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

FILE COPY

SEP 26 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review on Triadimefon (Bayleton)®

FROM: George Z. Ghali, Ph.D. G.Z. Ghali 7.31.90
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Susan Lewis, Acting PM 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

The Health Effects Division Peer Review Committee met on June 6, 1990, to discuss and evaluate the weight-of-the-evidence on Bayleton with special reference to its carcinogenic potential. The Committee concluded that Bayleton meets the criteria for group C, possible human carcinogen. Quantification of potential human risk, using a low dose extrapolation model (Q1*), was not recommended. Therefore, the reference dose (RfD) approach should be used for quantification of human risk.

This classification is considered tentative pending the submission of the final report on the second rat study and histopathological reevaluation of the liver slides from the CF1-W74 mice.

A. Individuals in Attendance

1. Peer Review Committee (Signature indicates concurrence with the peer review unless otherwise stated).

William L Burnam

Reto Engler

Karl Baetcke

Marcia Van Gemert

Kerry Dearfield

John Quest _____

Esther Rinde _____

William Sette _____

Julie Du _____

Hugh Pettigrew _____

George Ghali _____

2. Peer Review Members in Absentia (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee).

Penny Fenner-Crisp _____

Richard Hill —

Robert Beliles _____

Marion Copley _____

Yin-Tak Woo _____

3. Scientific Reviewer (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

George Ghali _____

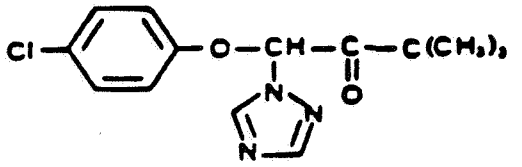
4. Scientific Observer (Bernice Fisher of the Science Analysis and Coordination Branch, HED).

B. Material Reviewed

The material available for review consisted of a summary of all relevant toxicology information, and Data Evaluation Records (DERs) for carcinogenicity studies in two strains of mice CF7-W74 and NMRI, and in Wistar rats.

C. Background Information

Triadimefon* [1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanone] is a triazole fungicide produced by Mobay Chemical Corporation, registered for use on varieties of raw agricultural commodities. Data submitted in support of Bayleton registration indicated that the chemical was not carcinogenic when tested in Wistar rats and CF1-W74 mice. In both studies the high dose tested was considered adequate for the evaluation of carcinogenic potential. Subsequently, the Agency has requested re-evaluation of the liver slides in the CF1-W74 mice and submission of a new rat study. Upto this date the Agency has not received these data.



Triadimefon
(Bayleton)

A recent submission by Mobay Chemical Corporation in compliance with FIFRA 6(a)(2), indicated that dietary administration of Bayleton to NMRI mice was associated with a statistically significant increase in the incidence of hepatocellular adenomas in both males and females. There was no increase in neoplastic lesions at other sites, and no uncommon neoplasms found. It is important to note that the same dose regimen was used in the two mouse studies with the CF1 and NMRI mice. The issue was referred, therefore, to the Health Effects Division Peer Review Committee for a weight-of-the-evidence determination and an appropriate classification.

D. Evaluation of Carcinogenicity Evidence

1. 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.

---

*Also known as Bayleton® and has been investigated under the code name MEB 6447.

a. Experimental Design

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

b. General Observations

Treated animals did not differ from controls in appearance, behavior, and activity. The treatment had no effect on food consumption. At 1800 ppm (HDT), body weight gains were significantly lower than controls.

The test chemical did not have an appreciable effect on the mortality rate after 6 months of administration. However, at 12 months, the mortality rate increased for males at dosage levels of 300 ppm (14.0%) and 1800 ppm (16.0%) and for females at the dosage of 50 ppm (8.0%), 300 ppm (10.0%), and 1800 ppm (6.0%) compared to a maximum mortality of 4.0 and 2.0 percent for the control males and females, respectively. There was no evidence whether this effect is treatment-related, since this effect has not been observed at 18 and 24 months.

c. Consideration of Adequacy of Dose Selection

The high-dose level was considered appropriate for a carcinogenicity bioassay based upon effects observed on hematological parameters (statistically significant increase in erythrocytes in both males and females, statistically significant lower mean corpuscular hemoglobin (MCH) values in males, statistically significant higher thrombocyte count, hemoglobin and hematocrit level in females), liver function (significantly higher activity of serum alkaline phosphatase, serum glutamic oxaloacetic transaminase, and glutamic-pyruvic transaminase) and a statistically significant increase in liver weights in males and females accompanied by histopathological changes.

d. Microscopic Pathology

Non-neoplastic Lesions - In the high-dose groups (1800 ppm), more mice had hyperplastic liver nodules than mice in the other treatment groups or the control groups (15 males and 15 females on 1800 ppm compared with 7 males and 4 females in the control groups). Other paranchymal lesions in the liver: necrotic foci or areas of infarction, variation in cell size and other lesions frequently encountered spontaneously in mice but as with nodules there was some evidence that livers in animals on the 1800 ppm were more affected than those in the other groups.

