range for this type of tumor in NMRI mice. This classification was considered tentative pending the submission of the final report on the study in Wistar rats and histopathological reevaluation of the liver slides from the CF1-W74 mice.

The registrant has since submitted a carcinogenicity study in Wistar rats. As requested by the Agency, the registrant also submitted a histopathological re-evaluation of the liver slides from the carcinogenicity study conducted with CF1-W74 mice (by Bayer AG Institute for Toxicology in April, 1978).

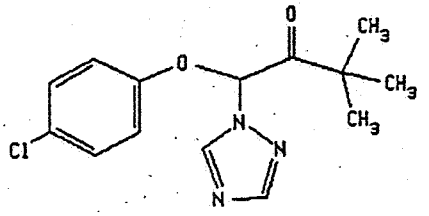

Figure 1

Structure of Bayleton (Triadimefon)
CAS #: 43121-43-3 PC Code #: 109901

D. Evaluation of Carcinogenicity Evidence:

1. Wistar Rat Carcinogenicity Study

Reference: Bayleton (MEB 6447) - Chronic Toxicity and Carcinogenicity Studies on Wistar Rats with Administration in Diet Over a Period of 105 Weeks. Bayer STUDY NUMBER: T-3027626; REPORT No: 101922; TESTING FACILITY: Bayer AG; Department of Toxicology; Germany; Authors:E. Bomhard and B. Schilde; REPORT ISSUED: October 25, 1991; SPONSOR: Mobay Corporation; MRID No:421539-01

a. Experimental Design

Bayleton (94.4% a.i.) was administered in the diet to groups of 50 male and 50 female Wistar rats at concentrations of 0, 50, 300, or 1800 ppm for 104 weeks, equivalent to an intake of approximately 0, 2.7, 16.4, or 114.0 mg/kg/day/male rat; 0, 3.6, 22.5, or 199.0 mg/kg/day/female rat). Additional groups of 10 rats/sex/group were assigned to the 12-month interim sacrifice. The age of animals were 6-7 weeks and their body weights were 117-184 g (males) and 114-144 g (females)..

b. Discussion of Tumor Data

Bayleton was associated with a positive dose-related trend in the incidence of thyroid follicular cell (TFC) adenomas/adenomas multiple in male Wistar rat (p=0.005 by the exact test for trend). The pairwise comparison of the high dose with the control group was only of "borderline" significance (p=0.0563). Increased incidences of thyroid follicular cell cystic hyperplasia, which did not attain statistical significance, were also observed in high dose males and females, but positive dose-related trends were achieved in both sexes for the combined incidences of thyroid follicular cell cystic hyperplasia and adenomas/adenomas multiple (incidences of adenomas are given in Table 1).

Table 1. Neoplastic Lesions in Wistar Rats treated with Bayleton for 24 Months

	Concentration of Bayleton in Test Diet (ppm)			
	0	50	300	1800
Thyroid Follicular Cell Lesions:				
Incidence of Adenomas				
Males	0/50	0/50	1/50 (2%)	3/49 (6%)
Females	0/50	1/50 (2%)	0/50	2/50 (4%)
Incidence of Adenomas Multiple				
Males	0/50	0/50	0/50	1/49 (2%)
Females	0/50	0/49	0/50	0/50
Incidence of Adenomas + Adenomas Multiple				
Males	0/50 p=0.0015**	0/50 p=1.0000	1/50 (2%) p=0.5000	4/49 (8%) p=0.0563*
Females	0/50 p=0.00519	1/50 (2%) p=0.5000	0/50 p=1.0000	2/50 (4%) p=0.2475

**Statistically significant Trend - Cochran Armitage trend test (by Exact test for trend, p=0.005)

*Borderline pairwise statistical significance (Fischer Exact test)

