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MEMORANDUM

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

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THROUGH: K. Clark Swentzel
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PC Code: 109901

On September 30, 1997, the Health Effects Division's Hazard Identification Review committee met to evaluate the toxicology data base of Triadimefon 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 1995 for chronic dietary risk assessment and addressed the sensitivity of infants and children from exposure to Triadimefon 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 Triadimefon 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 Triadimefon 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

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 gains during the entire course, 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 had cleft palate. (MRID No.00089023; HED Doc. No. 001533).

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

Comments about Study/Endpoint: This endpoint is supported by the results of studies in the open literature. *Crofton et al (1991)* observed 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 resulted in a neurotoxic syndrome in rats characterized by increased motor activity, stereotyped behaviors, and altered monamine metabolism. Triadimenol, a metabolite of Triadimefon, also increased motor activity in rodents. 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 retained**. Therefore, a **Margin of Exposure of 1000 is required** to ensure protection of this population from acute exposure to Triadimefon for reasons stated below:

- (i) Triadimefon is known to target the nervous system as a central stimulant, interfering with the dopamine. Evidence of hyperactivity has been observed following oral administration to rats in the developmental toxicity study as well as in studies published in the literature.
- (ii) Data gaps exist for an acute neurotoxicity study. Therefore, cholinesterase inhibition and FOB data as well as histopathology of the central and peripheral nervous system are not available for evaluation after a single oral exposure to Triadimefon.
- (iii) The prenatal developmental study in American Dutch rabbits and the multi-generation reproduction studies in rats indicate that there is apparent additional sensitivity to young animals following pre-and/or postnatal exposure to Triadimefon.
- (iv) The nature and severity of the effects observed with treatment by this chemical are of concern (cleft palate in the prenatal developmental toxicity studies in rats, reduced fertility in offspring in the two-generation reproduction study in rats).
- (v) Lack of an acceptable two-generation reproduction study in rats.

B. Chronic Dietary [Reference Dose (RfD)]

RfD Established in 1995:

Study Selected: Chronic Toxicity - Dog (§83 1 b)

MRID No. 00032539 & 00126261

Executive Summary: In a chronic toxicity study, beagle dogs (4/sex/dose) received diets containing Triadimefon (92.7%, pure) at 0, 100, 300, or 1000 ppm for 104 weeks. These doses were equivalent to 0, 5.7, 11.4 or 33.67 mg/kg/day. After 54 weeks, the high dose was increased to 2000 ppm (60.42 mg/kg/day) for both sexes. Treatment related effects observed at the high dose (1000/2000 ppm) included: decreased food intake in females (11% in the first year and 15% in the second year); decreases in body weight gain in males (20%) and females (11%); and significantly increased alkaline phosphatase activity in both sexes. The NOEL was 330 ppm (11.4 mg/kg/day) and the LOEL was 1000/2000 ppm (33.67/60.42 mg/kg/day) based on the effects described above.

Dose/Endpoint for establishing the RfD: NOEL= 11.4 mg/kg/day based on the decreased food intake in all females; decreases in body weight gain in both sexes; increased alkaline phosphatase activity in both sexes at 33.67/60.42 mg/kg/day (LOEL).

Uncertainty Factor (UF): An UF of 300 was applied to account for inter (10 x)-and intra- (10 x) species variation and the lack of an adequate 2-generation reproduction study (3 x).

$$\text{RfD} = \frac{11.4 \text{ mg/kg/day (NOEL)}}{300 \text{ (UF)}} = 0.04 \text{ mg/kg/day}$$

The above RfD was established in 1995. It was re-assessed by this Committee pursuant to the FQPA and is discussed below:

Re-Assessment of the RfD : The Committee selected the same endpoint and the NOEL from the dog study used in 1995. The Committee, however, determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained for a total UF of 1000** (i.e., 10 for inter-species variation x 10 for intra-species variation x 10 for FQPA; this includes the 3 x applied in the RfD of 1995). **Therefore, the revised RfD is: 0.011 mg/kg/day.** An UF of 1000 is supported by the following factors.

