THIABENDAZOLE

RISK CHARACTERIZATION DOCUMENT

Medical Toxicology and Worker Health and Safety Branches

Department of Pesticide Regulation

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I. SUMMARY

Thiabendazole [2-(4-thiazolyl)benzimidazole, trade names Apl-Luster® or RPH®] is used as a fungicide to control molds and rot. Thiabendazole is used in post harvest treatments as a dip or spray, as a wettable powder, or as a dry flowable. Approximately 15,861 lbs of thiabendazole were sold in California in 1997.

Environmental fate- Thiabendazole does not hydrolyze readily, nor is it metabolized in soil under aerobic or anaerobic conditions. In aqueous solutions, thiabendazole photodecomposes in minutes. However, in soil, photodecomposition did not cause more than a 40% reduction in thiabendazole. The compound is only slightly water soluble, and does not migrate in the soil.

Pharmacokinetics- Approximately 87% of an absorbed oral dose in humans was excreted in the urine (84% in the first 24 hours), 7% in the feces over the course of 5 days. Thus, humans appeared to absorb at least 87% of a single oral dose of thiabendazole. Similarly in rats, 70% of an absorbed oral dose was excreted in the urine, virtually all within 24 hours. The principal urinary metabolites (69-79%) were 5-hydroxythiabendazole as the sulfate and the glucuronide. Thiabendazole did not concentrate in the tissues of cattle, goats, pigs or sheep, and virtually all of the administered doses were excreted in the first 24 hours, principally in the urine.

Acute toxicity- Formulations of thiabendazole concentrate (60% thiabendazole) have an oral LD_{50} in rats of 5 g/kg, and 7.4 g/kg in mice. The 50% concentrate had an oral LD50 in rats of 13.5 g/kg. The 25% wettable powder had an oral LD_{50} in rats of 12.62 g/kg, a dermal LD_{50} in rabbits greater than 4 g/kg, and an inhalation LC_{50} in rats greater than 145 mg/L. The 1-day lowest observed effect level (LOEL) for clinical signs in humans was 25 mg/kg. The 1-day no observed effect level (NOEL) for clinical signs and blood chemistry changes in humans was 3.3 mg/kg-day.

Thiabendizole did not cause dermal sensitization in the guinea pig, and it did not cause dermal irritation in rabbits. No data were available on dermal absorption; therefore dermal absorption was assumed to be 100%.

Subchronic Toxicity- The principal target organs of thiabendazole in short term, repetitive dosing studies were the liver, the kidney, and the thyroid. The 98-day oral gavage NOEL in rats for hepatotoxicity and changes in hematology was 25 mg/kg-day. In a 14 week dietary study, the NOEL for hepatotoxicity and thyrotoxicity in rats was 10 mg/kg-day. The NOEL for emesis in dogs was 35 mg/kg-day in a 90 day study. Thiabendazole caused histopathological changes in the liver and kidneys of mice, and reduced several blood parameters.

Chronic Toxicity/Oncogenicity- The principal effects of chronic exposure to thiabendazole were thyroid toxicity, hepato/biliary toxicity, anemia and atrial thrombosis. In dogs, the NOEL for hepatotoxicity (inflammatory liver changes, depletion of liver glycogen, hemosiderosis), and histopathological changes in the urogenital tract was 10 mg/kg-day. In rats, the LOEL for mild anemia (reduced hemoglobin) was 100 mg/kg-day, with a NOEL of 50 mg/kg-day. The NOEL for adaptive liver response (centrilobular hypertrophy) in rats was 10 mg/kg-day. Male mice exhibited atrial thrombosis at 278 mg/kg-day, with a NOEL of 92 mg/kg-day. There was a significant, dose-related increase in thyroid follicular cell adenomas in male Sprague-Dawley rats. Thiabendazole was not oncogenic in mice.

Genotoxicity- Genotoxic potential for thiabendazole has been demonstated in laboratory studies. Thiabendazole was tested for mutagenicity in *Salmonella typhimurium*; for DNA damage in primary rat hepatocytes and human embyro fibroblasts *in vitro*; and for chromosomal effects. Three submitted studies, with detailed information, using various *Salmonella* strains, including TA98, did not report mutations. However, positive results were reportedly obtained in *Salmonella* strains TA98 and TA99 in a study published in summary form. In the absence of data from this study, it was not possible to evaluate the mutagenic potential of thiabendazole. Thiabendazole caused micronuclei formation *in vivo* in CFW mice, sister chromatid exchange *in vivo* in male mice, mouse ovarian hyperploidy *in vitro*, and chromosomal bridges in chinese hamster ovarian cells *in vitro*. These genotoxic effects involved spindle disruption, which is consistent with thiabendazole's known ability to disrupt tubulin assembly.

Reproductive Toxicity- The reproductive NOEL for mice was approximately 150 mg/kg-day, based on reduced numbers of mice born and weaned per litter, as well as reduced weanling weight. The NOEL for reduced pup weights in rats was 30 mg/kg-day. The NOEL for a significant decrement in parental rat weight gain was 10 mg/kg-day.

Developmental Toxicity- Thiabendazole caused major malformations of the skeletal system in mice, rabbits, and rats. The Estimated No Effect Level (ENEL) for mice was 26 mg/kg-day, based on skeletal abnormalities. The NOEL for developmental toxicity in rabbits was 24 mg/kg-day based on fetal resorption and hydrocephaly. The maternal NOEL in rabbits was 120 mg/kg based on decrement in food consumption and body weight gain. In the rat gavage study, the NOEL for decreased maternal food consumption was 10 mg/kg. The NOEL for decrement in fetal weight in the same study was 10 mg/kg. However, in two studies in which pregnant rats were exposed to thiabendazole in the diet, increased skeletal variations were noted. In addition to these variations, there was a significant increase in major malformations of the skeletal system, including cleft palates and the absence of the *os hyoideus*.

Hazard Identification- A 1-day, oral, human NOEL for clinical signs, 3.3 mg/kg, was used to assess the margins of exposure for potential acute exposures to thiabendazole. Repetitive dosing with thiabendazole caused thyrotoxicity, hepato/biliary toxicity, nephrotoxicity, anemia and atrial thrombosis in laboratory animals. The critical NOEL for hepato/biliary toxicity in dogs and centrilobular hypertrophy in rats, 10 mg/kg-day, was used for the assessment of both oncogenic and non-oncogenic risk from potential chronic exposure to thiabendazole.

Dietary Exposure- Based on the 95th percentile of user-days exposures for all specific population subgroups, the potential daily dietary exposure of thiabendazole from all labeled uses ranged from 27 to 81 µg/kg-day. Children, one to six years of age had the highest potential daily dietary exposure to thiabendazole. Potential mean daily dietary exposure for all population subgroups ranged from 1.3 to 4.5 µg/kg-day. Children, one to six years of age had the highest potential annual dietary exposure to thiabendazole.

Occupational Exposure- The estimated, arithmetic mean, absorbed daily dosages for occupational exposure to thiabendazole derived from surrogate data ranged from 15.8 µg/kg-day for packers of citrus fruit to 152.3 µg/kg-day for interior painters using a brush application. The 95% confidence limit on the average daily dosage (arithmetic mean plus two standard deviations) ranged from 20.7 µg/kg-day for mixer/loader/applicators working with mushrooms to 209 µg/kg-day for sorters of citrus fruit. The average annual daily dosage for occupational

exposures ranged from 5.9 µg/kg-day for mixer/loader/applicators working with mushrooms to 65.6 µg/kg-day for sorters of pears.

The potential combined daily exposure to thiabendazole ranged from 45 µg/kg-day for packers of citrus produce, to 181 µg/kg-day for interior painters using a brush application. Under annual exposure conditions the mean potential combined exposures ranged from 8 µg/kg-day (mixer/loader/applicators for mushrooms) to 67 µg/kg-day (pear sorters).

Risk Characterization- The margins of exposure for mean, potential, daily exposure, based on a critical acute NOEL of 3.3 mg/kg-day for clinical signs, ranged from 22 for interior painters using a brush to 209 for packers of citrus fruit. Considering the 95% confidence limit (arithmetic mean plus two standard deviations) on exposure for each work task, the MOEs ranged from 16, for sorters working with citrus, to 159 for mixer/loader/applicators working with mushrooms. MOEs for annual occupational exposure to thiabendazole, based on a critical chronic NOEL of 10 mg/kg-day for hepato/biliary toxicity in dogs, and centrilobular hypertrophy in rats, ranged from 152 for sorters of pears to 1,695 for mixer/loader/applicators working with mushrooms.

The MOEs for potential daily dietary exposure to thiabendazole, based on an acute NOEL of 3.3 mg/kg for clinical signs in humans, ranged from 41 for children (1-6 yrs) to 123 for females (13-19 yrs/not pregnant/ not nursing). The MOEs for annual dietary risk from the annualized daily dosage of thiabendazole, based on a critical chronic NOEL of 10 mg/kg-day for hepato/biliary toxicity in dogs, and centrilobular hypertrophy in rats, ranged from 2,200 for children (1-6 yrs) to 7,700 for males (13-19 yrs).

