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DATE: July 21, 1999

MEMORANDUM

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

FROM: Patricia S. Gaunt, Toxicologist
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THROUGH: Pauline Wagner, Co-chairman
And
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Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

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PC Code: 060101

On June 1 and June 17, 1999, the Health Effects Division (HED) Hazard Identification Assessment Review committee evaluated the toxicology data base of **THIABENDAZOLE**, established a Reference dose (RfD) and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. In addition, the HIARC also addressed the potential enhanced susceptibility of infants and children from exposure to thiabendazole as required by the Food Quality Protection Act (FQPA) of 1996. The committee's conclusions are presented in this report.

Committee Members in Attendance

	6/1/99	6/17/99
Members present were:	Dave Anderson	William Burnam
	Virginia Dobozy	Virginia Dobozy
	Karen Hamernik	Mike Ioannou
	Pam Hurley	Tina Levine
	Mike Ioannou	Susan Makris
	Tina Levine	Jess Roland
	Susan Makris	PV Shah
	Nancy McCarroll	Pauline Wagner
	Kathleen Raffaele	Nicole Paquette
	Jess Roland	
	PV Shah	
	Brenda Tarplee	
Member(s) in absentia:	William Burnam	Dave Anderson
	Nicole Paquette	Karen Hamernik
	Pauline Wagner	Pam Hurley
		Nancy McCarroll
		Kathleen Raffaele
		Brenda Tarplee

Data was presented by Patricia Gaunt of the Reregistration Branch 4

Also in attendance were:	Sanjivani Diwan/RRB4	Yung Yang/Tox1
	Ray Kent/RRB4	Kelly O'Rourke
	Abdallah Khasawinah/RRB4	Alberto Protozel/Tox1
	Gary Bangs/RCAB	Sanjivani Diwan/RRB4
	David Nixon/Tox1	Ray Kent/RRB4
	Suhair Shallal/RRB4	Suhair Shallal/RRB4

Data Presentation
and
Report Presentation: _____

Patricia S. Gaunt, Toxicologist

cc:RD
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I. INTRODUCTION

On June 1 and 17, 1999 the Health Effects Division (HED) Hazard Identification Assessment Review Committee evaluated the toxicology data base of **THIABENDAZOLE**, established a Reference Dose (RfD) and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to thiabendazole as required by the Food Quality Protection Act (FQPA) of 1996.

II. HAZARD IDENTIFICATION

A. Acute RfD

1. ACUTE DIETARY (Acute RfD)*–Females 13+

Study Selected: Developmental Study–Rat **Guideline #:83-3a**

MRID No.: 42942803

Executive Summary: In a developmental toxicity study (MRID 42842803), thiabendazole (technical, >98.9% a.i.) was administered by gavage to 25 female Sprague-Dawley rats [Crl:CD (SD) BR] in 0.5% methylcellulose at dose levels of 0, 10, 40, or 80 mg/kg/day from days 6 through 17 of gestation.

Maternal toxicity was noted at 40 and 80 mg/kg/day consisted of statistically significant ($p \leq 0.05$) decreases in mean body weight gain of 12 and 26%, respectively, throughout the treatment period. Statistically significant ($p \leq 0.05$) reduction in feed consumption was noted in mid- (11-15%) and high- (22-28%) dose animals during treatment. No treatment-related changes in body weight gain or feed consumption were noted at 10 mg/kg/day compared to controls. No deaths occurred, there were no treatment-related gross pathologic findings, and no abortions were observed at any treatment level. Clinical signs of toxicity observed during the study consisted of ptosis in 4 dams in the 80 mg/kg/day treatment group on gestational day 6.

The maternal LOAEL is 40 mg/kg/day, based on reduced maternal body weight gains and reduced feed consumption. The maternal NOAEL is 10 mg/kg/day.

At dose levels of 40 and 80 mg/kg/day, fetal body weights were slightly but significantly ($p \leq 0.05$) reduced (5-6%) in females and were slightly but significantly ($p \leq 0.05$) reduced in males (5%) at 80 mg/kg/day but not at 40 mg/kg/day (3%). No developmental effects were observed at treatment levels of 10 mg/kg/day. There were no treatment-related malformations or variations noted in the fetuses at any dose level.

The developmental LOAEL is 40 mg/kg/day, based on decreased fetal body weights. The developmental NOAEL is 10 mg/kg/day.

This developmental toxicity study in the rat is classified **Acceptable** and satisfies the guideline requirements for a developmental toxicity study **(83-3a)** in rats.

Dose and Endpoint for Establishing RfD: The developmental NOAEL is 10 mg/kg/day based on decreased fetal body weight at 40 mg/kg/day (LOAEL).

Uncertainty Factor(s): An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intra-species variability.

ACUTE RfD (females 13+): $\frac{10 \text{ mg/kg}}{100 \text{ (UF)}} = 0.1 \text{ mg/kg}$

Comments about Study/Endpoint/Uncertainty Factor(s): The decreased fetal body weight is presumed to occur after a single exposure (dose) and was also seen in studies with other species (mice and rabbits). Therefore, this endpoint is considered to be appropriate for this (acute) risk assessment. This dose/endpoint is applicable only to Female 13+

This Risk Assessment is required.

