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

JAN 29 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Triadimenol (Baytan)

FROM: George Z. Ghali, Ph.D. 12.5.87
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769C)

TO: Lois A. Rossi, PM 21
Fungicide-Herbicide Branch
Registration Division (TS-767C)

The Toxicology Branch Peer Review Committee met on October 1, 1987 to discuss and evaluate the weight of the evidence on Triadimenol, with particular reference to its oncogenic potential.

A. Individuals in Attendance:

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

Theodore M. Farber

Reto Engler

William Burnam

John A. Quest

Esther Rinde

Richard Levy

2. Peer Review Committee in Absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with the overall conclusion of the Committee.)

Anne Barton

Judith W. Hauswirth

Robert Beliles

Diane Beal

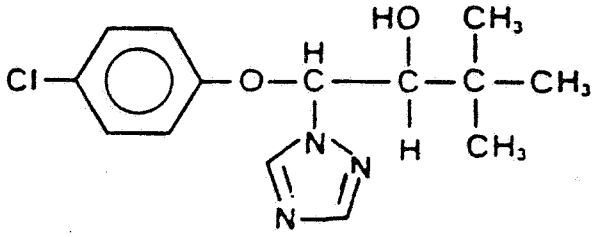
Richard Hill/Donald Barnes

B. Material Reviewed

The material available for review consisted of a package prepared by Dr. George Z. Ghali (Toxicology Branch/Hazard Evaluation Division [TB/HED]) containing data evaluation records (DER's) of mouse and rat oncogenicity studies on Triadimenol, historical control data on spontaneous tumors in CF1/W74 mice, a toxicology profile, and general background information on the chemicals in question.

C. Background Information

Triadimenol [β-(4-chlorophenoxy)-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol] is a systemic fungicide proposed for seed treatment for the control of certain diseases such as powdery mildew and rusts on small grains and corn.



Triadimenol
(Baytan)

Triadimenol is also a primary and major metabolite for Triadimefon (Bayleton®), another fungicide registered for use on a variety of raw agricultural commodities. Triadimenol is produced from Triadimefon in plants and animals by simple reduction of the carbonyl carbon.

Triadimenol exists as two stereoisomers usually designated as I and II (or A and B). The ratio of these two isomers in the technical product has not been reported. However, in almost all the toxicology studies submitted in support of the registration petition, testing was done using an isomer ratio of 4:1 of isomers I and II, respectively.