Neoplastic Lesions - The tumor profile provided no indication that Bayleton had any influence on total tumor incidence, on the number of mice with tumors or on incidence of single tumor types.

Comparison of the individual histopathological findings with the gross pathology findings for mice that died during the experiment shows that the treatment also had no influence on the time of tumor occurrence.

Few liver adenomas were observed in all dose groups. The incidence did not vary markedly, being almost identical in the four male groups (2/control group, 2/50 ppm, 1/300 ppm, 2/1800 ppm) and occurring at a similar level in the low (1) and high (2) treatment groups in females. In no animal was there any sign of gross malignancy or metastasis.

Adenomas of the lung formed the other principal type of benign tumor encountered. The incidence was not affected by treatment in either male or female groups. No malignant lung tumor was seen. The few other benign neoplasms at various sites were distributed in a manner unrelated to treatment.

Apart from an adenocarcinoma of the mammary gland seen in a male mouse at 300 ppm, lymphosarcomas and reticulum cell neoplasms formed the only malignant tumors seen in this study. These neoplastic lesions of the reticulo-endothelial systems are common in

mice. The incidence in female mice varied from 9 in the control group to 16 in the low (50 ppm) group and dropped to 7 in the medium group and 10 in the high-dose group. Treatment thus had no significant effect on incidence. Similarly, in male mice there was no dose response in the incidence of lymphosarcomas and reticulum cell neoplasms and differences between control and treatment groups were not significant (1/0, 4/50, 2/300, and 3/1800 ppm).

There is no evidence that treatment with Bayleton affected the types and frequencies of benign or malignant neoplasms. However. the Agency has requested histopathological re-evaluation of the liver slides.

2. Bomhard, E. (1986) Carcinogenicity study on NMRI mice. Study No. 87287 conducted by Bayer A.G., West Germany and submitted by Mobay Chemical Corporation (EPA Accession Nos. 407521-01, -02).

a. Experimental Design

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.

b. General Observations

There were no treatment-related effects on clinical signs and mortality. Males generally consumed more food than controls. Water consumption was also higher in high-dose males.

c. Consideration of Adequacy of Dose Selection

The high-dose level is considered to be adequate for a carcinogenicity bioassay based upon statistically significant increases in the absolute and relative liver weights in both sexes, gross and histopathological changes in the liver in both sexes, statistically significant increases in serum enzyme activities in one or both sexes, significant changes in hematological parameters in both sexes, and statistically significant decreases in mean body weight gain in males and sporadic decreases in mean body weight gain in females.

d. Microscopic Pathology

Non-neoplastic Lesions - There were several non-neoplastic changes in the livers of dosed mice and some were apparent in high-dose groups at the 12-month interim sacrifice. No hyperplastic hepatocellular nodules or altered cell foci were noted at 12 months. Table 1 summarizes frequent non-neoplastic findings in the main study. The liver was the only organ with any compound-related increase in lesions. There was an increase in altered cell foci and in hepatocellular hyperplastic nodules in males and females fed 1800 ppm. Hepatocellular hypertrophy was increased in both dosed males and females; in the low- and mid-dose groups, this change was confined to the centrilobular area of the liver and was predominantly grade 2 (slight to moderate). In high-dose males and females the hypertrophy was not only increased but was more diffuse and of increased severity. There was an increase in slight to moderate Kupffer cell proliferation, predominantly in high-dose males and mid- and high-dose females; the degree of severity was also increased in the above groups. Accumulation of lipofuscin pigment in liver macrophages was increased in high-dose males and mid- and high-dose females. The severity of the finding was increased in male but not female dose groups. The incidences of single cell necrosis was relatively high in control males and females, the incidence was increased in mid- and high-dose groups, and the severity increased in the high-dose groups. There was an increase in fine droplet fatty changes of the liver in high-dose groups but no increase in macrovesicular fatty changes.

Neoplastic Lesions - Table 2 summarizes neoplastic incidence data. The incidence of hepatocellular adenomas was significantly increased in both males and females receiving 1800 ppm. Trend analysis (by the authors) using the Peto method indicated a significant positive trend in males ($p = 0.037$) and females ($p < 0.001$). In high-dose males, 8 of the 11 adenomas were found at final sacrifice (days 630 to 634) and the first