2. ACUTE DIETARY (Acute RfD)*–General Population

Study Selected: Developmental Study–Rat **Guideline #:83-3a**

MRID No.: 42942803

Executive Summary: See II-1 above

Dose and Endpoint for Establishing the RfD: The Maternal NOAEL is 10 mg/kg/day based on decreased maternal body weight seen during gestation day 6-8 after 3 dosages.

Uncertainty Factor(s): An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intra-species variability.

ACUTE RfD (General Population): $\frac{10 \text{ mg/kg}}{100 \text{ (UF)}} = 0.1 \text{ mg/kg}$

Comments about Study/Endpoint/Uncertainty Factor(s): The decreased maternal body weight was seen during gestation days 6-8 after 3 dosages. Therefore, this endpoint is considered to be appropriate for this (acute) risk assessment.

This Risk Assessment is required.

B. CHRONIC DIETARY [Reference Dose (RfD)]

Study Selected: 2-Yr feed/chronic/Carcinogenicity **Guideline #:** §83-5

MRID No.: 43593201.

Executive Summary: In a combined chronic/oncogenicity study (MRID 43593201), thiabendazole (>98.9% a.i.) was administered to 50 Sprague-Dawley Crl:CD BR rats/sex/dose in the diet at dose levels of 0, 10, 30, or 90 mg/kg/day (achieved average doses of 0, 10.1, 30.2, or 91.8 mg/kg/day) for 104 weeks.

There were no treatment-related effects on survival, clinical signs, food consumption, ophthalmoscopic findings, urinalysis, or gross pathology. Body weights and body weight gains were generally lower (↓7-30%) throughout the study for the mid- and high-dose males and high-dose females. Reduced body weight gains (↓15, 28, and 19%, $p \leq 0.05$) for the mid- and high-dose males and high-dose females, respectively, compared to the controls were observed at week 103. A reduced body weight gain (↓10%, not statistically significant) was also noted at this time for the mid-dose females.

Significant increases (↑36-79%, $p \leq 0.05$) in total serum cholesterol observed in the high-dose group were judged to be treatment-related. In the high-dose males, increased (↑29%, $p \leq 0.05$) relative (to body) liver weights and an increased incidence of centrilobular hepatocellular hypertrophy (28/50 treated vs 0/50 controls) were also detected. Centrilobular hepatocellular hypertrophy was also observed in 7/50 mid-dose males. In the high-dose females, an increased (↑45%, $p \leq 0.05$) relative thyroid weights and increased incidences of thyroid focal cystic follicular cell hyperplasia (6/50 treated vs 2/50 controls) and diffuse follicular cell hypertrophy (2/50 treated vs 0/50 controls) were observed. Thyroid diffuse follicular cell hypertrophy was also observed (4/50 treated vs 0/50 controls) in the high-dose males.

The systemic LOAEL is 30 mg/kg/day based on reduced body weights and body weight gains and liver hypertrophy (males). The systemic NOAEL is 10 mg/kg/day.

This study is classified as **acceptable (§83-5a)** and satisfies the guideline requirements for a chronic/oncogenicity study in the rat.

Dose and Endpoint for establishing RfD: NOAEL = 10 mg/kg/day based on decreased body weight gains and liver hypertrophy at 30 mg/kg/day (LOAEL).

Uncertainty Factor(s): An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intra-species variability.

Chronic RfD: $\frac{10 \text{ mg/kg}}{100 \text{ (UF)}} = 0.10 \text{ mg/kg}$

Comments about Study/Endpoint/Uncertainty Factor(s): The results of the 14-week feeding study in rats (MRID No. 42942802) with a NOAEL of 9.4 mg/kg/day and a LOAEL of 37 mg/kg/day and the Two-Generation Reproduction Study in rats (MRID 43190301) with a NOAEL of 10 mg/kg/day and a LOAEL of 30 mg/dg/day provide support for the critical study.

C. OCCUPATIONAL / RESIDENTIAL EXPOSURE

1. DERMAL ABSORPTION

No dermal absorption studies are available. The estimated dermal absorption rate of 60% is based on results of an oral developmental toxicity study in rabbits and a 21-day dermal toxicity study in rabbits.

In the oral developmental toxicity study in rabbits, the NOAEL was 150 mg/kg/day and the LOAEL was 600 mg/kg/day based on decreased body weight gain and reduced feed consumption. (MRID No. 42942804).

In the 21-day dermal toxicity study in rabbits, the NOAEL was 1000 mg/kg/day and the LOAEL was > 1000 mg/kg/day (HDT) (MRID NO. 41259501).

A ratio of the LOAELs from the oral and dermal studies indicated an approximate absorption rate of 60% (oral LOAEL 600 mg/kg/day/dermal LOAEL of >1000 mg/kg/day x 100=60%).