MOEs for potential combined daily exposure to thiabendazole ranged from 18 for interior painters using a brush application, to 73 for packers of citrus produce. MOEs for potential combined annual exposure ranged from 149 for pear sorters, to 1,300 for mixer/loader/applicators working with mushrooms.

Conclusions- Margins of exposure for potential daily and annual exposures to workers associated with handling and application of thiabendazole, and to the general public exposed via dietary consumption were greater than the values conventionally recommended to protect people from the toxic effects of a chemical.

The USEPA tolerance for thiabendazole on apples does not provide a margin of exposure greater than the value conventionally recommended to protect people from the toxic effects of a chemical for theoretical daily dietary exposure to one or more population subgroups if commodities are consumed with residues at the tolerance level. Thiabendazole has adverse pre-natal effects and causes disruption of endocrine levels associated with body metabolism; effects which should be taken into consideration when USEPA reviews the tolerance levels under the Food Quality Protection Act.

II. INTRODUCTION

A. CHEMICAL IDENTIFICATION

Thiabendazole [2-(4-thiazolyl)benzimidazole] is a systemic fungicide which translocates through the cuticle and across leaves. The mechanism of action appears to be through the induction of abnormalities in spore germination, cellular multiplication and growth as a result of interference in tubulin formation (Davidse and Flach, 1978). Originally, thiabendazole was developed as an anthelminthic for treating round worm infestations in humans and livestock.

B. REGULATORY HISTORY

The USEPA has not developed a lifetime oral Reference Dose (RfD) for thiabendazole due to a lack of data (USEPA, 1997a). The World Health Organization RfD is 0.3 mg/kg-day (USEPA, 1997a).

C. TECHNICAL AND PRODUCT FORMULATIONS

Thiabendazole was introduced by Merck Chemical Co. in 1964 as an anthelminthic, and it later gained use as a fungicide. There are currently 24 products registered in California which incorporate thiabendazole, and one product which incorporates its salt. Thiabendazole is used in post harvest treatments as a dip or spray (0.1% - 50% a.i.), as a wettable powder (1.5% - 98.5% a.i.), gel paste (50% a.i.) or as a dry flowable (0.5% - 1.5% a.i.). Formulations may contain thiabendazole alone, or in combination with other fungicides such as captan, thiram, and PCNB.

D. USAGE

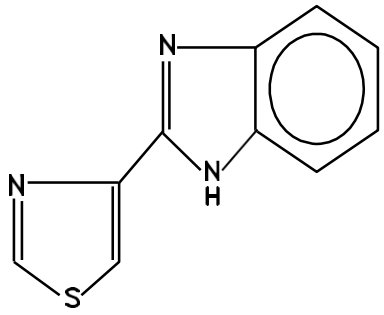
Thiabendazole is used as a fungicide to control green mold, blue mold, and stem end rot on citrus fruits. It controls Cercospora leaf spot on sugar beets; crown rot on bananas; blue mold rot, bully eye rot, and gray mold on apples and pears; black rot, scurf and foot rot on sweet potatoes; and to control Fusarium (dry rot) in potato storage. It can be used on soybeans to reduce the severity of pod and stem blight such as anthracnose, brown spot, frog-eye leaf spot and purple stain. Approximately 15,861 lbs of thiabendazole were sold in California in 1997 (DPR, 1998). The amount sold in California has not varied significantly over the past five years.

E. ILLNESS REPORTS

Thiabendazole has been associated with 22 illness reports in pesticidal use between 1984 and 1998 (Mehler, 2000). However, in only three instances was thiabendazole the indisputable, causal pesticide. All of the incidents involved the development of dermatitis, conjunctivitis, or rashes. The irritations occurred principally as a result of touching unprotected skin with contaminated gloves, from the pesticide passing through cotton gloves, or accidental direct spraying.

F. PHYSICAL AND CHEMICAL PROPERTIES*

Chemical Name:	2-(4-thiazolyl)benzimidazole
Common Name:	thiabendazole
Empirical Formula:	$C_{10}H_7N_3S$
Chemical Structure:	



Molecular Weight:	201.25
Melting Point:	299.4-300.6°C
Henry's Law Constant:	2.12x 10^{-11} atm m^3*mol^{-1} @25°C
Vapor Pressure:	4E-9 mmHg @25°C
Solubility (25°C):	<0.05 mg/ml @ 25°C
Octanol/Water Partition Coefficient	240

* (Mallinckrodt, 1969)

G. ENVIRONMENTAL FATE

Summary. Thiabendazole does not hydrolyze readily, nor is it metabolized in soil under aerobic or anaerobic conditions. In aqueous solutions the photolytic half-life for thiabendazole was approximately 24 minutes. The primary photolytic degradation products were benzimidazole, benzimidazole-2-carboxamide, 5-hydroxy thiabendazole, and benzimadazole-2-carboxylic acid. On dry surfaces, photolysis did not cause more than a 40% reduction in thiabendazole. The compound is only slightly water soluble, and does not migrate in the soil. Consequently, thiabendazole is unlikely to contaminate ground water.

Hydrolysis

The rate of degradation of thiabendazole was monitored at three incubation temperatures (20, 35, and 45°C), three pH levels (3, 6, and 9) and two concentrations (1 or 10 ppm) in duplicate (WARF, no date-a). The samples were maintained at constant temperature in the dark for up to 35 days. Thiabendazole was hydrolytically stable under these conditions.

Photolysis

Photolytic degradation of ^{14}C-thiabendazole in aqueous solution was studied with or without photoactivator (2% acetone) under incident light (300 nm) with an intensity of 1.1 E+17 quanta/sec (WARF, no date-b). The half-life in deionized water was 23.9 minutes, and with acetone, 5 minutes. The primary degradation products were benzimidazole, benzimidazole-2-carboxamide, 5-hydroxy thiabendazole, and benzimadazole-2-carboxylic acid. The study was considered unacceptable to DPR because the temperature was not given, the intensity of the artificial light was not related to sunlight, and the photoproducts were not quantified as a function of time.

^{14}C-Thiabendazole breakdown in sunlight was studied on sugar beet plants and glass plates (Jacob *et al.*, 1975). After 14 days exposure to sunlight on beet plants, only 78% of the labeled thiabendazole could be recovered. Nearly 60% of labeled thiabendazole survived 128 days exposure to sunlight on glass plates. The study was not acceptable to DPR because it did not follow USEPA guidelines.

Aerobic and Anaerobic Soil Metabolism

The persistence of thiabendazole in soil samples incubated at 25°C in small glass vials was examined (Aharonson and Kafkafi, 1975). Nine months after adsorption of this fungicide to the soil, 85-95% of the applied thiabendazole was recovered from air dried soils. In moist soil, only 75-90% of the applied thiabendazole could be recovered after 9 months incubation.

Thiabendazole was not metabolized in six different soils under aerobic or anaerobic conditions for 60 days (WARF, no date-e). The study was unacceptable to DPR because metabolite concentrations as a function of time were not identified; no material balance was given; no residue formation or degradation curves were given for the metabolites; and soil data were pooled rather than reported individually.

Soil Mobility

Radiolabeled thiabendazole was not leached from columns of soil (Elburn sandy loam, Plainfield sand, Plano silt loam, Kewaunee clay, Kidder sandy clay loam) when eluted rapidly or slowly with water (WARF, no date-c). Freundlich constants were determined for thiabendazole in rice paddy soils from Louisiana and California to be 490 and 700, respectively (Raltech, 1979). Radiolabeled thiabendazole found in soil 30 days after foliar application to soybeans or enrichment of soils directly was never deeper than 6 inches, and less than 3 inches in depth in most instances (WARF, no date-d).

III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

Summary- Approximately 87% of an administered oral dose in humans was excreted in the urine (84% in the first 24 hours), 7% in the feces over the course of 5 days. Thus, humans appeared to absorb at least 87% of a single oral dose of thiabendazole. Similarly in rats, 70% of an absorbed oral dose was excreted in the urine, virtually all within 24 hours. The principal urinary metabolites (69-79%) were 5-hydroxythiabendazole as the sulfate and the glucuronide. Thiabendazole did not concentrate in the tissues of cattle, goats, pigs or sheep, and virtually all of the administered doses were excreted in the first 24 hours, principally in the urine.

Oral- Sheep

Within four days after oral administration of ^{14}C- or ^{35}S-thiabendazole (50 mg/kg) to sheep, 75% of the radiolabel was excreted in the urine and 14% was excreted in the feces (Tocco *et al*., 1964). Radiolabel was distributed through most tissues of the body. The major metabolite isolated from the urine was 5-hydroxythiabendazole, either free or conjugated as the glucuronide or sulfate.