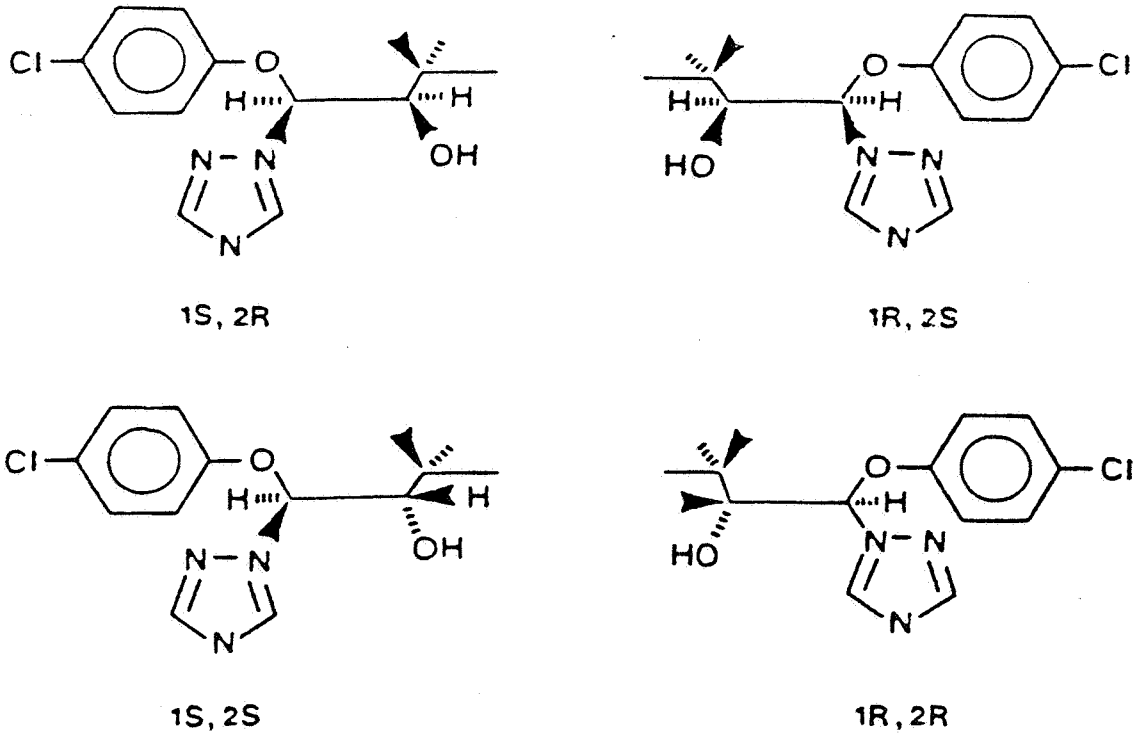


Figure 1. Diastereomeric and Enantiomeric Forms of Baytan

D. Evaluation of Oncogenicity Studies

1. Two-Year Feeding Study in Mice (1982) Bomhard, E.; Loeser, E.; Saxena, A.C.; Ehard, H. (Unpublished report prepared by Bayer, A.G., Germany; submitted to the Agency by Mobay Chemical Corporation, Kansas City, MO. EPA Accession No. 071467).

Technical Triadimenol with an approximate purity of 95% was administered into the diet to groups of male and female CF1/W74 mice for 2 years at dosage levels of 0, 125, 500, or 2000 ppm. Fifty animals per sex per dose level were used.

The treatment did not alter the spontaneous tumor profile in males. However, a treatment-related increase was observed in the incidence of hepatocellular adenomas in females. Relevant neoplastic lesions seen in this study are shown in Table 1.

Table 1. BAYTAN - Female Mice Liver Tumor Rates[+] and Trend or Fisher's Exact Test Results

Dose (ppm)	0	125	500	2000
Carcinoma[a]	1/43 (2)	0/40 (0)	1/45 (2)	0/47 (0)
Adenoma Only[b]	0/43** (0)	0/40 (0)	4/45 (9)	6/47* (13)
Carcinoma and/or Adenoma[a]	1/43* (2)	0/40 (0)	5/45 (11)	6/47 (13)

[+] Number of tumor-bearing animals/number of animals at risk (excludes all animals that died before the first year).
[a] First carcinoma appeared at week 87 (day 613) at 500 ppm.
[b] First adenoma appeared at week 71 (day 501) at 2000 ppm.

Note: Significance of trend analysis denoted at Control. Significance of pairwise comparison between control and dosed groups denoted at Dose level. **p < .01 and *p < .05. (Statistical analysis performed by C.J. Nelson, TB/HED).

Incidences of hyperplasia are shown in Table 2.

Table 2. BAYTAN - Female Mice Hyperplasia Rates[+] and Trend or Fisher's Exact Test Results

Dose (ppm)	0	125	500	2000
Hyperplasia Only[a]	2/43* (5)	1/40 (2)	1/45 (2)	5/47 (11)

[+] Number of non-neoplastic lesion-bearing animals/number of animals at risk (excludes all animals that died before the first year).
[a] First hyperplastic lesion appeared at week 71 (day 501) at 2000 ppm.

Note: Significance of trend analysis denoted at Control. Significance of pairwise comparison between control and dosed groups denoted at Dose level. **p < .01 and *p < .05. (Statistical analysis performed by C.J. Nelson, TB/HED).

There were no significant pairwise differences in liver carcinoma incidence between the control and dosed groups and no significant trend. Liver adenomas for the high-dose females was significantly different ($p = .017$) from the control and there was a significantly increasing trend ($p = .0025$) with increasing dose. There was a significantly increasing dose-response trend for liver hyperplasia ($p = .0325$).

Historical control data were provided for 13 different studies on the same strain of mouse between 1976 and 1980. Only one of the studies was run at the same lab in 1977. In this study, the control rate for adenomas was 5.1% (3/59) and the control rate for carcinomas was 3.4% (2/59). For the 13 studies, the pooled adenoma rate was 3.6% (24/661) and the pooled carcinoma rate was 2.0% (13/661). The incidence of liver adenomas is much greater in females of the mid- and hign-dose groups than the historical control incidence.

