Date: **October 14, 1997**

MEMORANDUM

BAYTAN

SUBJECT: ***TRIADIMENOL*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland
Branch Senior Scientist,
Science Analysis Branch, Health Effects Division (7509C)

THROUGH: K. Clark Swentzel
Chairman, Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)

TO: Rick Loranger
Branch Senior Scientist
Registration Action Branch, Health Effects Division (7509C)

PC Code: 127201

On September 30, 1997, the Health Effects Division's Hazard Identification Review committee met to evaluate the toxicology data base of Triadimenol to select toxicological endpoints for acute dietary as well as occupational and residential exposure risk assessments. The Committee also re-assessed the Reference Dose (RfD) established in 1988 for chronic dietary risk assessment and addressed the sensitivity of infants and children from exposure to Triadimenol methyl as required by the Food Quality Protection Act of 1996.

Committee Members in Attendance

Members in attendance were David Anderson, William Burnam, Susan Makris, Nancy McCarroll, Melba Morrow, Kathleen Raffeale, John Redden and Jess Rowland. Member in absentia was Karl Baetcke. Data was presented by Joycelyn Stewart of the Registration Action Branch 2.

Data Presentation: _____
Joycelyn Stewart, Ph.D

Report Preparation: _____
Jess Rowland, M.S

I. INTRODUCTION

On September 30, 1997, the Health Effects Division's Hazard Identification Review committee met to evaluate the toxicology data base of Triadimenol to select toxicological endpoints for acute dietary as well as occupational and residential exposure risk assessments. The Committee also re-assessed the Reference Dose (RfD) established in 1988 for chronic dietary risk assessment and addressed the sensitivity of infants and children from exposure to Triadimenol methyl as required by the Food Quality Protection Act of 1996.

II. HAZARD IDENTIFICATION

A. Acute Dietary (one-day)

Study Selected: Developmental Toxicity Study - Rabbit Guideline No. 83-3a

MRID No. 00089023).

Executive Summary: In a developmental toxicity study, pregnant Sprague-Dawley rats (19-21/dose) received **Triadimefon** (99%.) in 0.5% Cremaphor suspension at dose levels of 0, 10, 25, 50, or 100 mg/kg/day from days 6 through 15 of gestation. Maternal toxicity manifested as increased motor activity in dams at 25, 50 or 100 mg/kg/day. The degree and duration of these episodes were dose-related. In addition, dams at 50 and 100 mg/kg/day exhibited a statistically significant decrease in body weight gain during the dosing period. Weight gain during the entire course of the study, however, was not affected in these dams.. For maternal toxicity, the NOEL was 10 mg/kg/day and the LOEL was 25 mg/kg/day, based on dose-related increase in both degree and duration of motor activity. For developmental toxicity, the NOEL was 50 mg/kg/day and the LOEL was 100 mg/kg/day, based on increased incidences of cleft palates; two fetuses from two different litters were found to have cleft palate.

Dose/Endpoint for Risk Assessment: Maternal NOEL = 10 mg/kg/day based on increased motor activity in dams at 25 mg/kg/day.

Comments about Study/Endpoint: Effects observed in oral studies were not attributable to a single exposure of Triadimenol, a metabolite of Triadimefon in mammals, plants, and soil. **Therefore, the Committee decided to use the developmental toxicity study in rats conducted with the parent compound, Triadimefon.**

The neurotoxic endpoint seen with the parent compound is supported by the results of studies reported in the open literature. *Crofton et al (1991)* reported hyperactivity following oral exposure to Triadimefon with LOELs ranging from 50 to 100 mg/kg. *Walker and Mailman (1996)* reported that acute administration of Triadimefon and Triadimenol resulted in a neurotoxic syndrome in rats characterized by increased motor activity, stereotyped behaviors, and altered monamine metabolism. The authors postulated that increased synaptic concentrations of dopamine due to inhibition of dopamine uptake may play an important role in the neurobehavioral effects of these

compounds. *Crofton (1996)* reported that following oral dosing in corn oil, Triadimefon and Triadimenol induced hyperactivity in male Long-Evans rats. Details of these studies such as dose levels, duration of dosing and the doses at which the effects were observed were not available to the Committee.

Margin of Exposure: For acute dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children **(as required by FQPA) should be reduced to 3 x.**. Therefore, **a Margin of Exposure of 300 is required** to ensure protection of this population from acute exposure to Triadimenol for reasons stated below:

(i) No additional sensitivity in young rats or rabbits was seen following pre- and/or postnatal exposure to Triadimenol.