Oral- Cow, Goat, Pig

Cattle, goats, and swine were administered oral dosages of ^{14}C- or ^{35}S-thiabendazole (50-200 mg/kg) (Tocco *et al*., 1966b). Ninety percent of the radioactivity was excreted within 24 hours by each of the species. An average of 56, 66, and 65% of the radiolabel were excreted by 96 hours in the urine of cattle, goats, and swine, respectively. Less than 2% of the radiolabel in the urine was thiabendazole; 70-90% was in the form of 5-hydroxylated thiabendazole, either free or conjugated as the glucuronide or sulfate. The radiolabel did not concentrate in any of the body tissues.

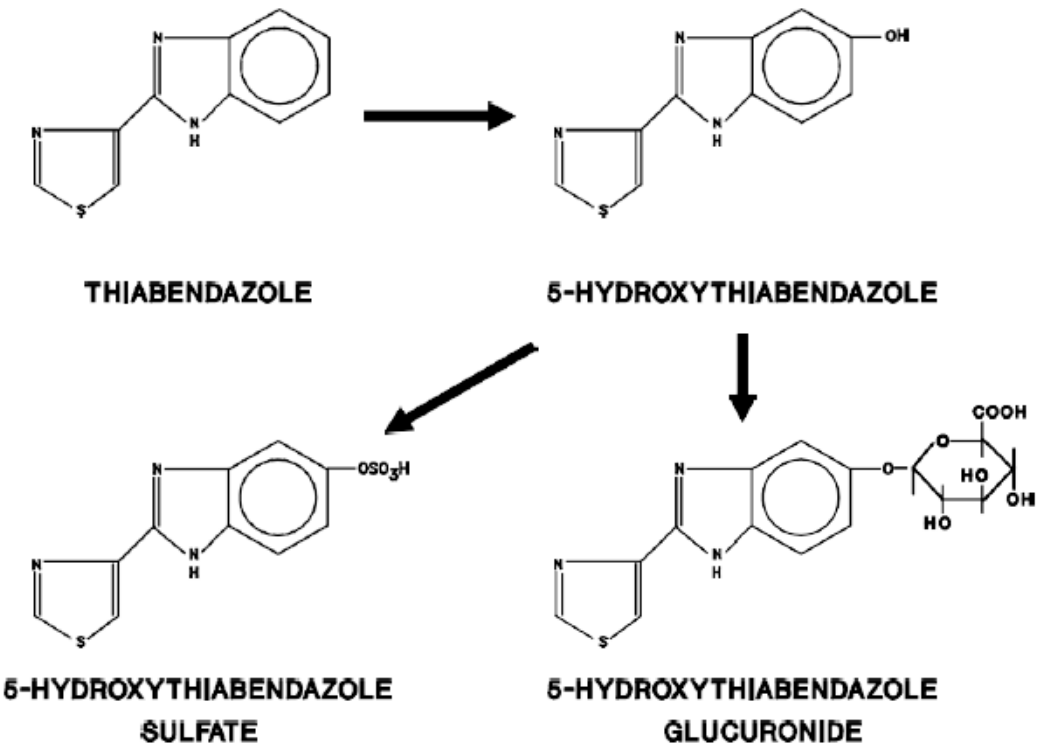
Oral- Human

Four male, human volunteers weighing 66-89 kg were given a single oral dose of 1 g ^{14}C-thiabendazole (Tocco *et al*., 1966a). Peak plasma concentrations were found about 1 hour after treatment. An average of 84% of radiolabel was excreted in the urine within 24 hours. Over the five days of collection, an average of 87% of the administered radiolabel was recovered in the urine. Glucuronide and sulfate esters of 5-hydroxythiabendazole comprised approximately 50% of the radiolabel recovered in the urine. Only an average of 7% of the thiabendazole was excreted in the feces during the 5 day observation period. Approximately 94% of the administered radiolabel was recovered in the urine and feces.

Oral- Rat

Charles River rats were given oral dosages of ^{14}C-thiabendazole ranging from 25.8 to 418 mg/kg (Craine, 1990). Only 0.01% of the administered radiolabel was exhaled through the lungs. At both high and low dosages approximately 70% of the administered dose was excreted in the urine. At the low dose, 80-90% was excreted within 24 hours, but at the high dose only 28% was excreted within 24 hours. Unaltered thiabendazole was not present in measurable levels in the urine. From 69 to 79% of the administered ^{14}C excreted in the urine was in the form of 5-hydroxythiabendazole sulfate or glucuronide (Figure 1). Other metabolites were not identified.

Figure 1. Metabolic pathway of thiabendazole in rats (Craine, 1990).



Special Studies

Gavage- Mouse

The metabolic fate of ^{14}C-thiabendazole was studied in pregnant mice in connection with its teratogenic activity (Tsuchiya *et al.*, 1986). Absorption of thiabendazole in olive oil occurred more rapidly than in gum arabic, and the maximum blood level in mice dosed by the former method were 7-fold higher than the latter. 5-Hydroxylated thiabendazole, its glucuronide, and its sulfate were identified as urinary and fecal metabolites. A very small quantity of *N*-methyl thiabendazole was also identified in the urine and feces. The percentages of thiabendazole, 5-hydroxylated thiabendazole, and the glucuronide and sulfate of 5-hydroxylated thiabendazole in the urine were 12-15, 22-24, 28-29, and 30-31% respectively. About 97% of the dose was excreted into the urine (60-62%) and the feces (34-37%) within 7 days in each group.

In Vitro- Mouse

Benzimidazoles exhibited an inhibitory action on the chondrogenesis in a mouse limb bud cell culture system (Tsuchiya *et al.*, 1987). In the mouse limb bud cell culture system for the assay of teratogenic potential, the concentrations of thiabendazole, 5-hydroxylated thiabendazole, and *N*-methyl thiabendazole necessary to reduced the amounts of cartilage proteoglycan by 50% were estimated to be about 0.09, 0.09 and 0.24 mM, respectively. The imidazole NH proton seemed to be important in the inhibitory action in the mouse cell system.

In the rat limb bud cell culture system, the concentrations of thiabendazole, 5-hydroxy-thiabendazole, and *N*-methyl-thiabendazole necessary to reduce the amounts of cartilage proteoglycan by 50% (TP_{50}) were estimated to be about 0.35, 0.25 and 0.7 mM, respectively. The TP_{50} of thiabendazole and 5-hydroxy-thiabendazole in the rat cell system were 3- to 4-fold higher than those in the mouse cell system.

B. ACUTE TOXICITY

The acute toxicological data for technical grade thiabendazole are summarized in Table 1. Formulations of thiabendazole concentrate (60% thiabendazole) have an oral LD_{50} in rats of 5 g/kg, and 7.4 g/kg in mice (McKinney, 1968). The 50% concentrate had an oral LD_{50} in rats of 13.5 g/kg (Peterson, 1972). The 25% wettable powder had an oral LD_{50} in rats of 12.62 g/kg, a dermal LD_{50} in rabbits greater than 4 g/kg, and an inhalation LC_{50} in rats greater than 145 mg/L (Mallinckrodt, 1970).

Thiabendizole did not cause dermal sensitization in the guinea pig (Nessel, 1981), or dermal irritation in rabbits (Lankas, 1981b). No data were available on dermal absorption.

Table 1. The Acute Toxicity of Technical Thiabendazole

Route/Species	Sex	Category	Dose (mg/kg)	References[a]
			TECHNICAL	
Oral LD_{50}				
Rat	(M)	III	3,970	1
	(F)	III	3,540	1
Rat	(M)	IV	5,070	2
	(F)	III	4,730	2
Rat	(M)	IV	6,400	3
	(F)	IV	6,100	3
Mouse		III	3,810	3
Rabbit		III	3,850	3
Inhalation LC_{50}				
Rat		III	>2 mg/L	4

a/ 1. Kukulinski, 1981; 2. Lankas, 1981a; 3. Nessel, 1981; 4. Welsh and Kukulinski, 1982.

Oral- Human

Human patients with helminthic infections received thiabendazole in three different dosage regimes for a single day: 25 mg/kg (29 males); 50 mg/kg (37 males); or 50 mg/kg divided into two doses (28 males) (Vakil *et al.*, 1966). Some patients exhibited abdominal pain, headaches, dizziness, nausea and vomiting at 50 mg/kg whether it was in a single dose or in two doses. At 25 mg/kg, 8 of 29 patients reported dizziness, but no other symptoms. There was no significant alteration in the blood count, urine analysis, or liver function tests two days

after therapy at either 25 mg/kg or 50 mg/kg in the 20 patients studied. The lowest observed effect level (LOEL) for clinical signs and symptoms was 25 mg/kg.

Human patients (20/dose) with helminthic infections were given thiabendazole in five different dosage regimes: 100 mg/kg as a single dose; 50 mg/kg daily for 3 days; 50 mg/kg as a single dose; 25 mg/kg twice a day for 2 consecutive days; and 25 mg/kg once daily for 3 consecutive days (Sabharwal *et al.*, 1966). There was a dose-related increase in dizziness, nausea, and vomiting. Only one person became dizzy at the lowest dosage, and none exhibited nausea. The LOEL for clinical signs and symptoms was 25 mg/kg.