TABLE 1. Frequent Nonneoplastic Lesions in Mice Fed MER 6447 for 21 Months

Histologic Finding	Dietary Level (ppm)							
	Males				Females			
	10	50	300	1800	0	50	300	1800
Liver	(50)[a]	(50)	(50)	(50)	(50)	(50)	(49)	(49)
Hepatocellular hypertrophy	16[TT]	19	33**	49**	3[TT]	24**	42**	47**
Hyperplastic nodules	2[TT]	1	3	23**	1	1	1	23**
Altered cell foci	0[TT]	0	2	36**	0	0	1	28**
Bile duct proliferation	0	1	1	1	0	0	0	5*
Kupffer cell proliferation	12[TT]	6	3	46**	5[TT]	9	19**	37**
Pigment accumulation	3[TT]	4	3	35**	6[TT]	9	19**	37**
Single cell necrosis	10[TT]	7	16	49**	10[TT]	12	22**	42**
Fatty change	12[TT]	10	13	18	12[TT]	12	9	28**
Microvesicular fatty change	0	1	2	14**	6	1	1	18**
Round cell infiltration	23	9	18	29	9[TT]	14	23	30**
Kidneys	(50)	(50)	(50)	(50)	(50)	(50)	(49)	(49)
Tubular atrophy	25	22	29	17	7	6	5	7
Cortical cysts	37	33	35	22	3	8	3	4
Chronic nephropathy	7	3	1	2	14	7	10	11
Tubular dilation	1	8	2	4	7	9	5	1
Stomach	(50)	(50)	(50)	(50)	(50)	(50)	(49)	(49)
Adnomatous hyperplasia	19	17	14	16	22	18	21	18
Adrenal	(50)	(50)	(50)	(50)	(50)	(50)	(49)	(49)
Medullary hyperplasia	3	1	0	5	7	2	1	2

[a]The number in parentheses is the number of animals with tissue examined histologically; includes animals that died after 12 months, were sacrificed moribund or were sacrificed at study termination.

**Significantly different from control incidence, $p < 0.01$ (Fisher exact test); analyses by reviewers,

[TT]Significant trend by Cochran-Armitage test, $p < 0.01$; [T] = $p < 0.05$.

TABLE 2. Neoplastic Findings in Mice Fed MEB 6447 for 21 Months

Histologic Finding	Dietary Level (ppm)							
	Males				Females			
	10	50	300	1800	0	50	300	1800
Lungs	(50)[a]	(50)	(50)	(50)	(50)	(50)	(49)	(49)
Bronchioalveolar tumor (M)[b]	15	18	19	11	9	12	13	7
Liver	(50)	(50)	(50)	(50)	(50)	(50)	(49)	(49)
Hepatocellular adenoma[c]	3	3	4	11*	2	1	0	9*
Hepatocellular carcinoma	1	2	1	2	0	0	0	0
Lymphoreticular	(50)	(50)	(50)	(50)	(50)	(50)	(49)	(49)
Malignant lymphoma	5	8	4	4	27	22	23	20
Harderian glands	(48)	(50)	(50)	(50)	(50)	(48)	(46)	(49)
Adenoma	4	4	3	0	3	1	1	0
Adrenal medulla	(50)	(50)	(49)	(50)	(50)	(50)	(49)	(49)
Benign tumor	0	0	0	1	1	0	1	1
Malignant tumor	0	2	0	0	0	0	0	0
Testes	(50)	(50)	(50)	(50)				
Leydig cell tumor	2	3	0	0	-	-	-	-
Ovaries					(50)	(50)	(48)	(49)
Theca-granulosa cell tumor (M)	-	-	-	-	0	1	1	1
Theca-granulosa cell tumor (B)	-	-	-	-	2	4	5	0
Pituitary	(49)	(46)	(49)	(48)	(49)	(49)	(49)	(48)
Adenoma	0	0	0	0	5	5	4	0
Mammary glands					(50)	(50)	(49)	(49)
Malignant tumor[d]	-	-	-	-	3	4	2	1

[a]The number in parentheses is the number of animals with tissue examined histologically; includes animals that died after 12 months were sacrified moribund or sacrificed at study termination. Does not include animals in the satellite groups sacrificed at 51 weeks.

[b]M = Malignant, B = Benign.

[c]Significant trend in each sex, $p < 0.05$; analysis by the study authors using the Peto method.

[d]Adenoacanthoma, carcinsarcoma, or adenocarcinoma.

*Significantly different from control incidence, $p < 0.05$ (Fisher exact test); analysis by our reviewers.

tumor was found at 592 days; in high-dose females, 5 of the 9 adenomas were at final sacrifice and the first tumor was found at 570 days. There were no hepatocellular carcinomas in females and no dose-related increases in males. Four high-dose males and six high-dose females had both findings. Nodules generally occurred late in the study; in high-dose males and females, 17/23 and 15/23, respectively, of mice with liver nodules were those sacrificed at study termination.