(ii) However, data gap exists for acute and neurotoxicity studies. Therefore, data on cholinesterase inhibition and FOB as well as histopathology of the central and peripheral nervous systems are not available for evaluation after single or repeated oral exposure to Triadimenol.

B. Chronic Dietary [Reference Dose (RfD)]

RfD Established in 1988:

Study Selected: 6-Month and 2-Year Chronic Toxicity - Dog (§83 1 b)

MRID Nos. 00151247 & 00150484

Executive Summary: In a subchronic toxicity study, beagle dogs (6/sex/dose) received diets containing Triadimenol (98%, pure) at 0, 10,30, or 100 ppm (0, 0.25, 0.75 or 2.5 mg/kg/day, respectively) for 26 weeks. No treatment-related effects were seen at any dose level. The NOEL was 100 ppm (2.5 mg/kg/day); a LOEL was not established.

In a chronic toxicity study, beagle dogs (4 dogs/sex/dose) received diets containing Triadimenol at 0, 150,600, or 2400 ppm (0, 3.75, 15 or 60 mg/kg/day, respectively) for 52 weeks. No specific target organ toxicity was seen. Treatment-related effects were limited to alterations in enzyme levels including statistically significant ($p < 0.05$) increases in: alkaline phosphatase, N-demethylase, and cytochrome P-450 at 2400 ppm (males); N-demethylase in at 600 and 2400 ppm (females); and cytochrome P-450 at 2400 ppm (females) when compared to controls. The NOEL was 3.75 mg/kg/day) and the LOEL was 15 mg/kg/day based on changes in enzyme levels.

Dose/Endpoint for establishing the RfD: NOEL= 3.75 mg/kg/day based on changes in enzyme levels at 15 mg/kg/day (LOEL).

Uncertainty Factor (UF): An UF of 100 was applied to account for inter (10 x)-and intra-

(10 x) species variation.

$$\text{RfD} = \frac{\text{3.75 mg/kg/day (NOEL}}{\text{100 (UF)}} = \text{0.038 mg/kg/day}$$

The RfD established in 1988 was reassessed by this Committee in pursuant of the FQPA and is discussed below:

Re-Assessment of the RfD : The Committee selected the same endpoint and the NOEL from the dog study that was used in 1988. The Committee, however, determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be reduced to 3 x for a total UF of 300** (i.e., 10 for inter-species variation x 10 for intra-species variation x 3 for FQPA). **Therefore, the revised RfD is: 0.013 mg/kg/day.** An UF of 300 is supported by the following factors.

(i) Developmental toxicity studies showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A multi-generation reproduction toxicity study in rats showed no increased sensitivity in pups as compared to adults.

(iii) However, data gap exists for acute and subchronic neurotoxicity studies. Therefore, data on cholinesterase inhibition and FOB as well as histopathology of the central and peripheral nervous systems are not available for evaluation after single or repeated oral exposure to Triadimenol.

C. Occupational/Residential Exposure

1. Dermal Absorption

A dermal absorption study with Triadimenol is not available. Therefore, the Committee decided to use the dermal absorption rate of not more than 10% estimated Triadimefon, the parent compound. In a 21-day dermal study with Triadimefon, no frank systemic toxicity was seen after 15 repeated dermal applications in rats thus indicating low dermal absorption. Therefore, the Committee estimated a dermal absorption rate of **no more than 10%** based on the ratio of the NOEL and LOEL of 10 and 25 mg/kg/day, respectively in the oral developmental study and the NOEL and LOEL of 300 and1000 mg/kg/day, respectively, in the 21-day dermal toxicity study in the same species (rat) with the parent compound (Triadimefon). A dermal absorption rate was estimated since an oral dose was identified for chronic dermal exposure risk assessment.

2. Short-Term Dermal (1-7 days)

Study Selected: 21-Dermal Toxicity - Rabbit Guideline No. §82-2

MRID No 00151246

Executive Summary: Groups of New Zealand White rabbits (5/sex/dose) received repeated dermal applications of Triadimenol (98%) at 0, 50, or 250 mg/kg/day, 6 hours/day, 5 days/week for a total of 15 applications over a 21 day period. The 250 mg/kg/day dosage was determined to be the highest that could be applied due to technical reasons (details not reported). No dermal or systemic toxicity was seen. The NOEL was >250 mg/kg/day (HDT); a LOEL was not established

Dose/Endpoint for Risk Assessment: NOEL = 250 mg/kg/day, the highest dose tested.