For six months, the physiological parameters from 42 male volunteers (average weight = 78 kg) given a single oral dose of 250 mg of thiabendazole (average dosage, 3.3 mg/kg-day) were compared with those of 35 male volunteers who received a single dose of placebo (Colmore, *et al*., 1965). Observations were made at weekly intervals during the study. No significant differences (P>0.1) between the treated and untreated groups were noted with regard to clinical signs and symptoms, blood urea nitrogen, complete blood count, serum bilirubin, fasting glucose, thymol turbidity, alkaline phosphatase, cholesterol, protein-bound iodine, prothrombin time, clotting time, urinalysis, and electrocardiograms. The single dose No-Observed-Effect-Level (NOEL) for clinical signs and symptoms, and blood chemistry changes in humans was 3.3 mg/kg-day.

C. SUBCHRONIC TOXICITY

Summary. The principal target organs of thiabendazole in short term, repetitive dosing studies were the liver, the kidney, and the thyroid. The 98-day oral gavage NOEL in rats for hepatotoxicity and changes in hematology was 25 mg/kg-day. In a 14 week dietary study, the NOEL for hepatotoxicity and thyrotoxicity in rats was 10 mg/kg-day. The NOEL for emesis in dogs was 35 mg/kg-day in a 90 day study. Thiabendazole caused histopathological changes in the liver and kidneys of mice, and reduced several blood parameters.

Oral- Rat

Thiabendazole (purity not stated) was administered by gavage at 0 (0.5% aqueous methylcellulose) 25, 100, or 400 mg/kg-day to Sprague-Dawley rats (20/sex/dosage) for 14 weeks (Kangas and Lankas, 1990). A dose-related increased incidence of alopecia was noted in all treated groups. A dose-related decrement in body weight gain, lesions in stomach mucosa, hepatocellular centrilobular hypertrophy, follicular cell hyperplasia, and reduced red blood cell counts, hematocrit, and hemoglobin were all observed in the two highest dose groups. The NOEL for changes in hematology and hepatotoxicity was 25 mg/kg-day. The study was considered supplemental information.

Sprague-Dawley rats (10/sex/group) received thiabendazole (99.4% pure) in the diet at 0, 200, 800, 3,200, or 6,400 ppm (approximately 0, 10, 40, 160, or 320 mg/kg-day based on consumption data) for 14 weeks (Myers and Lankas, 1990). Marked decreases in food consumption and body weight gain were noted at the two highest dosage levels. Increased relative (to body weight) liver and thyroid weights at dosages of 40 mg/kg-day or greater correlated with centrilobular and follicular cell hypertrophy in these groups, respectively. Slight pelvic mineralization was evident at the two highest dosages. The 14-week NOEL for hepatotoxicity and thyrotoxicity was 10 mg/kg-day. The study was considered supplemental information.

Male Crl:CD (Sprague-Dawley) BR rats (35/group) were dosed with thiabendazole (99% purity) at 0, 10, 90, or 270 mg/kg-day in the diet for 13/14 weeks to examine a possible mechanism for thyroid oncogenicity (Lankas, 1995). Fifteen males per group were necropsied after 13 weeks of compound administration. Five males/group were used in the thyroxine clearance assay in weeks 13 and 14, and were not necropsied. The remaining 15 males/group were necropsied after 13 weeks of recovery. Mean body weights were significantly reduced in the 90 and 270 mg/kg-day dose groups (12% and 32%, respectively). Food consumption was also reduced in these two groups (8% and 35%, respectively). Relative liver weights and thyroid weights were significantly elevated at the end of the treatment period, as were some serum hormone levels (Table 2). At the two highest doses there was a significant increase in centrilobular hypertrophy in the liver. This, and the increased relative weight of the liver suggested that the liver was being stimulated by higher doses of thiabendazole. There was a significant incidence of thyroid follicular cell diffuse hyperplasia at the two highest doses. The metabolic clearance rate of radiolabeled iodine was nearly doubled at the highest dose. After a 13 week recovery period, no treatment-related organ weight or microscopic changes were seen in the thyroids or liver of any of the rats in the treated groups. Although the serum levels of thyroxine (T4) and triiodothyronine (T3) were not significantly reduced in response to thiabendazole, the metabolic clearance of iodine was increased. The increased clearance rate of iodinated metabolites suggests that the thyroid was secreting more T3 and T4 in order to maintain normal serum levels. If the thyroid were being stimulated to increase hormonal output, one would expect to see increased levels of thyroid stimulating hormone (TSH). Serum levels of TSH were significantly elevated at the two highest doses. Further evidence of hyperstimulation of the thyroid to increase hormonal output was provided by the increased incidence of thyroid follicular cell diffuse hyperplasia. Hyperstimulation of the thyroid is also consistent with the notably significant, dose-related increase in relative thyroid weight. The data were considered supplemental, offering good correlation between thyroid histomorphological changes and increased TSH stimulation, possibly from increased liver metabolism of thyroid hormones and/or inanition due to thiabendazole exposure.

Table 2. Effects on liver and thyroid parameters by thiabendazole in the diet of male Sprague-Dawley rats (N = 5) for 13 weeks (Lankas, 1995).

Parameter	Dose			
	0 mg/kg-day	10 mg/kg-day	90 mg/kg-day	270 mg/kg-day
Absolute liver wt. (g)	15.36	14.78	15.42	13.15
Relative liver wt. (% bw)	2.88	2.89	3.09*	3.59**
Centrilobular hypertrophy	0/15	0/15	15/15	15/16
Absolute thyroid wt. (g)	0.20	0.20	0.24	0.28
Relative thyroid wt. (% bw)	0.0038	0.0040	0.0048*	0.0077**
Follicular cell hyperplasia	0/15	0/15	10/15	12/16
Metabolic clearance rate of iodine (ml/hr)	0.59 ± 0.01	0.65 ± 0.04	0.58 ± 0.02	0.83 ± 0.08**
TSH (% of control)	-	89	175**	197**
T_3 (% of control)	-	102	93	88
T_4 (% of control)	-	116	134	118

* Significantly different (P<0.05) from control by Student t test.
** Significantly different (P<0.01) from control by Student t test.

Oral- Mouse

Thiabendazole (purity unstated) was administered in the diet of Crj:CD-1 mice (10/sex/dose) at 0, 800 or 1600 ppm (approximately 0, 120, or 240 mg/kg-day as calculated by the default consumption value- 1 ppm = 0.15 mg/kg-day, Zielhuis and van der Kreek, 1979) for 13 weeks (Tada *et al.,* 1996). Mean body weights of male mice treated with 800 or 1600 ppm exhibited a significant ($P<0.05$) decrease compared to controls. Red blood cell counts, hemoglobin concentration, packed cell volume, mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) in treated male and female mice were lower than those of control mice. Glutamic oxaloacetic transaminase and glutamic pyruvic transaminase levels in treated males and females were increased compared to controls. Absolute and relative liver weights in treated male and female mice were significantly ($P<0.05$) increased compared with controls. Relative spleen weights in male and female mice of treated groups were significantly increased compared with controls. There was marked hemosiderosis and extramedullary hematopoiesis in the spleen of treated mice. In the liver, sinusoidal dilation and enlargement of liver cells were found in treated mice. Treated mice also exhibited atrophy of kidney tubules, with peritubular fibrosis, cell infiltration, and some tubular necrosis. The data, in summary form from a published study, were considered supplemental in providing information on the toxic effects of thiabendazole from repetitive dosing.

In a range-finding study, CD-1 (HaM/ICR) mice (10/sex/dose) were fed on a diet containing thiabendazole (purity unstated) at concentrations (adjusted for food consumption) calculated to give doses of 0, 50, 150, 300, 600, or 900 mg/kg-day for six weeks (Bagdon, 1977). Male mice dosed with 600 or 900 mg/kg-day ate less food (12% and 14%, respectively), and gained less weight (12% and 15%, respectively) than controls. Female mice given these doses showed only a slight decrease in food intake and weight gain in the first two weeks of the study, but not thereafter. No changes in food consumption or weight gain due to treatment were noted in either sex at any other dose. No pathology was done. The data were considered supplemental.

Oral- Dog

Thiabendazole (99.4% pure) was administered orally via gelatin capsule at concentrations of 0, 35, 75, or 150 mg/kg-day to beagles (4/sex/group) for 90 days (Batham and Lankas, 1990). A dose-related increased incidence of emesis was observed in the two highest dose group animals during the first 6 weeks. Slight, statistically significant increases in the ratio of liver weight to body weight were noted in all treated groups. The NOEL for emesis was 35 mg/kg-day. The range-finding study was considered supplemental information.