There were no increases in neoplasms at other sites that were related to dosing and no unusual neoplasms were found.

e. Spontaneous Liver Cell Tumors

The frequency of spontaneous hepatocellular adenomas in NMRI mice, in 12 experiments conducted between 1974 and 1979, fluctuated in males from 0.0 to 18.4 percent with an average of 5.9 percent, and in females from 0.0 to 2.0 percent with an average of 0.3 percent.

The duration of these experiments was 23 months compared to 21 months exposure in the NMRI mice study discussed above.

3. Bomhard, E., Loser, E. (1978) Chronic toxicity study on rats. Report No. 7707 prepared by Bayer A.G., West Germany and submitted by Mobay Chemical Corporation (Report No. 66484). EPA Accession Nos. 099412 and 099413.

a. Experimental Design

Groups of 50 male and 50 female Wistar rats were administered Bayleton in the diet at concentrations of 50, 500 or 5000 ppm for 21 months. A control group of 100 males and 100 females was included.

b. General Observations

Physical appearance and behavioral patterns of the low- and mid-dose groups did not differ from controls. Males and females of the high-dose group showed violent motor

reactions from about week 23 and consumed hardly any food. Following heavy loss of weight, the rats began to feed again and regained weight. Then, between week 31 and 37, there was a repetition of this process and most rats died. The last of the survivors were killed in moribund condition in week 39.

c. General Comments

Although this study was accepted by the Agency at the time of evaluation (G. Ghali, June 25, 1981), recent reevaluation indicated that the study did not meet current Agency standards for a carcinogenicity bioassay (G. Ghali, December 14, 1989). In this study, the high-dose animals died or had to be sacrificed early on the study (on or before week 39). The middle dose level was not high enough to meet the criteria established for an MTD, and therefore could not be used to substitute for the loss of the high-dose group.

Mobay Chemical Corporation conducted another chronic toxicity/carcinogenicity study in Wistar rats. An interim report (Mobay Report No. 100011-T dated February 19, 1990) was recently submitted to the Agency for consideration.

This study was conducted using dietary concentrations of 0, 50, 300 or 1800 ppm for 24 months. According to the registrant, the high dose proved to be toxic without exceeding the criteria set for the MTD.

According to the registrant's letter of March 8, 1990 "Mobay toxicologists indicated that the results from the [second] rat chronic/oncogenicity study in general support the findings of the first rat chronic study which was deficient only in that a clear MTD was not reached."

According to Mobay, the final report of the study will not be available for several months. The final report will be submitted to the Agency upon the completion of the histopathological report.

E. Other Relevant Toxicology Information

1. Developmental Toxicity

In a developmental toxicity study in F344 rats, treatment was associated with increased incidences of cleft palates, increased motor reactions, and depression of maternal body weight gain. These findings were further confirmed in a second study in the same strain of rats. The two studies combined provided a no-observed-effect level (NOEL) of 50 mg/kg/day for developmental effects and 25 mg/kg/day for maternal toxicity.

In a developmental toxicity study in the rabbit, treatment caused a marked decrease in mean maternal weight gain during the treatment and gestational period. The treatment was also associated with a significant increase in the number of fetal resorptions. The NOEL for maternal toxicity was considered to be 10 mg/kg/day and 30 mg/kg/day for developmental effects.

In a second developmental toxicity study in the rabbit submitted to the Agency in accordance with FIFRA section 6(a)(2) (Mobay Corporation, letter dated April 4, 1990), treatment was associated with reduction in maternal body weight, reduction in fetal weight, delayed ossification of several skeletal elements, and increase in the incidence of morphologic and skeletal variations of certain elements of the skeleton, and a statistically significant increase in malformations. This study is currently under evaluation.

2. Reproductive Toxicity

In a multigeneration reproduction study in the rat, treatment was associated with reduced litter size, reduced viability, reduced birth and lactational weights at 500 and/or 1800 ppm. A NOEL was established at 50 ppm.

In a second multigeneration reproduction study, treatment was associated with decreased maternal body weight gain and depressed lactation performance, decreased fertility, decreased litter size, decreased survival of pups, and decreased pup weight gains. A NOEL was established at 50 ppm.

3. Genotoxicity

Like most other triazole fungicides, Bayleton did not demonstrate mutagenic activity in a battery of tests including gene mutation tests in Salmonella typhimurium, Escherichia coli, Saccharomyces cerevisiae, and chromosomal aberrations in human lymphocytes. These assays satisfy the requirements for 2 of 3 categories of mutagenic testing, gene mutations and structural chromosomal aberrations. A test in the third category, other genotoxic effects, is required. Based on the evidence that the liver is a principle target for this chemical, an in vivo/in vitro UDS assay is recommended.

4. Metabolism

Data available on the biotransformation of Bayleton in rats indicate that the metabolism of Bayleton is initiated by an oxidative step leading to the hydroxylation of the side chain terminal carbon (KWG1323), or through the reduction of the carbonyl group to produce the isomers of Baytan (KWG0519). Baytan is a major and primary metabolite of Bayleton, and a registered fungicide. The reductive pathway leading to the formation of Baytan is the major pathway and is usually very rapid in males.