Survival was not affected by treatment. There were treatment-related decreases in the mean body weight gain of all male group (5.2-15.9%), and females of the mid- and high-dose groups (5.2-10.8%). The results of blood chemistry, organ weights, and gross and histologic examination indicated the liver as a target organ for the toxic effect of this chemical. There were time and dose-related increases in SAP, SGOT, and SGPT activities and increased incidences of enlarged livers and liver weights in both males and females of the mid- and high-dose groups.

The Committee felt that the MTD had been achieved at the high-dose levels in both males and females based upon depressed body weight gain.

The Committee requested that the registrant submit the liver slides to the Agency for reevaluation, since the incidence of carcinomas in the study was very low.

2. Chronic Feeding Study in Rats (1982) Loeser, E.; Schilde, B.; Kroetlinger, F. Unpublished report prepared by Bayer, A.G., Germany; submitted to the Agency by Mobay Chemical Corporation, Kansas City, MO. EPA Accession No. 071468.

Technical Triadimenol with purity of 94.9% was administered into the diet to groups of male and female BOR:WISW rats for 2 years at dosage levels of 0, 125, 500, or 2000 ppm. Sixty animals per sex per dose level were used.

The treatment did not alter the spontaneous tumor profile in this strain of rats.

The incidence of pituitary adenomas was higher in dosed than in control males, and tumors of the thyroid were increased in the low- and mid-dose male groups but not in the high-dose group as compared to controls. However, historical incidence of endocrine tumors in control rats are known to have a high variability. The incidence of thyroid tumors was also within the range of the historical control incidences. Furthermore, there was a lack of dose-response relationship in both of these tumors, confirming that the increased incidence of these tumors is not treatment-related. Thus the biological significance of these tumors in the study was dismissed on this ground. Three types of tumors occurred only in the high-dose males; three subcutaneous fibromas, one kidney adenoma, and one pinealoma and were considered to be "spontaneous tumors of rats of this age" and not atrributed to treatment.

Survival was not affected by the treatment. Mortality was as low in the high-dose groups as in controls (17.5 percent in both groups). Clinical chemistry findings suggest that the target organ for toxicity in this study may be the liver. The levels of SGOT and SGPT were consistently higher at 2000 ppm in males and females when compared to controls. Although there was an accompanying small increase in liver weight in 2000 ppm females, there were no accompanying increases in histopathologic changes of the liver in either sex. There were only marginal effects seen on other clinical chemistry parameters, and no effect of test compound on clinically observed signs of toxicity, food consumption, hematologic, or urinalysis parameters. Weight gains were lower in 2000 ppm males (8 percent) and females (19 percent) as compared to control.

The MTD seems to be achieved in females and, at least, approached in males of the high-dose groups.

E. Additional Toxicology Information

1. Mutagenicity

Triadimenol did not demonstrate mutagenic response in any of the following assays:

- o Ames Salmonella assay for point mutation.
- o Mouse micronucleus assay.
- o UDS in rat hepatocytes.
- o DNA damage in E. coli.
- o Forward mutation in mouse lymphoma.

2. Metabolism

There is no specific metabolism study available on Triadimenol per se, but data available on the metabolism of its parent compound triadimefon indicate that Triadimenol metabolism may be initiated by hydroxylation of the terminal carbon of the side chain, followed by an oxidation to the corresponding carboxylic acid. Both the alcohol and the acid derivatives of Triadimenol may be conjugated and then eliminated. The proposed metabolic pathway of Triadimenol is illustrated in Figure 2.

3. Reproduction and Teratology

In rabbits, oral administration of Triadimenol at 100 mg/kg during days 6 to 18 of gestation produced no indication of overt maternal toxicity, fetotoxicity, or teratogenicity.

The oral administration of Triadimenol at 100 mg/kg to the Long-Evans rats from days 6 to 15 of gestation did not produce any overt maternal toxicity, fetotoxicity, or teratogenicity.

However, these two studies were considered limited because animals were not exposed to doses permitting optimum test sensitivity in these studies.

In a 2-generation reproduction study in the rat, the reproductive indices were not affected. However, there were slight reductions in the fertility indices of animals in the 100 and 500 ppm groups in the second mating of the F_0 generation and in the 20, 100, and 500 ppm groups in the first and second matings of the F1b generation when compared with controls. In addition, other effects on body weight and organ weight, including testes and ovaries, were also observed.