Dermal Absorption Factor= 60% (estimated)

2. SHORT-TERM DERMAL (1 - 7 days)

Study Selected: Oral Developmental Toxicity–Rat **Guideline #:** 82-1a

MRID No.: 42942803

Executive Summary: See Acute RfD

Dose and Endpoint Proposed for Consideration: The developmental NOAEL is 10 mg/kg/day based on decreased fetal body weights at 40 mg/kg/day (LOAEL).

Comments about Study/Endpoint: although a 21-day dermal toxicity study in rabbits with a NOAEL of 1000 mg/kg/day is available, the HIARC selected an oral (developmental) NOAEL because of the concern for the developmental effects seen in three species (mice, rat, and r abbits). Since an oral NOAEL was selected, 60% dermal absorption factor should be used for risk assessment

This Risk Assessment is required.

3. INTERMEDIATE-TERM DERMAL (1-Week to Several Months)

Study Selected: Fourteen Week Oral Toxicity (Feeding) Study in Rats Guideline #: 82-1a
MRID No.: 42942802

Executive Summary: In a subchronic toxicity study (MRID 42942802), thiabendazole (99.4% a.i.) was administered to Crl:CD(SD) albino rats (10/sex/dose) in the diet at nominal dose levels of 10, 40, 160, or 320 mg/kg/day (achieved doses: 0, 9.4, 37, 149, and 302 mg/kg/day for males; 0, 9.4, 38, 152, and 302 mg/kg/day for females) for 13 weeks.

Clinical signs observed during the study included alopecia in animals dosed at 160 and 320 mg/kg/day and appeared to be treatment-related. In each of these groups 2/10 males and 2/10 females had alopecia and thin fur; 1/10 males and 1/10 females from the control, 10 mg/kg/day and 40 mg/kg/day groups were also affected. Histological examination of the skin did not reveal any abnormalities in these animals. No rats died as a result of treatment.

Body weights and body weight gains were adversely affected by treatment throughout the study. Mean body weights at week 13, statistically , and biologically (> 10%), significantly decreased in 40 mg/kg/day males (11%) and 160 and 320 mg/kg/day males (25 and 39%, respectively) and females (17 and 27%, respectively). Total mean body weight gains were also decreased in 40 mg/kg/day males (17%) and 160 and 320 mg/kg/day males (41 and 69%, respectively) and females (38 and 57%, respectively).

Clinical pathology revealed treatment-related changes in hematology and clinical chemistry, but not in the urinalyses. Male and female rats were slightly anemic (decreased RBC count, hemoglobin and hematocrit) at 160 and 320 mg/kg/day. Increased cholesterol levels and blood urea nitrogen values and decreased glucose levels were noted in 160 and 320 mg/kg/day males and females, compared to the controls.

There were statistically significant increases in liver and thyroid weights with increasing dose. Statistically significant increases in absolute liver weights were observed at 160 mg/kg/day and higher in females and relative liver weights at 40 mg/kg/day in females and 160 mg/kg/day and higher in males and females. Statistically significant increases in absolute thyroid weights were observed in females dosed at 160 mg/kg/day and higher and relative thyroid weights in males and female rats dosed at 160 mg/kg/day and higher.

Histopathological examination revealed treatment-related changes in the liver, thyroid, bone marrow, spleen, and kidney. At 40, 160, and 320 mg/kg/day, centrilobular hypertrophy was observed in the livers of males (7/10, 9/10, and 9/10, respectively) and females (1/10, 9/10, and 9/10, respectively). At these same doses, follicular cell hypertrophy was observed in the thyroids of males (1/10, 2/10, and 6/10, respectively) and females (3/10, 10/10, and 10/10, respectively). Very slight erythroid hyperplasia was observed in the bone marrow of 5/10 females dosed at 40 mg/kg/day 8/10 females each from the 160 and 320 mg/kg/day dose groups; affected males included 4/10 at 160 mg/kg/day and 8/10 at 320 mg/kg/day. The spleens of 9/10 rats per sex were very slightly to slightly pigmented with hemoglobin at 320 mg/kg/day and 1/10 males and 3/10 females, at 160 mg/kg/day; 1/10 females dosed at 10 mg/kg/day were also affected.

Rats in the 10 mg/kg/day treatment groups exhibited no treatment-related responses.

No neoplastic changes were observed in rats in the treatment and control groups.

The LOAEL for this study is 40 mg/kg/day (37 mg/kg/day), based on reduced body weight gains and histopathological changes in the bone marrow, liver, and thyroid. The NOAEL is 10 mg/kg/day (9.4 mg/kg/day).

This 90-day subchronic toxicity study (dietary) is classified **acceptable (guideline)** and satisfies the Subdivision F guideline requirement for a subchronic toxicity study in rodents.