Both products, i.e., KWG1323 and KWG0519, are further metabolized by reduction or oxidation, respectively, to produce a common metabolite known as KWG1342 which may undergo conjugation, or further oxidation to the respective acid followed by conjugation and then elimination.

In male rats, radioactivity was found mainly in feces whereas in females, radioactivity was equally distributed between urine and feces. No radioactivity was recovered in the expired air. Peak tissue levels were found in 2 to 4 hours and were highest in fat, liver, and kidney. The major metabolites were the acid and alcohol of Baytan. Several unidentified minor metabolites were also reported.

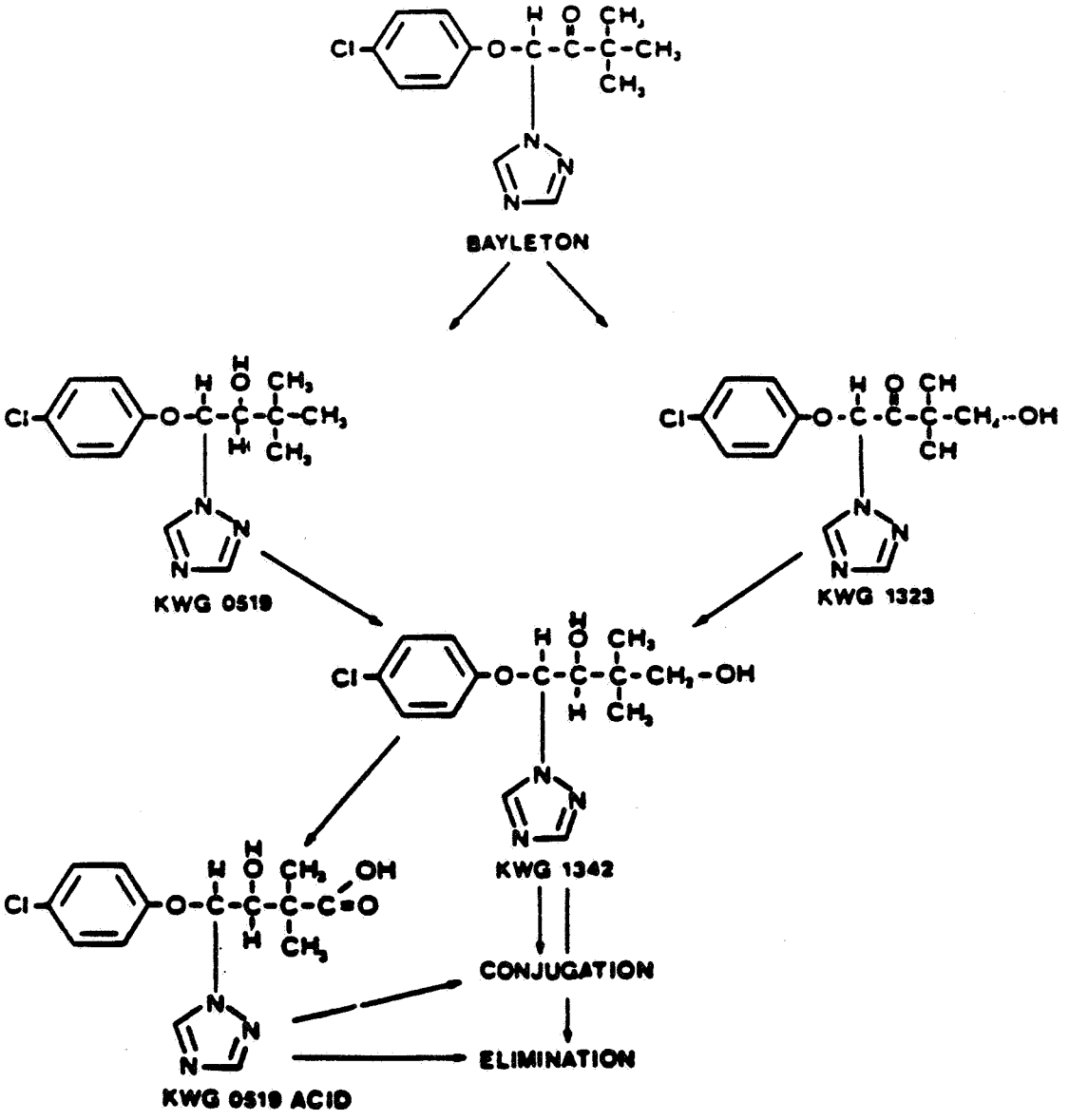


Figure 1. General Metabolic Pathway of Triadimefon (Bayleton)