Comments about Study/Endpoint: Although no systemic toxicity was observed at the highest dose tested, the Committee recommended the use of this dose for this risk assessment because: 1) no details were provided as to what the "technical reasons" were that prevented testing at higher dose levels: 2) only two dose levels were tested instead of three as recommended in the Subdivision F Guideline §82-2; 3) repeated dermal application of the parent compound (Triadimefon) did cause increased motor activity in rats; and 4) no rationale was provided for conducting this study in rabbits, while the rats were shown to be a more sensitive species for both oral and dermal routes in studies conducted with the parent compound (hyperactivity seen after exposure by oral and dermal routes)

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 21-Day Dermal Toxicity - Rabbit Guideline §82-2

Executive Summary: See Short-Term

Dose/Endpoint for Risk Assessment: NOEL= 250 mg/kg/day, the highest dose tested.

Comments about Study/Endpoint: See Short-Term

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: 6-Month and 2-Year Chronic Toxicity - Dog (§83 1 b)

MRID Nos. 00151247 & 00150484

Executive Summary: See Chronic Dietary

Dose/Endpoint for Risk Assessment: NOEL= 3.75 mg/kg/day based on changes in enzyme levels at 15 mg/kg/day (LOEL).

Comments about Study/Endpoint: Systemic toxicity was seen following chronic oral exposure and this dose/endpoint was used to establish the RfD. Since the dose selected is from an oral study, a dermal absorption factor of 10% should be used in margin of exposure calculations.

This risk assessment is required.

5. Inhalation Exposure (Any-Time period)

Based on the LC_{50} of >2.58 mg/L (Limit-Dose), the 25% dry flowable formulation of Triadimenol is placed in Toxicity Category IV. **Therefore, a separate risk assessment for this route is not required.**

D. Margins of Exposure for Occupational/Residential Exposure Risk Assessments.

The Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (**as required by FQPA) should be reduced to 3 x.**. Therefore, **a Margin of Exposure of 300 is required** to ensure protection of this population (residential) as well as the pesticide handlers (occupational) from dermal exposure to Triadimenol. A MOE of 300 is required for reasons stated below:

(i) Developmental toxicity studies showed no increased sensitivity to fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A multi-generation reproduction toxicity study in rats showed no increased sensitivity to pups as compared to adults.

(iii) However, due to the lack of an acute and subchronic neurotoxicity studies data on cholinesterase inhibition, FOB, and histopathology of the central and peripheral nervous system are not available for evaluation after a single or repeated exposure to Triadimenol.

III. FQPA CONSIDERATIONS

1. Determination of Sensitivity

The data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or post natal exposure to Triadimenol. In both the prenatal developmental studies in rat and rabbits, no evidence of developmental toxicity was seen, even in the presence of maternal toxicity. The developmental NOEL for the rat study was greater than the maternal NOEL, and the offspring NOEL in the two-generation reproduction study in rats was equivalent to the parental NOEL, based upon similar end points (body weight decrements).

2. Determination for a Developmental Neurotoxicity Study

The Committee determined that a developmental neurotoxicity study is required for Triadimenol based on the following factors: 1) Triadimenol is a known to target the nervous system as a central stimulant, interfering with dopamine; 2) Based upon the known mechanism of action of Triadimenol and related compounds, and since evidence of hyperactivity has been observed in the rat in studies submitted to the Agency as well as in studies published in the open literature; and 3) Data gaps exist for acute and subchronic neurotoxicity studies.)

IV. DATA GAPS

1. Acute Neurotoxicity Study in Rats §81-8

2. Subchronic Neurotoxicity Study in Rats §82-5

3. Developmental Neurotoxicity Study in Rats

V. REFERENCES

Crofton, KM. 1996. A structure-activity relationship for the neurotoxicity of triazole fungicides. *Toxicol. Lett* 84 (3): 155- 159.

Crofton, KM., Howard, JL., Moser, VC., Gill, MW, et al. 1996. Interlaboratory comparison of motor activity experiments: implications for neurotoxicological assessments. *Neurotoxicol.Teratol.* 13 (6): 599-609.

Walker, QD and Mailman, RB. 1996. Triadimefon and triadimenol: effects on monoamine uptake and release. *Toxicol. Appl. Pharmacol.* 139 (2); 227-233.