The registrant suggested that Bayleton may induce thyroid neoplasm through an endocrine effect, e.g., through a disruption of the pituitary-thyroid hormonal balance, since Bayleton and other Bayleton-like fungicidal azoles are known to induce the liver microsomal cytochrome P-450 enzyme system. Specific evidences such as goitrogenic activity in vivo, changes in serum levels of thyroid hormone and thyroid stimulating hormone, decreased synthesis/increased metabolism of thyroid hormone, lesions progression/reversibility were however not investigated in this study to lend support to this suggestion.

c. Non-neoplastic Lesions and Other Findings:

Incidences of clinical signs and abnormal appearance/behavior were comparable between groups or were not dose-related. Various clinical signs were observed including rough coat, poor general condition, hair loss, emaciation, tilted head, eye opacity, bloody eyes/muzzles, red tears, accelerated breathing, discolored urine, distended abdomen, diarrhea, palpable mass, and apathy.

Survival rates were comparable between groups. In the main study, survival rates appeared to be slightly decreased in all treated female groups. A global comparison of the survival curves, using the generalized Wilcoxon test, indicated that these decreases were not statistically significant. One mid-dose female died in the 12-month phase of the study.

Mean body weight (BW) of the low- and mid-dose groups were not affected by treatment with Bayleton for 24 months. Consistently decreased body weight and body weight gains (BWG) were observed in both sexes of the high dose (1800 ppm) group. BW (% below control) was 7-9%, wks 1-103 in males; 5-10%, wks 1-53 and 10-12%, wks 53-103, in females. BWG (% below control) was 12%, wks 1-53 and 9%, wks 0-103 in males; 15%, wks 1-53 and 23%, wks 0-103 in females].

Feed consumption of high dose males and females were increased moderately and markedly, respectively (group overall average increases were 19% in males and 53% in females). This sex-related differential increase may be a reflection of the greater compound intake in females. The concomitant body weight decrease and feed consumption increases are suggestive of a stimulatory effect of the test material on the metabolic function of the thyroid.

At the interim sacrifice, some significant ($p < 0.05$) alterations in organ weight were observed, including an increase in relative (to body) weight of the testes in high dose males (23%) and an increase

in liver weight in high dose females (absolute increase of 15% and relative increase of 27%). There was no evidence of kidney damage, based on urinalysis, necropsy, and histological findings. In the main study, liver weight was increased in a dose-related manner in females treated with 300 and 1800 ppm (absolute increases were 11% at 300 ppm and 17% at 1800 ppm; relative increases were 8% at 300 ppm and 32% at 1800 ppm). Other alterations in organ weight were also observed at the high dose but they were probably related directly to the observed decreases in terminal body weight. Relative weight was increased in liver (5% in males), testes (5%), spleen (9% in females) and brain (5% in males; 14% in females). Absolute weight was decreased in heart (11% in males and 6% in females), lungs (10% in males), and spleen (18% in males and 16% in females). The thyroid was not weighed.

Treatment with Bayleton 50 to 1800 ppm did not affect any of the hematology parameters examined in males and in 50 ppm females. High dose females showed concomitant minor decreases ($p < 0.05$) in RBC count and hemoglobin (6-7%; wks 26, 78, and 104), hematocrit (4-5%; wks 26 and 104), and mean corpuscular hemoglobin concentrations (MCHC) (3%; wks 26 and 104). This slight anemia is probably a real effect, since it was also observed in a previous 2-year study with Bayleton (Accession No. 099412 and 099413) as well as in a 90-day oral toxicity study with Baytan (MRID No. 421927-01), a pesticide which is also the major metabolite of Bayleton. Slight decreases ($p < 0.05$) in leucocyte counts were also observed in mid- and high dose females at weeks 26 (23%), and 104 (39 and 32% respectively).

Treatment with Bayleton 50 to 300 ppm did not affect any of the clinical chemistry parameters examined. High dose males showed minor increases in SGPT at weeks 26 (22%) and 104 (37%) which were statistically significant ($p < 0.05$). High dose females showed significant ($p < 0.05$) increases in blood cholesterol (24%, wk 26; 32%, wk 53; and 27%, wk 78), and urea (22%, wk 26; 17%, wk 53; and 10%, wk 78).