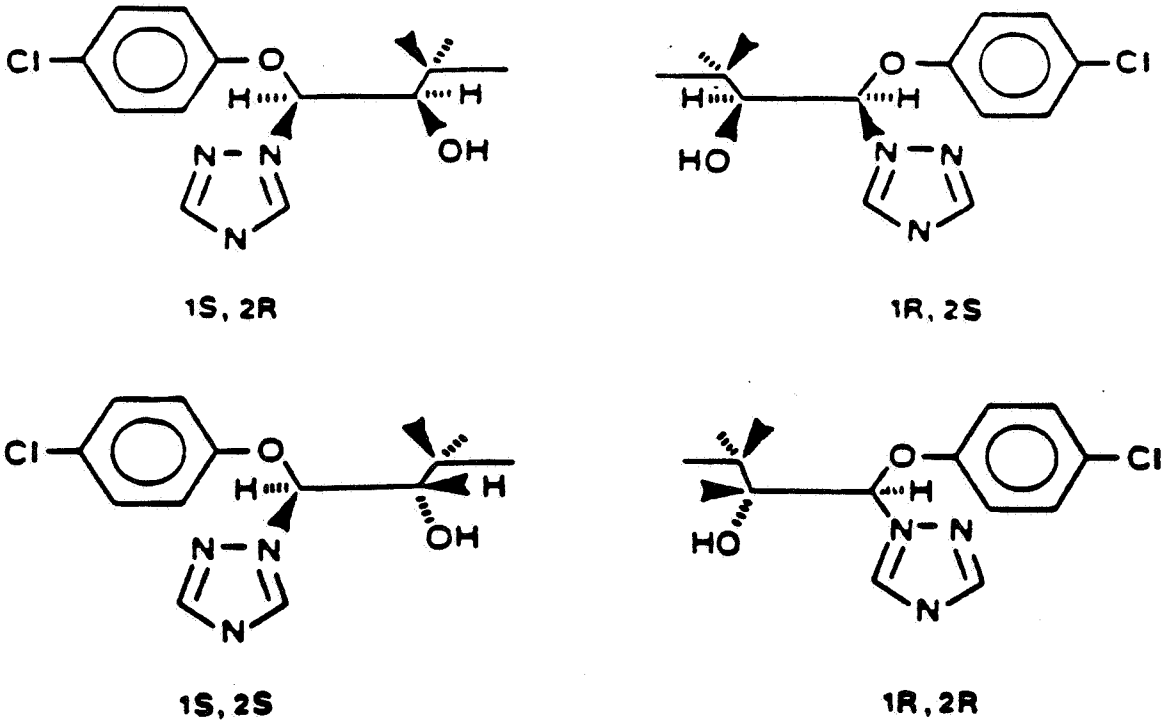


Figure 1[a]. Diastereomeric and Enantiomeric Forms of Baytan, the Major Metabolite of Bayleton.

5. Enzyme Induction

Administration of relatively high doses of Bayleton to rats and mice resulted in microsomal enzyme induction. The induction was found to be species, sex, and dose-dependent. Female rats are more responsive to induction than males. In mice, at a reasonably nontoxic dose (50 mg/kg), the response in both males and females was quantitatively equal. However, at higher doses (100 mg/kg), the induction was not increased in males, but increased significantly in females.

The binding of Bayleton with cytochrome P-450 resulted in a binding spectra typical of type II substrates.

6. Subchronic Toxicity

Subchronic feeding studies (3 months) in the rat and dog indicated that the treatment was associated with decreased body weight gains and food consumption which the authors attributed to palatability. In addition, in the dog study, the treatment caused decreased hematocrit and red blood cell count, hemoglobin volume, and increased serum alkaline phosphatase activity.

7. Structure-Activity Relationship

Bayleton is structurally similar to other triazole pesticides such as triadimenol (Baytan®), propiconazole (Tilt®), uniconazole (Prunit®), terbuconazole (Folicur®) etaconazole (Sonax, Vangard®), bitertanol (Baycor®), cyproconazole (SAN 619F®), azaconazole, and hexaconazole.

Triadimenol, a primary and major metabolite of Bayleton, was classified by the HED Peer Review Committee in their meeting of October 1, 1987 as a group C, possible human carcinogen based upon increased incidences of liver adenomas in female CF1-W74 mice (HED Report dated January 29, 1988.) This classification was upheld by the FIFRA Scientific Advisory Panel in their meeting of December 15, 1987 (report dated December 23, 1987).

Propiconazole was associated with increased incidences of hepatocellular adenomas and carcinomas in male CD-1 mice, and was classified by the HED Peer Review Committee in Group C, possible human carcinogen (HED Reports dated April 29, 1987, July 21, 1988, April 28, 1989, and January 22, 1990).

Etaconazole was associated with increased incidence of liver adenomas and carcinomas in both male and female Albino Swiss mice. However, the registration application was voluntarily withdrawn by the registrant and therefore no further action was taken regarding its cancer classification.