- (i) Triadimefon is known to target the nervous system as a central stimulant, interfering with the dopamine. Evidence of hyperactivity has been observed following oral administration to rats in the developmental toxicity study as well as in studies published in the literature.
- (ii) Data gaps exist for a subchronic neurotoxicity study. Therefore, cholinesterase inhibition and FOB data as well as histopathology of the central and peripheral nervous systems are not available for evaluation after repeated oral exposure to Triadimefon.
- (iii) The prenatal developmental study in American Dutch rabbits and the multi-generation reproduction studies in rats indicate that there is apparent additional sensitivity to young animals following pre-and/or postnatal exposure to Triadimefon.
- (iv) The nature and severity of the effects observed with treatment by this chemical are of concern (cleft palate in the prenatal developmental toxicity studies in rats, reduced fertility in offspring in the two-generation reproduction study in rats).
- (v) Lack of an acceptable two-generation reproduction study in rats.

C. Occupational/Residential Exposure

1. Dermal Absorption

A dermal absorption study is not available. No frank systemic toxicity was seen after 15 repeated dermal applications in rats which indicates low dermal absorption for Triadimefon. 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 developmental study and the dermal NOEL and LOEL of 300 and 1000 mg/kg/day, respectively in the 21-day dermal toxicity study in the same species (rat). Dermal absorption was estimated for use with the oral dose identified for chronic dermal exposure risk assessment.

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

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

MRID No 42341501

Executive Summary: Groups of Sprague-Dawley rats (5/sex/dose) received repeated dermal applications of Triadimefon (95.9%) at 0, 100, 300 or 1000 mg/kg/day, 6 hours/day, 5 days/week for a total of 15 applications over a 21 day period. The NOEL was 300 mg/kg/day and LOEL was 1000 mg/kg/day based on increased reactivity in all females on days 11 through 18.

Dose/Endpoint for Risk Assessment: NOEL= 300 mg/kg/day based increased reactivity in females at 1000 mg/kg/day (LOEL).

Comments about Study/Endpoint: Endpoint was seen following treatment via the appropriate route and exposure (i.e, dermal) of concern. In addition, increased (motor) activity has been reported after single and repeated oral administration in rats and rabbits, respectively (see Acute Dietary). Since the dose identified is from a dermal study there is no need to use a dermal absorption factor.

This risk assessment is required.

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

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

Executive Summary: See Short-Term

Dose/Endpoint for Risk Assessment: NOEL= 300 mg/kg/day based on increased activity seen in female rats following repeated dermal applications at 1000 mg/kg/day (LOEL).

Comments about Study/Endpoint: Endpoint was seen following treatment via the appropriate route and exposure (i.e, dermal) of concern. In addition, increased (motor) activity was also seen after single and repeated oral dosing in rats and rabbits, respectively (see Acute Dietary). Since the dose identified is from a dermal study there is not need to use a dermal absorption factor.

This risk assessment is required.

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

Study Selected: Chronic Toxicity - Dog (83 1 b)

MRID No. 00032539 & 00126261

Executive Summary: See Chronic Dietary

Dose/Endpoint for Risk Assessment: NOEL= 11.4 mg/kg/day based on the decreased food intake (females), decreased body weight gain (both sexes) and increased alkaline phosphatase activity (both sexes) at 33.67/60.42 mg/kg/day.

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 LC₅₀ of >3.57 mg/L (Limit-Dose), Triadimefon is placed in Toxicity Category IV. **Therefore, a separate risk assessment for this route is not required.**

D. Margins of Exposure for Occupational/Residential Risk Assessments

The Committee has determined that the **10 x factor** to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained**. Therefore, a **Margin of Exposure of 1000 is required** is required to ensure protection of this population (residential exposure) as well as the pesticide handlers (occupational exposure) from dermal exposure to Triadimefon. A MOE of 1000 is required for reasons stated below:

- (i) Triadimefon is known to target the nervous system as a central stimulant, interfering with dopamine. Evidence of hyperactivity has been observed in rats in following oral and dermal exposures.
- (ii) Data gaps exists for acute and subchronic neurotoxicity studies.

Therefore, data on cholinesterase inhibition and FOB as well as histopathology on the central and peripheral nervous systems are not available for evaluation after single or repeated exposure to Triadimefon.

- (iii) The prenatal developmental study in American Dutch rabbits and the multi generation reproduction studies in rats indicate that there is apparent additional sensitivity to young animals following pre-and/or postnatal exposure to Triadimefon.
- (iv) The nature and severity of the effects observed in the rat developmental toxicity (cleft palate) and two generation reproduction (effects in the offspring) studies.
- (v) Lack of an acceptable two-generation reproduction study in rats.