No treatment related gross pathology changes were observed.

Three of the 10 high dose males sacrificed at the interim phase showed slightly increased lipopexia of hepatocytic plasma (fat in hepatocytes). In the main study, the incidence of lipopexia of hepatocytic plasma was also increased at the high dose (male incidence = 32/49; female incidence = 22/50). Both male and female increases were statistically significant. In addition, a positive trend (Cochran Armitage trend test) was observed with the females. The incidence of thyroid follicular cell cystic hyperplasia was increased in high dose males (3/49) and females (4/50) but the

increases were not statistically significant (Table 2).

Table 2. Non-Neoplastic Lesions in Wistar Rats treated with Bayleton for 24 Months

	PPM in Diet			
	0	50	300	1800
LIVER LESIONS				
Fat in Hepatocytes				
Male Incidence (%)	8/50(16)	10/50(20)	15/50(30)	32/49*(60)
Female Incidence (%)	3/49*(6)	2/49(4)	4/50(8)	22/50*(44)
Focal Necrosis				
Male Incidence (%)	0/50(16)	1/50(2)	2/50(4)	4/49(8)
Female Incidence (%)	2/49(4)	2/49(4)	5/50(10)	2/50(4)
Clear cell foci				
Male Incidence (%)	15/50(30)	25/50(50)	9/50(18)	8/49(16)
Female Incidence (%)	2/49(4)	2/49(4)	4/50(8)	1/50(2)
THYROID FOLLICULAR CELL LESIONS				
Cystic Hyperplasia				
Male Incidence (%)	2/50(4)	3/50(6)	1/50(2)	3/49(6)
Female Incidence (%)	2/50(4)	0/50	1/50(2)	4/50(8)

Data excerpted from part 2 of report (Number of animals with microscopic findings by organ/group/sex; pp 407-431).
* at control: Positive trend (Cochran Armitage trend test).
* at treated group: $p < 0.05$; treated vs. control.

Based on the adverse effects described above, the systemic NOEL is 300 ppm (males=16.4 mg/kg/day; females=22.5 mg/kg/day) and the LOEL is 1800 ppm (males=114.0 mg/kg/day; females 199.0 mg/kg/day).

The registrant has submitted historical control data for thyroid adenomas and carcinomas in male and female Wistar rats at the testing facility [MRID #:101922-2; Testing Facility: Bayer AG, Germany; Report Issued: November 11, 1993]. Based on the historical control data (Table 3), the highest incidences of adenomas (6%/4%, ♂/♀), and adenomas plus adenomas multiple (8%/4%, ♂/♀) observed in males in the Bayleton study were slightly higher than the control ranges of spontaneous thyroid follicular adenomas (5.2%/2.0%, ♂/♀) in the Wistar rat. Data on the spontaneous incidence of cystic hyperplasia was not provided in the historical data; however, the increase in cystic hyperplasia observed in the test animals of the Bayleton study suggests that the chemical has a stimulatory effect on the thyroid.

Table 3. Comparison of the highest incidences of thyroid adenoma, adenoma + adenomas multiple in the Bayleton study (at 1800 ppm) with the highest incidences of adenoma reported from the last 10 historical control studies (1987-1989)

	Males		Females	
	Bayl-eton	Historical Controls	Bayl-eton	Historical Controls
Follicular adenoma	6%	5.2% (Mean=1.8%; range=0 - 5.2%)	4%	2.0% (Mean=0.4% range=0 - 2.0%)
Follicular adenoma + adenomas multiple	8%	*	4%	*

* The historical control data does not separate single from multiple adenomas.