Oral- Human

A 32-year-old woman developed severe and protracted intrahepatic cholestasis following oral ingestion of four doses of 25 mg/kg of thiabendazole over an 8 day period to treat an helminthic infestation (Jalota and Freston, 1974). The cholestatic reaction was associated with nausea, intense pruritus, and a generalized rash. The jaundice persisted for more than 1 month without signs of remission. The data were considered supplemental in confirming thiabendazole can cause hepato/biliary toxicity in humans.

D. CHRONIC TOXICITY AND ONCOGENICITY

Summary. The principal effects in laboratory animals of chronic exposure to thiabendazole were thyroid toxicity, hepato/biliary toxicity, anemia and atrial thrombosis. In

dogs, the NOEL for hepatotoxicity (inflammatory liver changes, depletion of liver glycogen, hemosiderosis), and histopathological changes in the urogenital tract was 10 mg/kg-day. In rats, the LOEL for mild anemia (reduced hemoglobin) was 100 mg/kg-day, with a NOEL of 50 mg/kg-day. The NOEL for adaptive liver response (centrilobular hypertrophy) in rats was 10 mg/kg-day. Male mice exhibited atrial thrombosis at 278 mg/kg-day, with a NOEL of 92 mg/kg-day. There was a significant, dose-related increase in thyroid follicular cell adenomas in male Sprague-Dawley rats. Thiabendazole was not oncogenic in mice.

Oral- Rat

Thiabendazole (98.9% purity) was administered to Sprague Dawley Crl:CD BR rats 50/sex/dose at 0, 10, 30 or 91 mg/kg-day (males) and 0, 10, 30 or 92 mg/kg-day (females), (based on food consumption data, ppm not available) for 104 weeks (Wolfe and Squibb, 1994). Males treated with 30 and 91 mg/kg-day exhibited a significant ($P<0.05$) decrement in body weights (9% and 18%, respectively) compared to controls. Females at 92 mg/kg-day also had a significant ($P<0.05$) decrement in body weight (13%) compared to controls. Relative liver weight was significantly ($P<0.05$) increased (35%) in males at 91 mg/kg-day compared to controls, accompanied by centrilobular hypertrophy at the mid and high doses (Table 3). Centrilobular hypertrophy, like an increase in liver weight, represents an adaptive response by the liver to the stress of metabolizing large amounts of toxin (Greaves and Faccini, 1984). There were no significant changes in serum levels of alanine amino transferase, alkaline phosphatase, aspartate aminotransferase, or lipid concentration which would be indicative of liver damage (Zimmerman, 1982). The NOEL for the adaptive liver response (centrilobular hypertrophy) was 10 mg/kg-day. Relative, but not absolute thyroid weight was significantly ($P<0.05$) increased (33%) in females at 92 mg/kg-day compared to controls. There was no increase in the incidence of thyroid follicular cell hypertrophy or hyperplasia in males or females. However, there was a significant ($P<0.05$), dose-related increase in thyroid follicular cell adenomas in males, but not females. No historical control data were provided. Non-vehicle control males did not have any thyroid follicular cell tumors, but control males receiving vehicle did have a single incidence of a tumor. The two control groups are combined in Table 3. The first adenoma appeared in week 78. Thiabendazole did not significantly affect the incidence of thyroid follicular cell carcinomas, but the combined incidence of carcinomas and adenomas was significantly ($P<0.05$) greater in the middle and high dose males than in the controls. However, the principal investigator suggested that the etiology of thyroid adenomas in the rats was secondary to hepatic stimulation. The expressed hypothesis was that increased clearance of T3 and T4 by the liver may lead the pituitary to chronically stimulate thyroid follicular cells with elevated levels of TSH. The elevated TSH could then cause thyroid follicular cell hyperplasia and adenomas. Some experimental confirmation of this hypothesis was shown in a study (Lankas, 1995) presented in the preceding Subchronic Toxicity section. In that study, thyroid follicular cell hyperplasia was induced by thiabendazole. Further discussion of this issue is included in the Hazard Identification section. The study was acceptable to DPR under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA) guideline requirements (USEPA, 1984).

Table 3. Histopathological effects of thiabendazole in the diet of Sprague-Dawley rats dosed for 2 years (Wolfe and Squibb, 1994).

	Male Dosage (mg/kg-day)				Female Dosage (mg/kg-day)			
Tissue	0	10	30	91	0	10	30	92
Thyroid								
Follicular cell Adenoma	+0/91 (0%)	1/43 (2%)	5/40* (13%)	6/45* (13%)	3/82 (4%)	0/39 (0%)	1/44 (2%)	5/44 (11%)
Follicular cell Carcinoma	1/91 (1%)	0/43 (0%)	0/40 (0%)	1/45 (2%)	1/82 (1%)	0/39 (0%)	0/44 (0%)	0/44 (0%)
Combined	+1/91 (1%)	1/43 (2%)	5/40* (13%)	7/45* (16%)	4/82 (5%)	0/39 (0%)	1/44 (2%)	5/44 (11%)
Liver								
Centrilobular hypertrophy	0/50 (0%)	0/50 (0%)	7/50 (14%)	28/50 (56%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)

* Significantly different (P<0.05) from controls by Fisher's Exact Test.
\+ Statistically significant (P<0.05) by Peto's trend test
Tumor incidence is expressed for animals surviving past 78 weeks, which was when the first thyroid follicular cell adenoma appeared.

Thiabendazole (99.1% pure) was placed in the diet of Charles River rats (35/sex/group) at 0, 1,600, or 2,400 ppm (0, 80, or 120 mg/kg-day, as calculated by the default consumption value- 1 ppm = 0.05 mg/kg-day; Zielhuis and van der Kreek, 1979) for 104 weeks (Woodard, 1965). In a second study, thiabendazole (99.1% pure) was placed in the diet of Charles River CD rats (35/sex/group) at 0, 200, 800, or 3,200 ppm (0, 10, 40, or 160 mg/kg-day, as calculated by the default consumption value- 1 ppm = 0.05 mg/kg-day) for 104 weeks (Woodard and Cronin, 1964). Although neither study was acceptable to DPR under FIFRA guideline requirements (insufficient histopathology), together the data were sufficient to derive a chronic NOEL of 40 mg/kg-day for decrement in body weight (6-7%).

Thiabendazole (purity not stated) was administered to F344/DuCrj rats (30/sex/dose) in the diet at 0, 500, 1000, 2000 or 4000 ppm (approximately 0, 25, 50, 100 or 200 mg/kg-day as calculated by the default consumption value- 1 ppm = 0.05 mg/kg-day) for 104 weeks (Hayashida *et al*., 1985a). At the two highest doses, there was a significant (p<0.05) decrease in body weight in males (13% and 41%, respectively) and females (19% and 39%, respectively). Doses causing decrements in body weight exceeding 10% are generally considered to exceed the maximum tolerated dose (Eaton and Klaassen, 1996: Foran, 1997). Chemically related effects on hematological parameters and clinical chemistry were also noted (Table 4). The NOEL was 50 mg/kg-day for statistically significant (P<0.05) decreases in SGOT and SGPT in females, which can be an indication of hepatotoxicity (Dhami *et al.,* 1979; Waner and Nyska, 1991), and changes in hematology. The histopathological results from the study were reported in a second paper (Hayashida *et al*., 1985b). Dose-related effects in the liver were seen. These effects were increases in hepatocellular foci and bile duct proliferation in females at the two highest dosages. Hepatic microgranulomas were seen in both sexes at all dosages. Urinary tract hyperplasia was present in both sexes at the top three dosages; and statistically significant adenomas of the preputial (7/30; 23%) and clitoral glands (4/30; 13%) were noted at the highest dosage, compared to controls (0/30 for either). The study reports were not

acceptable to DPR under FIFRA guideline requirements as the published data were in summary form, only.

Table 4. Effect of dietary exposure to thiabendazole for 104 weeks on the hematology and clinical chemistry of rats (Hayashida *et al.,* 1985a).

Dose	N	SGOT	SGPT	RBC	Hb
Males		(IU/L)	(IU/L)	(10^{-6}/ml)	(g/dl)
control	20	79.6 ±24.2	28.0 ± 6.8	8.17 ± 1.46	17.0 ± 2.8
25 mg/kg-d	21	85.1 ± 16.9	29.5 ± 7.4	7.87 ± 0.94	16.1 ± 1.9
50 mg/kg-d	20	74.9 ± 15.9	28.1 ± 6.2	7.90 ± 1.17	16.3 ± 2.0
100 mg/kg-d	23	99.7 ± 52.6	32.0 ± 17.3	7.50 ± 0.65	15.5 ± 1.2*
200 mg/kg-d	24	69.5 ± 18.3	25.7 ± 5.3	6.54 ± 0.45*	14.0 ± 0.7*
Females					
control	20	152 ± 56	49.8 ± 17.3	7.36 ± 0.93	15.9 ± 1.6
25 mg/kg-d	26	147 ± 56	59.4 ± 19.6	7.83 ± 0.39*	16.5 ± 1.7
50 mg/kg-d	22	129 ± 42	50.8 ± 16.4	7.70 ± 0.47	16.2 ± 1.2
100 mg/kg-d	26	95.2 ± 24.6*	37.5 ± 10.2*	7.25 ± 0.40	15.1 ± 1.6
200 mg/kg-d	27	82 + 20.7*	34.0 + 7.5*	6.19 + 0.53*	13.4 + 1.0*

* Significantly different (P<0.05) from control by Student's t test.