4. Structure Activity Relationship

Triadimenol is the reduced form of the triazole fungicide triadimefon (Bayleton®). It is structurally similar to other triazole fungicides such as propiconazole (Tilt®) and bitertanol (Baycor®).

Propiconazole was reported to be oncogenic in male mice (increased incidence of hepatocellular adenomas and carcinomas). Triadimenol appears to increase the incidence of hepatocellular adenomas in female mice.

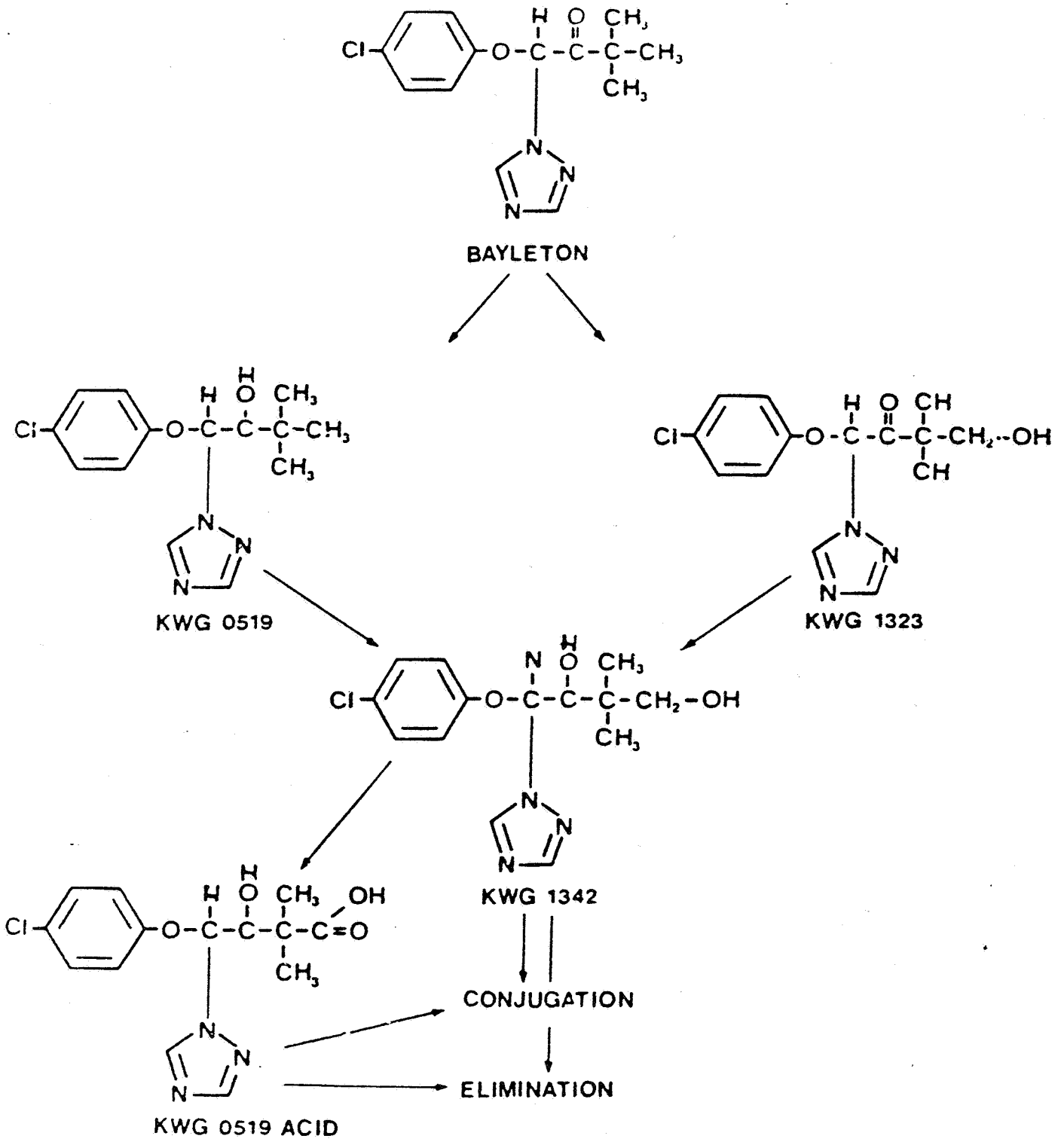
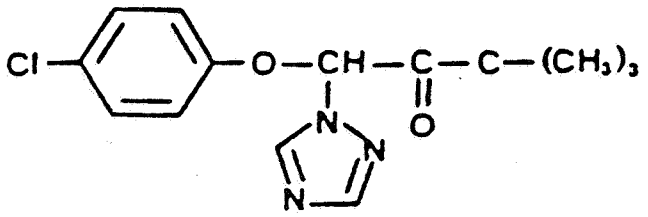