Dose and Endpoint for risk Assessment: The NOAEL is 9.4 mg/kg/day based on **reduced body weight gains and histopathological changes in the bone marrow, liver, and thyroid at 37 or/40 mg/kg/day (LOAEL).**

Comments about Study/Endpoint: A 21-day dermal toxicity study in rabbits is available. However, no effects were seen at the highest dose (1000 mg/kg/day). An oral value was selected because: 1) of the consistent pattern in the effect observed (i.e., decrease in body weight gain) in the chronic study at the same LOAEL (40 mg/kg/day); and, 2) the duration of this study is appropriate for this exposure period of concern (i.e., 7-days to several months). Since an oral NOAEL was selected , a dermal absorption factor of 60% should be used for this risk assessment.

The Risk Assessment is required.

4. LONG-TERM DERMAL (Several Months to Lifetime)

Study Selected: 2-Yr feed/chronic/Carcinogenicity **Guideline #:** §83-5a

MRID No.: 43593201.

Executive Summary: See - 3. Chronic Dietary (Reference Dose RfD) section

Dose and Endpoint for Risk Assessment: NOAEL = 10mg/kg/day based on decreased body weight gains and liver hypertrophy at 30 mg/kg/day (LOAEL).

Comments about Study/Endpoint: [Chronic dermal exposure to thiabendazole may be likely for some industrial preservative uses].

If there is no potential for chronic dermal exposure to thiabendazole, then this risk assessment is not required. However if there is a potential for dermal exposure, then the above dose/endpoint should be used. This dose/endpoint/study was used to establish the chronic RfD. Since an oral value was selected, 60% dermal absorption should be used.

This risk assessment is required.

5. INHALATION Exposure (ANY-TIME PERIOD)

Thiabendazole is non volatile at room temperature. There is no potential for acute and intermediate-term duration exposure. [However, chronic inhalation exposure to thiabendazole may be likely for some industrial preservative uses.]

Inhalation Exposure (Any Period)

Study Selected: 2-yr feed/chronic/carcinogenicity **Guideline #: 83-5**

MRID No.: 43593201

Executive Summary: See IB Chronic Dietary

Dose and Endpoint Proposed for Risk assessment: NOAEL = 10 mg/kg/day based on decreased body weight gains and liver hypertrophy at 30 mgm/kg/day (LOAEL)

There are no inhalation toxicity studies available. The acute inhalation studies are waived. Therefore, HIARC selected the oral values for inhalation risk assessment. Since the NOAEL selected for inhalation risk assessment are from oral studies, route to route extrapolation should be as follows:

Step I: The inhalation exposure component (i.e. *ug* a.i./day) using a 100% absorption rate (default value) and an application rate should be converted to an **equivalent oral dose** (mg/kg/day)

Step II: The dermal exposure component (i.e. mg/kg/day) using a 60% dermal absoprtion factor and an application rate should be converted to an **equivalent oral dose**. This dose should the be combined with the converted oral dose in Step I.

Step III: The combined dose from Step II should then be compared to the following oral NOAELS to calculate the MOE:
Short-term: 10 mg/kg/day–developmental rat
Intermediate: 10 mg/kg/day–14 week subchronic rat
Long-term: 10 mg/kg/day–2 year rat

This Risk Assessment is required only if there is potential long-term exposure.

D. Margin of Exposure (MOE): A MOE of 100 is adquate for occupational exposure. There are no residential uses. Residential risk assessment is not required.

E. Recommendation for Aggregate (Food, Water, Dermal, Inhalation) Exposure Risk Assessments. Since there are no residential uses, aggregate exposure risk asessments will be limited to food plus water. For actue and chronic aggregate risk, combine the hight end (for

acute) and average (for chronic) values for food and water and compare it to the respective RfDs.

III. CARCINOGENICITY SCREEN:

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Executive Summary In a combined chronic/oncogenicity study (MRID 43593201), thiabendazole (>98.9% a.i.) was administered to 50 Sprague-Dawley Crl:CD BR rats/sex/dose in the diet at dose levels of 0, 10, 30, or 90 mg/kg/day (achieved average doses of 0, 10.1, 30.2, or 91.8 mg/kg/day) for 104 weeks.

There were no treatment-related effects on survival, clinical signs, food consumption, ophthalmoscopic findings, urinalysis, or gross pathology. Body weights and body weight gains were generally lower (↓7-30%) throughout the study for the mid- and high-dose males and high-dose females. Reduced body weight gains (↓15, 28, and 19%, $p \leq 0.05$) for the mid- and high-dose males and high-dose females, respectively, compared to the controls were observed at week 103. A reduced body weight gain (↓10%, not statistically significant) was also noted at this time for the mid-dose females.

Significant increases (↑36-79%, $p \leq 0.05$) in total serum cholesterol observed in the high-dose group were judged to be treatment-related. In the high-dose males, increased (↑29%, $p \leq 0.05$) relative (to body) liver weights and an increased incidence of centrilobular hepatocellular hypertrophy (28/50 treated vs 0/50 controls) were also detected. Centrilobular hepatocellular hypertrophy was also observed in 7/50 mid-dose males. In the high-dose females, an increased (↑45%, $p \leq 0.05$) relative thyroid weights and increased incidences of thyroid focal cystic follicular cell hyperplasia (6/50 treated vs 2/50 controls) and diffuse follicular cell hypertrophy (2/50 treated vs 0/50 controls) were observed. Thyroid diffuse follicular cell hypertrophy was also observed (4/50 treated vs 0/50 controls) in the high-dose males.