Thiabendazole (98.5% pure) at concentrations of 0, 500, 1000, 2000 or 4000 ppm (approximately 0, 25, 50, 100 or 200 mg/kg-day as calculated by the default consumption value- 1 ppm = 0.05 mg/kg-day) was given in the diet to F344/DuCrj rats (30/sex/group) for 2 years (Fuji *et al.*, 1991). Body weight gain of both males and females exhibited a dosage-related decrement (approximately 20% and 40% at the top two doses, respectively). Doses causing decrements in body weight exceeding 10% are generally considered to exceed the maximum tolerated dose (Eaton and Klaassen, 1996: Foran, 1997). Significant (P<0.05) histopathological changes were noted in the kidney (Table 5). A significant (P<0.05) incidence of benign tumors of the preputial gland were observed in males at the highest dosage. Females exhibited a non-significant increase in clitoral gland tumors at the highest dosage. The NOEL for nephrotoxicity (transition cell hyperplasia) was 25 mg/kg-day. The study was not acceptable to DPR under FIFRA guideline requirements as the published data were in summary form, only.

Table 5. Histopathological changes in thiabendazole treated rats (Fuji *et al.*, 1991).

Site and lesion	Thiabendazole (mg/kg-day)				
	0	25	50	100	200
Kidney- transitional cell hyperplasia					
Males	1/29	0/30	11/30*	21/30*	24/30*
Females	2/29	4/30	11/29*	22/30*	30/30*
Kidney- tubular and/or ductal hyperplasia					
Males	1/29	3/30	4/30	7/30*	7/30*
Females	0/29	0/30	0/29	1/30	10/30*
Preputial gland- adenomas	0/27	1/28	0/28	2/27	7/30*
Clitoral gland- adenomas	1/22	0/25	2/22	1/22	4/40

* Significantly different (P<0.05) by Fischer's exact test from the concurrent control group.

Oral- dog

Beagles (4/sex/dose) were dosed orally with thiabendazole (99% purity) at 0, 10, 40, or 160 mg/kg-day in gelatin capsules for one year (Lankas, 1993). Body weight and food consumption were not affected at any dose level. No ophthalmic changes related to treatment were noted. One male dog died at 40 mg/kg-day on week 2, and its death was related to failed liver function. Absolute liver weights were significantly ($P<0.05$) increased in high dose male dogs (145%) compared to controls. Gall bladder epithelial vacuolation and inspissation were noted at all doses, and also occurred in the controls (Table 6). The incidence of the effects exhibited no dose response. The individual data from both sexes indicated an increase in the severity of epithelial vacuolation, but not inspissation over the dosage range tested (data not shown). The physiological significance of the gall bladder epithelial vacuolation was not clear to either the study's pathologist, or Dr. James Swenberg at CIIT (personal communication). Consequently, neither the incidence of gall bladder epithelial vacuolation, nor gall bladder inspissation were considered for setting a NOEL. All other histopathological effects occurred at the two highest doses in both males and females. Bile duct vacuolation, noted at the two highest doses in males and females, also exhibited no increase in severity. Distal tubular vacuolation in the kidney (females) and uroepithelial cytoplasmic inclusions (males and females) were noted at the two highest doses. Focal cellular infiltration of the epididymis was noted at the two highest doses in males. Mild anemia in males and females at the high dose was indicated by reduced erythrocyte count (11% and 19%, respectively), hemoglobin (15% and 19%) and hematocrit (12% and 14%), as well as an elevated platelet count (186% and 138%). The NOEL for hepato/biliary toxicity and histopathological changes in the urogenital tract was 10 mg/kg-day. The study was acceptable to DPR under FIFRA guideline requirements.

Table 6. Effect of thiabendazole on the histopathology of some body tissues in dogs following one year of oral dosing (Lankas, 1993).

	Male Dose (mg/kg-day)				Female Dose (mg/kg-day)			
Histopathology	0	10	40	160	0	10	40	160
Gallbladder epithelial vacuolation	1/4	4/4	4/4	4/4	0/4	4/4	3/4	4/4
Gallbladder inspissation	0/4	4/4	3/4	4/4	2/4	4/4	3/4	4/4
Bile duct vacuolation	0/4	0/4	4/4	3/4	0/4	0/4	2/4	3/4
Urogenital Tract								
Kidney distal tubular vacuolation	0/4	0/4	0/4	0/4	1/4	1/4	3/4	4/4
Uroepithelial cytoplasmic inclusions	0/4	0/4	3/4	4/4	0/4	0/4	2/4	4/4
Epididymal focal cell infiltration	0/4	0/4	1/4	3/4	-	-	-	-
Thyroid								
Thyroid follicular cell hypertrophy	0/4	0/4	0/4	1/4	0/4	0/4	0/4	2/4

Beagles (3/sex/group) received capsules containing thiabendazole (99.1% pure) to give dosages of 0, 20, 50, or 125 mg/kg-day, 5 days per week for 104 weeks (Woodard and Cronin, 1964). Mild lacrimation and scleral injection, and weight loss were noted at the two highest

doses. At the highest dose there was salivation, dry skin, reduced hemoglobin and hematocrit, seizures, and mortality (2/3 males). At 125 mg/kg-day, there was evidence of moderate chronic inflammatory liver changes, inspissated material in the gall bladders of two dogs, and slight, liver glycogen depletion. At 50 mg/kg-day only some depletion of liver glycogen was noted, and inspissated material was found adherent to the gall bladder mucosa in one dog. The NOEL was 20 mg/kg-day for hepatotoxicity, weight loss, lacrimation and scleral injection. The study was unacceptable to DPR under FIFRA guideline requirements due to inadequate numbers of animals and lack of histopathology data.

Thiabendazole (99.1% pure) was given orally to beagles (2/sex/group) daily for 104 weeks at 0, 20, 100, or 200 mg/kg-day (Nessel, 1981a). Reduced body weights, red blood cell counts, hematocrits and hemoglobin were seen at the highest dose. The NOEL was 20 mg/kg-day for hemosiderosis of the liver and bone marrow (seen at the two highest dosages). The study was unacceptable to DPR under FIFRA guideline requirements due to inadequate numbers of animals and lack of histopathology.

Oral- Mouse

CD1-mice (50/sex/group) were given thiabendazole (99.3-99.8% pure) in 1% vegetable oil in the diet at 0, 60, 660 or 2000 ppm (approximate average 0, 7, 92, or 278 mg/kg-day from consumption data) for males, or 0, 60, 2000 or 5330 ppm (approximate average 0, 7.8, 289, or 770 mg/kg-day from consumption data) for females for up to 106 weeks (Bagdon *et al*., 1980). There was no indication of thiabendazole-related oncogenicity. High dose males had a 19% decrement in body weight gain over the course of the study. Females at the middle and high doses had decrements in body weight gain (10% and 24%, respectively). Males exhibited a significant ($P<0.001$) increase in atrial thrombosis at 278 mg/kg-day, with a NOEL of 92 mg/kg-day (Table 7). Females also exhibited a dose-related increase in atrial thrombosis, with a NOEL of 7.8 mg/kg-day. Atrial thrombosis was first seen in week 31 in one high dose female mouse. Less than half the animals with atrial thrombosis died as a result of the thrombi (Table 7). No historical control data were available on this parameter. The difference between the NOELs in male and female mice for this parameter appears to be due to dose selection. The range finding study used to establish the dosing regime in this study indicated that males were more sensitive to thiabendazole toxicity than females, based on body weight decrement (Bagdon, 1977). A few factors suggest that the overall NOEL for atrial thrombosis should be based on the NOEL for atrial thrombosis in male mice, rather than female mice. 1) The data indicate that male mice were at least as sensitive to thiabendazole toxicity as female mice in both this study and the range-finding study with regard to effects on body weight. 2) The middle dose in males, which resulted in the identical rate of atrial thrombosis as in the controls, was between the middle and low dose in the females. Thus , the overall NOEL for atrial thrombosis in mice was considered 92.5 mg/kg-day. This study was acceptable to DPR under FIFRA guideline requirements.

Table 7. Incidence of atrial thrombosis in CD1 mice following dietary exposure to thiabendazole for 106 weeks (Bagdon *et al*., 1980).

	Male Dose (mg/kg-day)				Female Dose (mg/kg-day)			
Parameter	0	7.0	92	278	0	7.8	289	770
Atrial Thrombosis	9/150^{+} (6%)	0/50 (0%)	3/50 (6%)	24/50*** (48%)	1/150^{++} (<1%)	1/50 (2%)	19/50*** (38%)	33/50*** (66%)
Atrial Thrombosis as cause of death	1/9	-	1/3	8/24	0/1	0/1	7/19	7/33

*** Significantly (P<0.001) greater than control values by Fisher's exact test.
\+ Significant (P<0.05) trend test.
++ Significant (P<0.01) trend test.