Figure 2. General Metabolic Pathway of Triadimefon

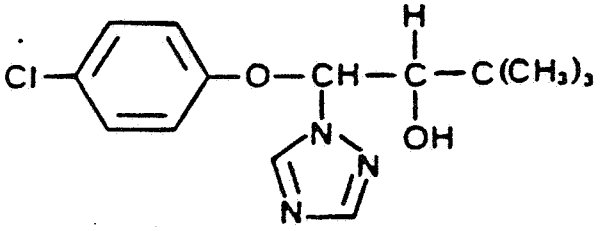
Bitertanol and triadimefon, on the other hand, caused cleft palates in rats. These results are summarized in the following table:

	Oncogenicity		Teratogenicity	
	Rat	Mouse	Rat	Rabbit
Triadimefon	-	-	+ (1)	-
Triadimenol	-	+(2)	? (4)	? (4)
Bitertanol	-	-	+ (1)	? (4)
Propiconazole	-	+(3)	-	-

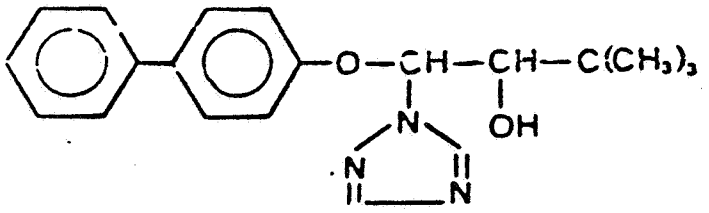
(1) Cleft palate.
(2) Hepatic adenomas and hyperplastic nodules in females.
(3) Hepatocellular adenomas and carcinomas in males.
(4) No data available, or data available are inadequate.



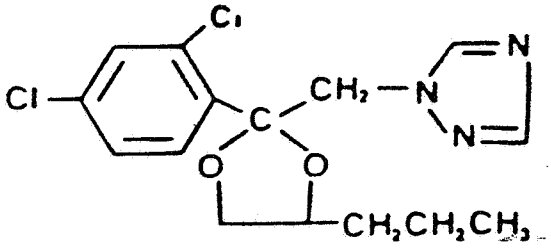
TRIADIMEFON
(Bayleton)



TRIADIMENOL
(Baytan)



BITERTANOL



PROPICONAZOLE

Figure 3. Structurally Related Chemicals

F. Weight of Evidence Consideration

The Committee considered the following facts regarding the toxicology data on Triadimenol to be of importance in a weight of the evidence determination of its oncogenic potential.

1. Administration of Triadimenol to CF1/W74 mice was associated with a statistically significant increase in hepatocellular adenomas with a significant dose-response trend in the females. Hyperplastic lesions observed also had a significant trend.

2. Historical control data from the performing laboratory and other laboratories indicated that the incidence of hepatocellular adenomas was higher than the historical control.

3. The MTD was reached or at least approached at the high-dose level in both male and female mice based upon depressed body weight gain.

4. Triadimenol was not oncogenic to BOR:WISW rats up to 2000 ppm. The MTD was reached in females and approached in males based upon depressed body weight gain.

5. Triadimenol was negative in a battery of genotoxicity tests.

6. Triadimenol is structurally related to Triadimefon and Bitertanol, which have been reported to be negative for oncogenicity in two species; and to Propiconazol, which has been classified as a C oncogen by the TB Peer Review Committee.

G. Classification of Oncogenic Potential

The Committee agreed that Triadimenol should be classified as a category C oncogen since its administration was associated with an increased incidence of benign tumors in female but not in male mice or male and female rats. In the CF1/W74 mice, dietary administration of Triadimenol was associated with a statistically significant increase in hepatocellular adenomas in the high-dose females. However, the Committee recommended that the slides be requested from the registrant for re-evaluation. The final oncogenic classification could change if the re-evaluation of slides provided different results.

In view of the above, the Committee concluded that no quantitative risk assessment would be required in this case, i.e., benign liver tumors in only one sex (female) of mice.