III. FQPA CONSIDERATIONS

1. Determination of Sensitivity

The prenatal developmental toxicity data in American Dutch rabbits (but not the study in Himalayan rabbits) as well as the multi generation reproduction studies in rats indicated a potential for increased sensitivity in infants and children from exposure to Triadimefon.

- (i) In the developmental study with American Dutch rabbits, Triadimefon (in aqueous carboxymethyl cellulose and Tween 80) was administered to pregnant animals at oral doses of 0, 20, 50 or 120 mg/kg/day on gestation days 6-18. For maternal toxicity, the NOEL was 50 mg/kg/day and the LOEL was 120 mg/kg/day based on marginal body weight loss. For developmental toxicity, the NOEL was 20 mg/kg/day and the LOEL was 50 mg/kg/day based on significant increase in the incidence of incomplete ossification of the anterior and posterior phalanges, irregular spinous processes, and incomplete ossification of the pubes. At 120 mg/kg/day, the following observations were noted: decreased fetal body weight, increased incidence of rudimentary/missing tail, increased incidence of skeletal alterations (incomplete ossification of the skull; enlargement of fontanelles; incomplete or nonossification of sternbrae 1, 2 or 5; posterior talus; and posterior phalanges); extra ribs; malformations of the caudal vertebral arches and centra (MRID NO. 41446202, 42089601; (HED Doc. No. 008467).

(ii) In the developmental study with Himalayan rabbits, Triadimefon (in 0.5% aqueous Cremaphor Tween 80) was administered to pregnant animals at oral doses of 0, 10, 30 or 100 mg/kg/day on gestation days 6-18. For maternal toxicity, the NOEL was 10 mg/kg/day and the LOEL was 30 mg/kg/day based on a marked decrease in body weight gain during the dosing period and during the overall gestation period. For developmental toxicity, the NOEL was 30 mg/kg/day and the LOEL was 100 mg/kg/day based on significant increases in fetal resorptions (MRID No. 00149335; HED Doc. No. 006841).

(iii) In a three-generation reproduction study, Triadimefon was administered in the diet to Wistar rats at 0, 50, 300 or 1800 ppm (0, 2.5, 15 or 90 mg/kg/day, respectively) for three successive generations. For parental systemic toxicity, the NOEL was 15 mg/kg/day and the LOEL was 90 mg/kg/day based on decreased fertility (no litters were produced in the second mating of the F₁ generation) and body weight of adult F₀ females and F₁ animals of both sexes. The NOEL for effects on offspring was 2.5 mg/kg/day and the LOEL was 15 mg/kg/day based on apparent decrease in F_{2b} and F_{3b} body weight gain. Also at 1800 ppm, decreased litter size and decreases in survival of the F₁ pups during lactation were observed. This study was classified as supplementary (MRID No. 0003254, 92188019, 92188020; HED Doc. No. 004695).

(iv) In a two-generation reproduction study, Triadimefon was administered in the diet to rats at 0, 50 or 1800 ppm (0, 2.5, or 90 mg/kg/day, respectively) for two successive generations. For parental systemic toxicity, the NOEL was 2.5 mg/kg/day based on decreases in body weights at 90 mg/kg/day. The NOEL for effects on the offspring was 2.5 mg/kg/day based on decreased F₁ and F₂ pup body weight at birth and viability. This study was submitted as a supplement to the 3-generation study discussed above. However, it was NOT adequate to upgrade the 3-generation study. (MRID No. 00155075, 92188019, 92188020; HED Doc. No. 006563, 010310).

2. Determination for a Developmental Neurotoxicity Study

The Committee determined that a developmental neurotoxicity study is required for Triadimefon based on the following factors: 1) Triadimefon is known to target the nervous system as a central stimulant, interfering with dopamine; 2) It has been used as a representative positive control chemical for findings of increased motor activity in standard neurotoxicity testing; 3) 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 4) Data gaps exist for acute and subchronic neurotoxicity studies.

IV. DATA GAP

1. Acute Neurotoxicity Study in Rats §81-8
2. Subchronic Neurotoxicity Study in Rats §82-5
3. 2-Generation Reproduction Study in Rats §83-4
4. 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.

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