E. GENOTOXICITY

Summary. Genotoxic potential for thiabendazole has been demonstated in laboratory studies. Thiabendazole was tested for mutagenicity in *Salmonella typhimurium*; for DNA damage in primary rat hepatocytes and human embyro fibroblasts *in vitro*; and for chromosomal effects. Three submitted studies, with detailed information, using various *Salmonella* strains, including TA98, did not report mutations. However, positive results were reportedly obtained in *Salmonella* strains TA98 and TA99 in a study published in summary form. In the absence of data from this study, it was not possible to evaluate the mutagenic potential of thiabendazole. Thiabendazole caused micronuclei formation *in vivo* in CFW mice, sister chromatid exchange *in vivo* in male mice, mouse ovarian hyperploidy *in vitro*, and chromosomal bridges in chinese hamster ovarian cells *in vitro*. These genotoxic effects involved spindle disruption, which is consistent with thiabendazole's known ability to disrupt tubulin assembly.

Table 8. Genotoxicity studies with thiabendazole.

Test Type	Regimen	Effects	Reference
Mutagenicity			
thiabendazole	*Salmonella* TA1535, TA1538, TA98, TA100, G46 and *E.coli* WP2 hcr ± rat liver S9;0 to 2,500 µg/plate	-	1*
thiabendazole	*Salmonella* TA97a, TA98, TA100, TA1535 and E. coli WP2, WP2uvrA, and WP2uvrA pKM101 ± rat liver S9; 0-6,000 mg/plate	-	2*
thiabendazole	*Salmonella* TA98; 0 to 2,000 µg/plate	-	3
thiabendazole	*Salmonella* TA1535, TA1537, TA1538, TA98, and TA100; ± rat liver S9	-	4
thiabendazole	*Salmonella* TA98, TA99	+	5
DNA Damage			
thiabendazole	Primary male rat hepatocytes; 0-1.3 mM	-	6*
thiabendazole	Human embryo fibroblasts; 0-50 µg/ml	-	7
Chromosomal Effects			
thiabendazole	rat; single dose 0-1,000 mg/kg; 5 doses 0-300 mg/kg	-	8*
thiabendazole	C3H/HeCr mice; 0, 200 or 600 mg/kg	-	9
thiabendazole	CD-1 mice; 0-500 mg/kg	-	10
thiabendazole	ICR female mice; 0-150 mg/kg; ovarian hyperploidy	+	11
thiabendazole	CFW mice; 0-200 mg/kg, micronucleus	+	12
thiabendazole	CHO cells; 0-0.6 µg/ml;chromosomal bridges	+	12
thiabendazole	male mice; 0-200 mg/kg; SCE	+	12
thiabendazole	102/ElxC3H/EL mice:0-500 mg/kg;micronucleus	-	13
thiabendazole	Swiss mice; 640 mg/kg; micronucleus	-	14

References: 1. Shirasu *et al.,* no date-c; 2. Sina, 1992; 3. Merck, 1977; 4. Merck, 1969; 5. Zeiger *et al*., 1988; 6. Lankas *et al.,* 1989; 7. Shirasu et al, no date-d; 8. Shirasu *et al.,* no date-a; 9. Shirasu *et al.,* no date-b; 10. Hite *et al.,* 1977; 11. Mailhes *et al*., 1997; 12. Pargament *et al.,* 1988; 13. Adler *et al.,* 1981; 14. Ohuchida *et al.,* 1989.

* Acceptable to DPR under the Toxic Substances Control Act guidelines (Federal Register, 1985).

F. REPRODUCTIVE TOXICITY

Summary. The reproductive NOEL for mice was approximately 150 mg/kg-day, based on reduced numbers of mice born and weaned per litter, as well as reduced weanling weight. The NOEL for reduced pup weights in rats was 30 mg/kg-day. The NOEL for a significant decrement in parental rat weight gain was 10 mg/kg-day.

Oral- Rat

In a two-generation rat reproduction study, thiabendazole (99% purity) at 0, 10, 30, or 90 mg/kg-day (based on food consumption data, ppm not available) was administered in the diet of one litter per generation of Sprague-Dawley [Crl:CD©(SD)BR] rats (33 rats/sex/dose for F_0, and 25 rats/sex/dose for F_1)(Lankas and Wise, 1992). F_0 and F_1 parental rats received the treated diet for 9 weeks and 14 weeks prior to mating, respectively. No specific reproductive effects were reported. In the F_0 parental rats, there was a significant ($P<0.05$) decrement in weight gain at 30 mg/kg-day and 90 mg/kg-day in males (10% and 29%, respectively), and at 90 mg/kg-day in females (29%). In the F_1 parental rats, there was also a significant ($P<0.05$) decrement in weight gain at 30 mg/kg-day and 90 mg/kg-day in males (7% and 13%,

respectively), and at 90 mg/kg-day in females (14%). Decrements in food consumption were noted at 90 mg/kg-day in both males and females of both generations (8-16%). The NOEL for decrement in parental weight gain was 10 mg/kg-day. The decrements in pup body weight were only noted at the highest dose (90 mg/kg-day), at all time points in the F_1 generation, 14 and 21 weeks in the F_2 generation, and ranged from 6-10% in both males and females. The NOEL for reduced pup weights was 30 mg/kg-day. This study was acceptable to DPR under FIFRA guideline requirements.

In another multigenerational reproductive toxicity study, thiabendazole (98.8% pure) was administered orally in the diet (young rats) or by gavage (older rats) from mating through weaning to FDRL rats (10/sex/group) at 0, 20, 40 or 80 mg/kg-day (Vogin, 1968). No effect was observed on any of the reproduction parameters. The NOEL for reproductive effects was >80 mg/kg-day. This study was acceptable to DPR under FIFRA guideline requirements.

Oral- Mouse

Mice (25/sex/group) were dosed with thiabendazole (purity unstated) at concentrations of 0, 0.02, 0.1 or 0.5% in the diet for five generations (Nessel, 1981b). The NOEL was approximately 150 mg/kg-day for reduced numbers of mice born and weaned per litter, as well as reduced weanling weight. The data were in summary form only.

G. DEVELOPMENTAL TOXICITY

Summary. Thiabendazole caused major malformations of the skeletal system in mice, rabbits, and rats. The Estimated No Effect Level (ENEL) for mice was 26 mg/kg-day, based on skeletal abnormalities. The NOEL for developmental toxicity in rabbits was 24 mg/kg-day based on fetal resorption and hydrocephaly. The maternal NOEL in rabbits was 120 mg/kg-day based on decrement in food consumption and body weight gain. In the rat gavage study, the NOEL for decreased maternal food consumption was 10 mg/kg-day. The NOEL for decrement in fetal weight in the same study was 10 mg/kg-day. However, in two studies in which pregnant rats were exposed to thiabendazole in the diet, increased skeletal variations were noted. In addition to these variations, there was a significant increase in major malformations of the skeletal system, including cleft palates and the absence of the *os hyoideus*.

Gavage- Mouse

Three different dosage regimes were utilized with pregnant Jcl:ICR mice to identify the dosage and sensitive time point for thiabendazole to cause skeletal abnormalities (Ogata *et al.*, 1984). In the first dosage regime, mice (39 mated females) were given thiabendazole (98.5% purity) at 0, 700, 1300 or 2400 mg/kg-day orally in olive oil on days 7-15 of gestation. Dose-dependent external and skeletal anomalies, especially cleft palate and fusion of vertebrae were observed. Maternal deaths were reported at the two highest dosages, 5/39 and 24/39 respectively. In the second regime, a single dosage of 2400 mg/kg-day was used on any one of days 6-12 of gestation. Maternal deaths were noted on each of the treatment days. Various types of malformations occurred, especially in mice treated on day 9. Reduction deformity of limbs was found in mice treated on days 9-12. The third dosage regime was to give one of 17 dosages of thiabendazole, ranging from 30 to 2400 mg/kg-day, on day 9 of gestation. No maternal deaths were observed at dosages less than 1667 mg/kg-day. The NOEL for decrement in maternal body weight gain was 965 mg/kg-day. The number of litters having fetuses with reduction deformity of limbs and those having fetuses with skeletal fusion increased in proportion to the dose of thiabendazole. The estimated no effect level (ENEL)

(ED_{01} determined by probit analysis by the authors) for the incidence of 9 litters with fetuses having skeletal fusion was 26 mg/kg-day. In a separate experiment, maternal weight loss was induced by starvation to see if weight loss alone would cause the appearance of skeletal malformations. No malformations were associated with weight loss in the absence of thiabendazole. The published information was considered supplemental.