Uniconazole, a new pesticide currently under evaluation, was associated with statistically significant increase in the incidence of liver adenomas, carcinomas and adenomas/carcinomas combined in male CD-1 mice, and was classified by the HED Peer Review Committee on July 25, 1990 as a Group C, possible human carcinogen.

Cyproconazole was associated with statistically significant increases in the incidences of hepatocellular adenomas and carcinomas in male and female CD-1 mice and was classified by the HED Peer Review Committee on June 20, 1990 as a Group C, possible human carcinogen.

Bitertanole and azaconazole were reported to be negative for carcinogenicity in mice when administered in the diet up to 500 ppm. 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, all other triazole fungicides (except for cyproconazole which has a somewhat different structure, i.e., the cyclopropane moiety) were tested at dietary concentrations of 1500 ppm or higher before inducing any carcinogenic response in mice. Therefore, there is a question of whether these chemicals were tested at a high enough dosage.

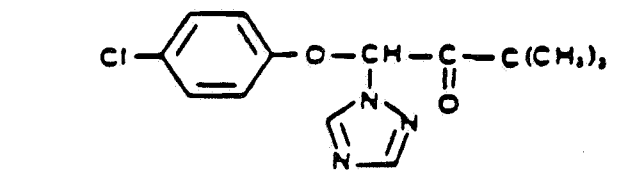
Hexaconazole, on the other hand, was associated with increased incidence of benign leydig cell tumor in the testes of rats and has been classified by HED Peer Review Committee as a group C, possible human carcinogen on June 27, 1990.

Among all triazole pesticides reviewed by the HED Peer Review Committee, Hexaconazole was the only chemical to induce this type of carcinogenic response in rats. Other triazoles were either negative or were not tested at adequete dose levels in the rat studies.

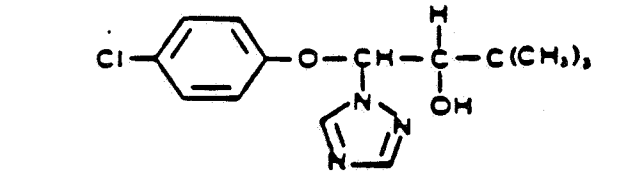
Among all triazole pesticides reviewed by the HED Peer Review Committee, only two chemicals, i. e. Uniconazole and Cyproconazole were reported to have potential to induce genotoxic response.

Uniconazole was slightly positive in the mouse micronucleus assay when tested in male mice. Uniconazole was also positive for chromosomal aberrations when tested up to cytotoxic levels with metabolic activation, but was negative when tested without metabolic activation. Uniconazole was also negative for bacterial gene mutation in Salmonella typhimurium when tested up to cytotoxic levels with metabolic activation, and up to solubility levels without metabolic activation. Uniconazole gave negative responses in E. coli with and without metabolic activation. Uniconazole did not appear to induce unscheduled DNA synthesis in primary mouse hepatocytes when tested in vivo/in vitro.

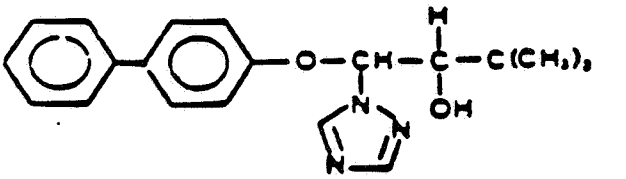
Cyproconazole was positive for potential to induce chromosomal aberrations in CHO cells with and without metabolic activation. The chemical was negative in micronucleus assay in mice, for gene mutation in the Salmonella assay, and for cell transformation with Syrian hamster embryo cells with and without metabolic activation. However, Cyproconazole has somewhat slightly different structure than other triazole pesticides, in that it has a cyclopropane moiety that is unique to Cyproconazole.



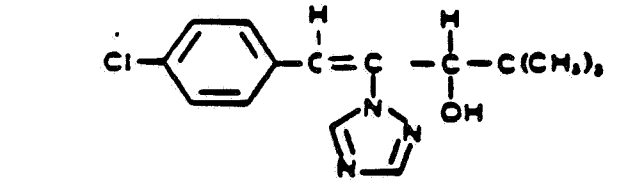
Triadimefon
(Bayleton)



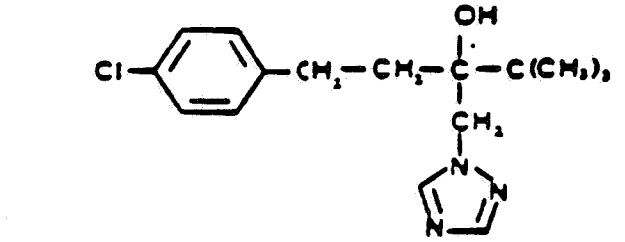
Triademenol
(Baytan)