The systemic LOAEL is 30 mg/kg/day based on reduced body weights and body weight gains and liver hypertrophy (males). The systemic NOAEL is 10 mg/kg/day.

An increase in benign thyroid follicular cell adenoma was observed in the mid-dose (5/50) and high-dose (6/50) males (vs 0/50 controls) and the high-dose females (5/50 treated vs 2/50 controls). The increase was statistically significant ($p \leq 0.05$) in the high-dose males. Also, in the male rats, there was a statistically significant trend ($p \leq 0.05$) in the incidence of thyroid follicular cell adenomas with increasing dose. No statistically significant trend in the incidence of any other neoplasm in either sex was observed. Thiabendazole may affect the rat thyroid indirectly by altering thyroxine clearance via increased hepatic metabolism. This mechanism is specific to the rat. The Sponsor has submitted for Agency review a 14 week thyroxin clearance study (MRID 43592302) in support of this hypothesis.

The study demonstrated that thiabendazole induces thyroid adenomas at dosages of ≥30

mg/kg/day.

Discussion of Tumor Data An increase in benign thyroid follicular cell adenoma was observed in the mid-dose (5/50) and high-dose (6/50) males (vs 0/50 controls) and the high-dose females (5/50 treated vs 2/50 controls). The increase was statistically significant ($p \leq 0.05$) in the high-dose males. Also, in the male rats, there was a statistically significant trend ($p \leq 0.05$) in the incidence of thyroid follicular cell adenomas with increasing dose. The incidences in mid and high dose males and high dose females were outside the historical control range for Sprague-Dawley rats in another study (1990-1991 data: Males: range 0-6.4%; Females: range 0-2%). No statistically significant trend in the incidence of any other neoplasm in either sex was observed. **There was evidence of carcinogenicity.**

Adequacy of the Dose Levels Tested Adequate dosages of Thiabendazole were tested since endpoints of reduced body weights and body weight gains and liver hypertrophy were seen in this study.

2. Carcinogenicity Study in Mice

Executive Summary In a 105-week carcinogenicity toxicity study (Accession No. 242116), Thiabendazole, 98.5% a.i. was administered to 50 mice (Charles River CD-1)/sex /dose in diet at dose levels of 0, 5.6-8.3, 31-42, 63-121, 184-372 mg/kg/day for males and 0, 5.7-9.9, 94-131, 209-368, and 534-1005 mg/kg/day for females.

There was an increase in mortality in all dose groups. Body weight gains were significantly lower in high dose females (28%)and males (18%). There was an increase in the absolute liver weight of high-dose females, and an increase in the relative liver weight in mid-dose females and high-dose males and females. There was an increase in the relative liver: brain weight ratio in high-dose males and females.

The LOAEL for systemic toxicity is 209-368 mg/kg/day for females and 63-121 mg/kg/day for males, based on decreased body weight gains and increased liver weights. The NOAEL is 5.7-9.9 mg/kg/day for females and 5.6-8.3 mg/kg/day for males.

This study is unacceptable due to variation in sample times of mice and not enough survivors to assess the oncogenetic effects of Thiabendazole. This study does not satisfy the guideline requirement for a carcinogenicity study (83-5) in mice.

At the doses tested, there was no treatment related increase in tumor incidence when compared to controls in this strain of mice. Adequacy of dosing could not be determined due to increased mortality at all dose levels (18-36%).

Discussion of Tumor Data: **There was no evidence of carcinogenicity.**

Adequacy of the Dose Levels Tested: Adequacy of dosing could not be determined due to

increased mortality at all dose levels (18-36%).

IV. MUTAGENICITY

Several mutagenicity studies have been submitted. All studies indicate that thiabendazole is not a mutagen. The following table summarizes the mutagenicity database.