** Cystic hyperplasia is not included in the historical control data

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dose range used was adequate as shown below:

1. Decreased body weight and body weight gains (BWG) in both sexes of the high dose (1800 ppm) group. BW (% below control) was 7-9%, wks 1-103 in males; 5-10%, wks 1-53 and 10-12%, wks 53-103, in females. BWG (% below control) was 12%, wks 1-53 and 9%, wks 0-103 in males; 15%, wks 1-53 and 23%, wks 0-103 in females.

2. At the interim sacrifice an increase in liver weight in high dose females (absolute increase of 15% and relative increase of 27%) were observed. In the main study, liver weight was increased in a dose-related manner in females treated with 300 and 1800 ppm (absolute increases were 11% at 300 ppm and 17% at 1800 ppm; relative increases were 8% at 300 ppm and 32% at 1800 ppm). Other alterations in organ weight were also observed at the high dose but they were probably related directly to the observed decreases in terminal body weight. Relative weight was increased in liver (males), testes, spleen (females) and brain (both sexes) (Table 3).

3. High dose females showed minor decreases ($p < 0.05$) in RBC count and hemoglobin (6-7%), hematocrit (4-5%), and mean corpuscular hemoglobin concentrations (MCHC) (3%). Slight decreases ($p < 0.05$) in leucocyte counts were also observed in mid- and high dose females at weeks 26 (23%), and 104 (39 and 32% respectively).

4. High dose males showed increases in SGPT at weeks 26 (22%) and 104 (37%) ($p < 0.05$). High dose females showed increases ($p < 0.05$) in blood cholesterol (24-32%), and urea (10-22%).

2. Histopathological re-evaluation of the liver slides from a carcinogenicity study conducted with CF1-W74 mice [Bayer AG Institute for Toxicology in April, 1978].

The following conclusions are quoted from the Pathology Report of Experimental Pathological Laboratories (EPL), Inc., of RTP, NC (MRID No. 417797-01; HED Doc. 010640 dated July 26, 1993, memo from N. B. Thoa to S. Lewis/J. Stone): "The results of this reevaluation of liver sections from male and female mice given 0, 50, 300, and 1800 ppm of Bayleton in a chronic

oncogenicity study in mice indicate that several of the lesions diagnosed as hyperplastic or regenerative nodules by the study pathologist were considered to be either hepatocellular adenomas or hepatocellular carcinomas during this review. Since all livers were not available for microscopic evaluation, it is not possible to draw conclusions concerning possible treatment-related differences in the incidence of proliferative hepatocellular changes between control and treated groups". [NOTE: Due to unusual circumstances (the laboratory which originally conducted the mice study, Consultox, UK, went out of business), only a very small number of the slides (males=6 controls, 8 LDs, 7 MDs, and 13 HDs; females = 0 controls, 3 LDs, 1 MDs, and 2 HDs) were available for reexamination].

F. Weight of Evidence Considerations:

The Committee was asked to consider the following facts regarding the toxicology data on Bayleton in a weight-of-the-evidence determination of carcinogenic potential.

Weight of evidence previously presented to Committee

1. Bomhard, E. (1986). Carcinogenicity study on NMRI mice. EPA MRID No. 407521-01 and 407521-02

   Groups of 50 male and 50 female NMRI mice were maintained for 21 months on diets containing Bayleton (90% purity) at concentrations of 0, 50, 300 or 1800 ppm. Additionally, 10 mice per sex per dose were included in the study for laboratory tests and intermediate necropsies.

   Dietary administration of Bayleton for 21 months was associated with increased incidence of hepatocellular adenomas in male and female NMRI mice in the high-dose group (1800 ppm). The increase was statistically significant ($p < 0.05$, Fisher exact test). Trend analysis using the Peto method indicated a significant positive trend in males ($p = 0.037$) and females ($p < 0.001$). The incidence of hepatocellular adenomas observed in the study was outside the historical control range for this lesion in NMRI mice. Also there was high incidence of liver hyperplastic nodules in males (23%) and females (23%) of the high-dose group compared to 2% and 1% respectively in males and females of the control group. The high-dose tested in both mouse studies was considered adequate for a carcinogenicity bioassay based upon statistically significant increases in serum enzyme activity (alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase in one or both sexes of high dose group), increases in the absolute and relative liver weights in both sexes accompanied by gross (increases in surface areas with changed appearance and increases in nodules) and histopathological (increase in altered cell foci, hepatocellular hypertrophy, hyperplastic nodules, bile duct proliferation, Kupffer cell proliferation, pigment accumulation, single cell necrosis, fatty change, microvesicular fatty change and round cell infiltration) changes in the liver in both sexes, and decreases in mean body weight gain in males (up to 20%) and sporadic