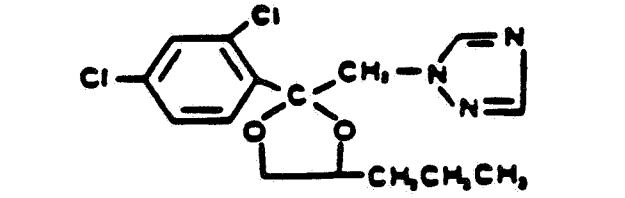
Bitertanol
(Baycor)



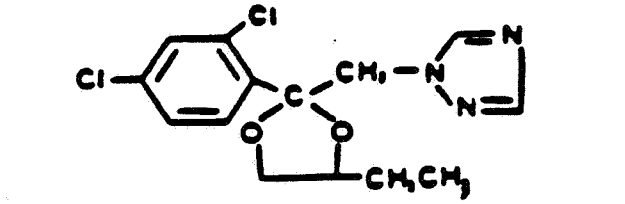
Uniconazole
(Prunit)



Terbuconazol
(Folicur)

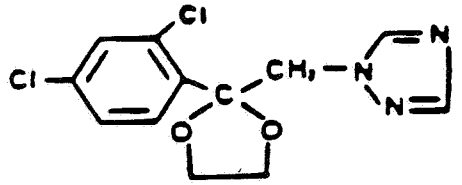


Propiconazole
(Tilt)

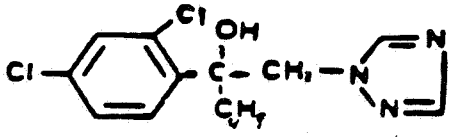


Etaconazole
(Vangard)

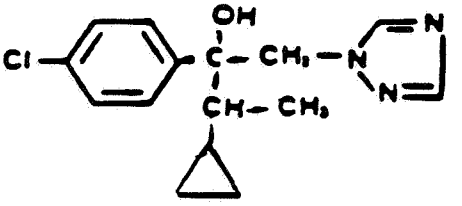
Figure 2. Chemicals Structurally Related to Triadimefon (Bayleton)



Azaconazole



Hexaconazole



Cyproconazole

Figure 2[a]. Chemicals Structurally Related to Triadimefon (Bayleton)●

In addition, most of these triazole pesticides were associated with some developmental toxicity, particularly skeletal variations and malformations. For example, bitertanol was reported to induce cleft palates, a rare effect in rats. This effect was also induced by other triazole fungicides such as Bayleton and cyproconazole. Cyproconazole was reported to be associated with increased incidence of supernumerary ribs in rats, an effect that was demonstrated also by Baytan. Uniconazole was associated with increased incidence of 14th rib in rats. Whether other triazole fungicides have the potential to induce such effects or not is totally based on whether they were adequately tested for developmental toxicity and on the species and strain tested.

F. Weight-of-the-Evidence

The Committee considered the following facts regarding the toxicity of Bayleton to be important in the weight-of-the-evidence determination:

1. 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 a 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.

2. 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.

3. 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.

4. 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. The final report has not been submitted to the Agency.

5. Bayleton did not induce genotoxic response in several mutagenicity testing systems including gene mutation in Salmonella typhimurium, Escherichia coli, and Saccharomyces cerevisiae, and chromosomal aberration in human lymphocytes. The Committee was also aware that there were several mutagenicity studies currently under reevaluation by HED scientists.

6. 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.

G. Classification of Carcinogenic Potential

Considering criteria contained in the Agency's Guidelines for the Classification of Carcinogens [FR 51:33992-34003, 1986], the Committee concluded that Bayleton should be placed in Group C, possible human carcinogen.

This conclusion was based upon a statistically significant increase in hepatocellular adenomas, with a positive dose-related trend, in both male and female NMRI mice. The incidences were outside the historical control range for this type of tumor in NMRI mice.

This conclusion was further supported by structural similarity of Bayleton to other carcinogenic triazole pesticides, especially triadimenol, a primary and major metabolite of Bayleton, which has been classified as group C by HED Peer Review Committee and the FIFRA Scientific Advisory Panel. Other triazole analogues such as propiconazole, etaconazole and cyproconazole were associated with increased incidences of hepatocellular adenomas, carcinomas or both in one or both sexes in mice.

Quantification of potential human risk, using the low dose extrapolation model ($Q1^*$), was not recommended at this time since the carcinogenic response is of a benign nature and limited to one tissue and one strain of one species, and occurs only at the highest dose level. In addition, the chemical does not appear to be genotoxic. The reference dose (RfD) approach will be employed for the quantification of potential human risk.

This classification is considered tentative pending reevaluation of liver slides from the CF1-W74 mice study and the submission of the final report on the second rat study recently conducted by the registrant.