Mutagenicity Profile for Thiabendazole

Guideline #	TYPE OF STUDY SUBMITTED	MRID No(s)	Comments (NOAEL/LOAEL)	Classification
84-2	Chromosome aberration assay	00098002	In vivo cytogenetic assay: The test was negative in Wistar rats admnistered single doses of 10-1000 mg/kg by oral gvage or 30-300mg/kg once daily for 5 consectuvie days. Lethality was seen in the high-dose group but there was no evidence of bone marrow cytotoxicity.	Acceptable/ Guideline
84-2	Mutagenic -Ames	42361801	Five doses of thiabendazole ranging from 100ug/plate to 6000 ug/plate +/-S9, did not induce mutations in Salmonella typhimurium strains TA 1535, TA97A, TA98, or TA100 and Escherichia soli strains WP2, WP2 UvrA, or WP2 uvrA pKM101. Compound precipitation and cytotoxicity for the majority of strains was observed at levels ≥ 1000 ug/plate +/-S9. Similar results were obtained in a repeat assay conducted in three strains (S.typhimurium TA 97Aand E.coli WP2 uvrA and WP2 uvrA pKM101) with a lower dose range (3-300 ug/plate +/-S9). Based on these findings, it was concluded that thiabendazole was tested over an appropriate range of concentrations and was not genotoxic.	Acceptable/ Guideline
84-2	Mutagenicity / DNA damage/repair	41170103	In a DNA damage/repair assay, the test material was first assayed in a cytotoxicity test (MRID No. 41170103) employing trypan blue exclusion as a measure of cell viability in cultures exposed for 3 hours at concentrations up to precipitating levels (ca. 1.3 mM) in culture medium (Leibowitz, L-15). Concentrations selected for testing in the main assay were 0.3, 0.7, 1.0, and 1.3 mM, applied for 3 hours to duplicate monolayer cultures of hepatocytes, following which cells were gently scraped from culture dishes and suspended in fresh medium. Cell viability was determined from a small aliquot, and the remainder lysed and fractionated under tetrapropyl ammonium hydroxide, then eluted for fluorometric determinations of DNA according to conventional (published) procedures. Aflatoxin B1 (AFL, 1 uM) in DMSO served as the positive control. Data from these fractions were transformed into elution slopes, which were then compared to known standards, according to the following criteria for defining positive results. At none of the concentrations tested (0.3 to 1.3 mM) did the test material produce a significant (at least threefold) increase in elution slope relative to concurrent negative control. By contrast, the positive control, AFL produced a twentyfold increase, indicating that the cells were responding to a known strand-breaking mutagen. **Based on these results the author concluded that thiabendazole did not induce DNA strand breakage in primary rat hepatocytes exposed to concentrations up to the level of its insolubility in culture medium.**	Acceptable/ Guideline

V. FQPA CONSIDERATIONS

1. Adequacy of the Data Base

The requirement for an acute neurotoxicity study is inapplicable. Developmental toxicity studies in rat, mice, and rabbits and a reproductive toxicosis study in rabbits with thiabendazole have been submitted and were classified as acceptable.

2. Neurotoxicity

The requirement for an acute neurotoxicity study is considered inapplicable by the Agency. The literature search did not produce any neurotoxicity studies. There was little weight of evidence for requiring a delayed neurotoxicosis study. In the prenatal developmental rat study (MRID 42942803), ptosis was seen in 3/25 rats. There were no neurological signs in any of the other studies with this chemical with the exception of the acute oral toxicity study (1981). In the acute oral toxicity study, the majority of deaths occurred within 24 hours of treatment. Animals were dosed by gavage and received 2222, 3333, 5000, 7500, and 11,250 mg/kg. Pre-death clinical signs included: decreased activity, bradypnea, ptosis, alopecia, loss of righting reflex. The HIARC noted that there was no neuropathology reported in any of the studies and voted not to require the delayed neurotoxicity study.

3. Developmental & Reproductive Toxicity

(i) Developmental Toxicity: There is no evidence for increased susceptibility of rat, rabbit, or mouse fetuses to *in utero* exposure in developmental studies. The effects observed in these species occurred at maternally toxic doses.

In the rat developmental study, there were significant decreases in maternal mean body weights and feed consumption noted at 40 and 80 mg/kg/day. Ptosis was present in 3/25 animals at 80 mg/kg/day. The female fetal body weights were decreased at $\geq$ 40 mg/kg/day and in males at 80 mg/kg/day. Therefore, the rat maternal and developmental LOAEL/NOAEL are 40/10 mg/kg/day.

In the mouse prenatal developmental toxicity study, there were reductions in maternal body weight at mid (100 mg/kg/day) and high dose (200 mg/kg/day)dose treatment groups. There were accompanying reductions in feed consumption in the HDT group. There was decreased fetal body weight at 100 mg/kg/day for both sexes. The mouse maternal and developmental LOAEL/NOAEL are 100/25 mg/kg/day.

In the rabbit developmental study, decreased maternal body weight gains and decreased food consumption were seen in the HDT (600 mg/kg/day). There was decreased fetal body weight and increased resorptions at 600 mg/kg/day. The rabbit maternal and developmental LOAEL/NOAEL are 600/150 mg/kg/day.

(ii) Reproductive Toxicity: In the two generation reproduction study, the parental

systemic LOAEL is based on decreased body weight gain and food consumption seen at 30 mg/kg/day. The NOAEL is 10 mg/kg/day. The offspspring LOAEL is based on decreased body weight gain in offspring during lactation seen at 30 mg/kg/day. The NOAEL is 10 mg/kg/day. The reproductive LOAEL is > 90 mg/kg/day. The effects in the offspring were observed at higher dosages (90 mg/kg/day) than dosages (30 mg/kg/day) causing parental toxicity. Therefore, there was no increased susceptibility.