decreases in mean body weight gain in females (about 16%).

2. Bomhard, E., Loser, E. (1980) Chronic toxicity study on mice; two year feeding. Study No. 9344, conducted by Bayer, AG, West Germany, submitted by Mobay Chemical Corp., Report No. 68960, dated April 1978. EPA Accession No. 099912

   Groups of 50 male and 50 female CF1-W74 mice were maintained for 24 months on diets containing Bayleton (97% purity) at concentrations of 0, 50, 300 or 1800 ppm. Additionally, 10 mice per sex per dose were included in the study for laboratory tests and intermediate necropsies.

   In the CF1-W74, more mice in the high dose groups had hyperplastic liver nodules than mice in the other treatment groups and controls. The treatment did not appear to alter the spontaneous tumor profile for this strain of mice. However, the Agency has requested histopathological re-evaluation of the liver slides in this study.

   [NOTE: The same dose regimen was used in the two mouse studies with the CF1 and NMRI mice. The high-dose tested in both mouse studies was considered adequate for a carcinogenicity bioassay based upon changes in hematological parameters and liver functions, and increase in liver weight accompanied by histopathological changes].

3. Bomhard, E., Loser, E. (1978) Chronic toxicity study on rats. EPA Accession No. 099412 and 099413

   Groups of 50 male and 50 female Wistar rats were maintained for 21 months on diets containing Bayleton at concentrations of 50, 500 or 5000 ppm. A control group of 100 males and 100 females was included.

   The chemical did not appear to alter the spontaneous tumor profile in Wistar rats under testing conditions. However, the study was considered unacceptable since all animals in the high dose groups died or had to be sacrificed on or before week 39. The middle dose level was not high enough to substitute for the high dose level. The registrant has just completed another study in the rat.

4. Bayleton did not induce a genotoxic response in several mutagenicity testing systems including gene mutation in Salmonella typhimurium, Escherichia coli, and Saccharomyces cerevisiae, and chromosomal aberration in human lymphocytes.

5. Bayleton is structurally similar to other triazole pesticides such as triadimenol, propiconazole, uniconazole, terbuconazole, etaconazole, bitertanol, cyproconazole, azaconazole, and hexaconazole. Most of these triazole analogues were associated with hepatocellular adenomas, carcinomas or both in mice, in one or both sexes.

6. NOTE: In the previous Cancer Peer Review Document on Bayleton dated Sept. 29, 1990 (paragraph 5 of page 17), it was stated that terbuconazole and hexaconazole were reported to be negative for carcinogenicity in mice when administered in the diet up to 180 and 200 ppm, respectively. However, new studies showed that both terbuconazole and hexaconazole were positive for carcinogenicity in mice and rats, respectively. Terbuconazole administered in the diet at 1500 ppm in mice induced increased incidence of liver adenomas and carcinomas in mice. Hexaconazole administered in the diet at 1000 ppm in rats induced increased incidence of benign Leydig cell tumors in the testes.

New weight of evidence

I. Bayleton induced a positive dose-related trend in the incidence of thyroid follicular cell (TFC) adenomas/adenomas multiple in male rats. There was also a borderline statistically significant increase in thyroid adenomas at the highest dose in males. There were no apparent increases in carcinomas or in any tumors in female rats.