The benzimidazole compounds such as parbendazole, cambendazole and mebendazole posssess tertogenic and embryotoxic properties. The studies in the published literature indicate that thiabendazole can cause developmental effects after single in utero exposure of pregnant animals at high doses. However, these studies do not suggest that fetuses are selectively susceptible following in utero exposure to thiabendazole. These studies are summarized below.

1). In a teratogenicity study in rats (Khera et al., 1979), thiabendazole administered to dams from GD 6-15 at doses ranging from 125 to 500 mg/kg/day produced increased incidence of anomalous fetuses at the highest dose (500 mg/kg/day) level. No details on maternal effects were reported.

2). The developmental toxicity of thiabendazole (TBZ) was assessed in Sprague-Dawley rats and New Zealand (NZB) rabbits (Lankas and Wise, 1993). Rats received TBZ at 10, 40, or 80 mg/kg/day and rabbits received TBZ orally at doses ranging from 24 to 600 mg/kg/day (in two studies) as an aqueous suspensions on GD 6-17.

TBZ produced decreased maternal body weight gain (12 to 26%) and decreases in fetal body weights (5-7%) at doses of 30 and 80 mg/kg/day. NOAEL was 10 mg/kg/day and no teratogenic effects were noted.

In rabbits, decreased maternal weight gain and decreased fetal weights were noted at 600 mg/kg/day, but there was no evidence of developmental anomalies. The NOAEL was 120 mg/kg/day.

3). Thiabendazole was administered orally in olive oil (Ogata et al., 1984) to pregnant Jcl:ICR mice at doses of 700, 1300 or 2400 mg/kg/day TBZ on GD 7-15. No maternal effects were reported in this study. A dose-dependent external and skeletal anomalies, especially cleft palate (although in a non-dose related manner) and fusion of vertebrae, were observed. In mice given single dose of 2400 mg/kg/ TBZ on any one of the GD 6-13, an increased number of malformations were observed. Various malformations occurred, especially in the mice treated on GD 9. Groups of mice given one of the 17 doses (30-2400 mg/kg) on GD 9, the number of litters with fetuses having shortened limbs and fetuses with skeletal fusion increased in a dose-related manner. Based on these findings FAO/WHO recommended that the acceptable daily intake (ADI) of TBZ should be 0.05 mg/kg.

4). In a 2-Generation reproduction study(Wise et al., 1994), Sprague-Dawley rats received TBZ at dietary doses of 10, 30 or 90 mg/kg/day during premating, gestation and lactation. The parental toxicity was seen at ≥30 mg/kg/day based on decreased

body weight gain (37-46%) and food consumption (3-16%) . The NOAEL was 10 mg/kg/day. Decrease in pup body weight (5-10%) was noted between postnatal days 4 and 21. The NOAEL was 10 mg/kg/day. Thus, no selective sensitivity to TBZ was noted in pups.

4. Determination of Susceptibility

The data submitted to the Agency as well as those from the published literature demonstrate no increased sensitivity of rats, mice, or rabbits to in utero or early postnatal exposure to thiabendazole with one exception in the published literature that shows cleft palate formation in fetuses following thiabendazole admnistration to mothers (Ogata et al. , 1986). The developmental effects in fetuses or neonates occurred at or above doses that caused maternal or parental toxicity.

There was concern over fetal susceptability in developmental studies conducted with thiabendazole. In the rabbit developmental study conducted by Argus Laboratory, (MRID No.42993602), both the maternal and fetal NOAELS were 24 mg/kg/day. The question was whether the hydrocephaly seen at 120 mg/kg/day (1) and 600 mg/kg/day (2) indicated increased susceptibility. The one case at 120 mg/kg/day was within historical control. The 600 mg/kg/day group of rabbits was mistakenly overdosed with 840 mg/kg/day, and there was maternal death within this group. It was therefore decided not to apply the FQPA susceptibility factor here (See Susan Makris memo from 06/02/99).

5. Determination of the Need for Developmental Neurotoxicity Study

There was other no evidence in the data base that would support a requirement for a developmental neurotoxicity study with thiabendazole.

6. Determination of the FQPA Factor:

Based on hazard alone, the HIARC recommended that a factor of 10 be removed since there is no evidence of increased fetal susceptibility in the mice, rat, and rabbit developmental studies. However, the final recommendation will be made by the FQPA Safety Factor Committee.