Increased incidences of thyroid follicular cell cystic hyperplasia, which did not attain statistical significance, were also observed in high dose males and females, but positive dose-related trends were achieved in both sexes for combined incidences of thyroid follicular cell cystic hyperplasia and adenomas/adenomas multiple.

II. The registrant has responded to revocation of Section 409 (Food Additive Regulations) for Bayleton as follows:

A. Rat Chronic/Oncogenicity Study (1991)

"No treatment related malignancies (cancer) were found at any dose of triadimefon [Bayleton] in groups of male and female Wistar rats. If, the increased incidence of follicular cell thyroid adenomas is related to treatment, the increase is likely to be secondary to hormonal imbalance and not indicative of an induction of cancer by triadimefon."

"Whether treatment with triadimefon actually was responsible for the slightly increased incidence of thyroid follicular cell adenomas is simply not established by the current study. However, I conclude that if the increases are treatment related they are likely to be the result of increased levels of TSH and not due to any direct effect of triadimefon."

The registrant further stated that "Treatment related increases in tumor incidence which are secondary to physiological changes (e.g., hormonal imbalance) have thresholds and occur only at doses which exceed those thresholds. For this reason, decisions on carcinogenicity should be based on doses that do not exceed the maximum tolerated dose ("MTD") and, hence, are unlikely to exceed such thresholds. As the highest dose (1800 ppm) administered exceeded the MTD and in

view of the fact the mid-dose (300 ppm) provides an adequate MTD, conclusions about carcinogenicity should be based on the low (50 ppm) and mid-dose (300 ppm)."

B. Mouse Oncogenicity Study (1986)

"The 1800 ppm dose level was severely cytotoxic to hepatocytes resulting in necrosis and hyperplasia and/or hypertrophy. Extensive liver damage in mice followed by restorative hyperplasia is considered a means by which liver tumors can arise secondarily to toxic injury."

"As the highest dose (1800 ppm) administered exceeded the MTD, conclusions about carcinogenicity should be based on the low (50 ppm) and mid-dose (300 ppm). Accordingly, Dr. Flamm concludes that triadimefon is neither an animal carcinogen nor can it be "found" in light of the available scientific evidence and current scientific knowledge to "induce cancer."

The CPRC Response:

The registrant did not provide data to support a mode of action for the thyroid tumors. The CPRC considered the dosing to be adequate in both male and female rats; the CPRC did not see signs of excessive toxicity in either sex; survival in both sexes was comparable with that of controls.

In the NMRI mouse study, the CPRC noted decreases in body weight gain >15%, Kupffer cell and macrophage proliferation, increases in liver weight, non-neoplastic proliferative lesions and other histopathologic changes. These changes were considered in support of the liver as a target and were not considered to be excessive. There were no clinical signs of excessive toxicity and survival was comparable to that of controls. The CPRC considered the dosing to be adequate in both sexes of the NMRI mouse.

G. Classification of Carcinogenic Potential:

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

The Peer Review Committee agreed that Bayleton should be classified as a Group C - possible human carcinogen and that for the purpose of risk characterization the RfD approach should be used for quantification of human risk. This decision was based on the borderline statistically significant increase in thyroid adenomas in male Wistar rats and the increases in liver adenomas in both sexes of the NMRI mouse, statistically significant by both pair-wise and trend analysis - at doses that were adequate. The incidence of all tumors exceeded the mean and/or the upper range of historical controls. Bayleton is structurally related to other triazole pesticides, most of which are associated with hepatocellular tumors in mice. There is no apparent concern for genotoxicity of Bayleton and all of the tumors were benign; therefore, the RfD approach was recommended.

H. Induces Cancer Call -- Bayleton

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, the Committee concludes that exposure to Bayleton resulted in an increased incidence of thyroid adenomas in male Wistar rats and adenomas of the liver in both sexes of the NMRI mouse. Data from structurally related chemicals which also are associated with liver tumors in mice, provided additional support. There does not appear to be evidence of genotoxicity for Bayleton.

The Committee agrees that Bayleton induces cancer in animals.