VI. ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of Thiabendazole

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	41258201	LD_{50} = 4735 mg/kg	III
81-2	Acute Dermal	41258202	LD_{50} = >2000 mg/kg	III
81-3	Acute Inhalation	Waived	HED Doc. No. 010140	
81-4	Primary Eye Irritation	40789806	Non-irritating	IV
81-5	Primary Skin Irritation	40789807	Non-irritating	IV
81-6	Dermal Sensitization	40271701	Non-sensitizer	IV
81-8	Acute Neurotoxicity	Waived	HED Doc. No. 006934	

VI. HAZARD CHARACTERIZATION

Thiabendazole has a low acute oral toxicity (Category III) to rats [LD50 = 4735 mg/kg/day (M+F), and a low dermal toxicity (Category III) [LD50 = >2000 mg/kg/day] (M+F) . The acute inhalation study was waived because the only product registered for use in the U.S. is thiabendazole hypophoshite salt (20% a.i.), and it has little opportunity for vaporization or aerolization. Therefore, there is a negligible risk of inhalation exposure to vapor or aerosol during use. In primary eye and primary skin irritation studies, thiabendazole was found to be non-irritating. Thiabendazole is not a dermal sensitizer. In the rat, death and clinical signs of toxicity were observed at high dosages. There was an increased incidence of clinical signs with increasing dosage and duration. No effects were observed in the structural neuropathological (gross and histopathology) measurements. Death was reported at dosages ≥ 2222 mg/kg after a single dosage (Acute Oral Study, MRID 41258201) in males and females.

The thyroid and liver are the primary target organs of thiabendazole. In the rat dietary subchronic study (MRID 42942802), there were absolute increases in liver and thyroid weights at ≥160 mg/kg/day in females. Relative liver weights were increased at ≥40 mg/kg/day in females and ≥160 mg/kg/day in males. Absolute thyroid weights were increased in females at ≥160 mg/kg/day and relative thyroid weights in males and females at ≥160 mg/kg/day. Histologically, hepatic centrilobular hypertrophy and thyroid follicular cell hypertrophy of males and females were observed at ≥40 mg/kg/day.

In the rat gavage subchronic study (MRID 42942801), there was hepatic centrilobular hypertrophy in males and females at ≥100 mg/kg/day, increased absolute liver weight in females ≥100 mg/kg/day and in males at 400 mg/kg/day. Relative liver weight was increased in males and females at ≥100 mg/kg/day. There was follicular cell hyperplasia in males and females at ≥100 mg/kg/day. Relative thyroid weight was increased in males and females at ≥100 mg/kg/day. Absolute thyroid weight was increased at 400 mg/kg/day.

The rat carcinogenicity study incidated that thiabendazole produced a marginally statistically significant increase in thyroid adenomas. The CARC met on May 26, 1999, and concluded that thiabendazole is a likely carcinogen. In the mouse oncogenicity study, there were decreases in body weights of HDT mice, increases in the absolute liver weight of HDT females and increases in the relative liver weight in MDT females and HDT males and females. There were increases in the relative liver:brain weight ratio in HDT males and females. There were variations in sacrifice times of different groups and variable dosages of thiabendazole were used; therefore this study was unacceptable.
The chronic dog study indicated that thiabendazole produced a treatment-related increase in absolute and relative liver weights in both sexes. In HDT animals, the absolute and relative thyroid weights were increased. On histopathology there was bile duct vacuolization in the MDT and HDT males and females. There was thyroid follicular enlargement in males and females at HDT. There were increases in spleenic erythropoiesis and hemosiderosis in the MDT and HDT males and females.

VII. DATA GAPS

There is no acceptable mouse oncogenicity study. The mouse data gap was confirmed by CARC on May 26, 1999. The available genotoxicity studies although acceptable are inadequate to fulfill the guideline requirements. A data gap exists for two *in vitro* studies namely, *in vitro* mammalian gene mutation and *in vitro* chromosome aberration assay. Requirements for a 90-day inhalation and acute delayed neurotoxicity studies were waived by HED in 1993 (HED Doc. No. 010140) and 1988 (HED Doc. No. 006934) respectively.

IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The dosages and toxicological endpoints proposed for various exposure scenarios are summarized below.

There are sufficient data for selecting acute and chronic dietary endpoints:

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (females 13+)	NOAEL=10 mg/kg/day UF = 100	Decreased fetal body weight (females 13+)	Developmental Study–Rat
Acute Dietary (general population)	NOAEL=10 mg/kg/day UF = 100	Decreased maternal body weight seen during gestation (general population)	Developmental Study–Rat
	Acute RfD = 0.1 mg/kg (General Population) Acute RfD for Females 13+ = 0.1 mg/kg		
Chronic Dietary	NOAEL=10 mg/kg/day UF = 100	Based on decreased body weight gains and liver hypertrophy	2-Year Feed/chronic/carcinogenicity
		Chronic RfD = 0.1mg/kg/day	
Short-Term (Dermal)	NOAEL=10 mg/kg/day	Based on decreased fetal body weights	Oral Developmental Toxicity–Rat
Intermediate-term (Dermal)	NOAEL=10 mg/kg/day	Based on reduced body weight gains and histopathological changes in the bone marrow, liver, and thyroid	Fourteen Week Oral Toxicity (Feeding) Study
Long-Term (Dermal)	NOAEL=10 mg/kg/day	Based on decreased body weight gains and liver hypertrophy	2-Yr feed/chronic/Carcinogenicity
Short Term Inhalation	Waived		
Long Term Inhalation	NOAEL=10 mg/kg/day	Based on increased liver weight, splenic erythropoiesis, and hemosiderosis	53-Week chronic dog

References

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