In a range finding study, pregnant Jcl:ICR mice (20/group) were dosed with thiabendazole (99.8% purity) at 0 (olive oil), 25, 100, 200, 400, or 800 mg/kg-day on days 6-15 of gestation (Nakatsuka, 1995a). There were statistically significant decrements in maternal body weight at 200 (15.6%), 400 (30.2%), and 800 mg/kg-day (39%), as well as reduced RBC counts, hemoglobin, and hematocrit. Fetal weights were reduced in a statistically signficant ($P<0.05$), dose-related fashion from 100 mg/kg-day upward. At the high dose there was an increased incidence of cleft palate (15 fetuses in 4 litters) compared to controls (1 fetus in 1 litter). The data were considered supplemental.

Thiabendazole (99.8% purity) was administered via gavage at concentrations of 0 (olive oil), 25, 100, or 200 mg/kg-day to 25 Jcl:ICR mice/group during days 6 through 15 of gestation (Nakatsuka, 1995b). The fetuses of two litters at 200 mg/kg-day had cardiovascular malformations, compared to fetuses in 1 litter at each of the other doses and controls. No other malformations or developmental anomalies, potentially chemically related, were reported. There were slight decrements in body weight gain of the pregnant females at the high and middle doses in the first four days of the study. Differences in litter sizes, which were not due to treatment effects, may have caused the decrement in body weight gain to be more pronounced over the course of the study. Thus, the maternal NOEL was 25 mg/kg-day for decrement in body weight gain. Reduced mean fetal weights (in a dose related fashion) at the two higher doses, despite smaller litter size, indicated a treatment effect. The developmental NOEL was 25 mg/kg-day for statistically significant ($P<0.05$) decrements in mean fetal weight. This study was acceptable to DPR under FIFRA guideline requirements.

Gavage- Rabbit

Thiabendazole (98.9% purity) was administered by gavage at concentrations of 0, 24, 120, or 600 mg/kg-day to artificially inseminated Hra (New Zealand White) SPF rabbits (18/dosage) on days 6 through 18 of gestation (Hoberman, 1989). The NOEL for maternal toxicity was 120 mg/kg-day based on a statistically significant ($P<0.05$) decrement in food consumption (53% of control at 600 mg/kg-day) and weight gain (23% less average body weight compared to controls in the 600 mg/kg-day group). The NOEL for developmental toxicity was 24 mg/kg-day based on fetal resorption (4/18 litters resorbed with whole litter resorption at 120 mg/kg-day) and hydrocephaly (2 fetuses in 2 litters at 600 mg/kg-day and one fetus at 120 mg/kg-day). This study was acceptable to DPR under FIFRA guideline requirements.

Thiabendazole (98.9% purity) was administered by oral gavage at concentrations of 0 (0.5% methylcellulose), 50, 150, or 600 mg/kg-day to mated New Zealand White rabbits (18/dose) on days 6 through 18 of gestation (Lankas and Wise, 1991). A statistically significant ($P<0.05$) increase in litter resorptions per implant was reported at 600 mg/kg-day (11.8%) compared to controls (8.1%) (Table 9). There were also statistically significant ($P<0.05$) increases in lung lobations (10% compared to 2% in controls), incomplete ossification of the metacarpal (28% compared to 8% in controls) and talus/calcaneus (8% compared to 0% in control), and skeletal malformations (8% compared to 1% in controls) reported at the highest dose (600 mg/kg-day). The developmental NOEL for malformations and increased litter resorptions was 150 mg/kg-day. There was a significant ($P<0.05$) decrement in maternal

weight gain (69%) at 600 mg/kg-day. The NOEL for maternal toxicity (decrement in weight gain) was 150 mg/kg-day. The study was acceptable to DPR under FIFRA guideline requirements.

Gavage- Rat

Impregnated Sprague-Dawley rats (25/dose group) were given thiabendazole by gavage at dosages of 0 (0.5% methylcellulose), 10, 40 or 80 mg/kg-day on days 6 through 17 of gestation (Wise, 1990). A slight decrement in body weight gain (1.7 to 4.8%) was seen in the high dosage rats (80 mg/kg-day) on days 8 through 14. Food consumption was significantly ($P<0.05$) reduced at dosages of 40 (11-15%) or 80 mg/kg-day (22-28%) compared to controls. The NOEL for decreased maternal food consumption was 10 mg/kg-day. Fetuses exhibited significantly ($P<0.05$) lower body weights at 40 (4.9%) and 80 mg/kg-day (6.3%) compared to controls. The NOEL for decrement in fetal weight was 10 mg/kg-day. The study was acceptable to DPR under FIFRA guideline requirements.

Diet- Rat

Thiabendazole (purity not stated) was administered in the diet to mated female Wistar rats (20/dose) at 0, 2, 15, 50 or 100 ppm during days 6-17 of gestation (IPTP, 1985). No significant maternal effects were observed. The developmental NOEL was approximately 1.5 mg/kg-day (using a default conversion of 0.1 mg/ppm; Zielhuis and van der Kreek, 1979) for significantly ($P<0.05$) lower body weights, or 5 mg/kg-day for a significant increase in major malformations of the skeletal system, including cleft palates and the absence of the *os hyoideus* (LOEL = 10 mg/kg-day) (Table 10). The study was considered unacceptable to DPR under FIFRA guideline requirements due to lack of analysis of the test chemical, a lack of individual maternal food and water consumption data, and a lack of individual data for fetal visceral, skeletal, external effects and body weights.

Table 9. Effects of thiabendazole by the oral route on maternal weight gain, fetal resorption, and structural changes in developing rabbit fetuses (Lankas and Wise, 1991).

Parameter	Dose (mg/kg-day) 0	50	150	600
Maternal weight gain (% of control)	100	123	102	31*
Litters Examined	12	16	17	16
Fetuses Examined	59	95	103	96
Resorptions + dead fetuses (%)	8.1	2.0	3.8	11.8*
mean implant number				
Variation Incidence				
litters with variations	1	0	3	1
fetuses with lung lobation	1	7	3	10*
Incomplete Ossification				
fetal incidence, metacarpal	5	15	14	27*
fetal incidence, talus/calcaneus	0	1	4	8
Skeletal Malformations				
litters with malformations	1	1	1	4
fetal incidence, atlas	0	0	0	1
fetal incidence, cervical vertebra	0	0	0	1
fetal incidence, thoracic vertebra	0	1	0	2
caudal vertebra	0	0	1	3

* Significantly different from control (P<0.05) by Student's t test.

Table 10. Effect of dietary administration of thiabendazole on fetal development in Wistar rats (IPTP, 1985).

	Dose (mg/kg-day) 0	0.2	1.5	5.0	10
Fetuses examined	206	200	207	217	221
Litters examined	20	18	20	20	20
Skeletal					
Major skeletal mal.	9[a]	11	11	13	18*
Skeletal variations	126	96	118	142	157*

* Significantly different from controls (P<0.05) by Fisher's exact test.

a/ Incidence presented as total number of fetuses affected.

Thiabendazole (approximately 98% purity) was given in the diet to mated Wistar rats at approximately 0, 1,250, 2,500, 5,000, or 10,000 ppm (approximately 0, 92, 155, 224, and 188 mg/kg-day based on consumption data; the high dose was less because of decreased food consumption) during days 7 to 17 of gestation (Tanaka *et al*., 1982). The maternal NOEL was approximately 92 mg/kg-day for decrement in weight gain and food consumption, and clinical signs (piloerection, listlessness and/or general weakness). The developmental NOEL was 92 mg/kg-day for retardation of ossification (Table 11). Decrement in body weight, and increased skeletal variations were noted at the two highest dosages. At the highest dose, 1/181 of the fetuses examined had scoliosis. A significant (P<0.01) increased incidence of fetal death (13% compared to 2% in controls) was observed at the high dose, and a decrement in fetal body weight and skeletal variations were seen at 224 mg/kg-day (due to reduced dietary intake the actual dosing was 155 mg/kg-day). The information was in published, summary form and was considered supplemental.

Table 11. Effect of dietary exposure to thiabendazole on rat fetal development (Tanaka *et al.*, 1982).

	Dose (mg/kg-day)				
	0	92	155	224	188
Fetuses examined	173	175	175	171	181
Litters examined†					
Variations					
Skull Bone Hypoplasia	0[a]	4	0	15	82**
Cervical Arch	1	2	1	2	44**
Sternebrae	76	87	96	100**	162**
Average Ossification State[b]					
metacarpus	7.5	7.5	6.9**	6.7**	6.3**
metatarsus	8.0	8.0	8.0	8.0	7.6**
sacro-caudal vertebrae	7.8	7.7	7.6	7.4	6.4**

† Data not available.
a/ Total number of fetuses affected.
b/ Percent of incidence in total fetuses.
** Significantly different from control (P<0.01) by Student's t test.

H. NEUROTOXICITY

Data for delayed neuropathy, acute neurotoxicity, and developmental neurotoxicity are not currently required under FIFRA guidelines.

I. IMMUNOTOXICITY

Studies have examined the effect of thiabendazole on the mammalian immune system. Some have reported immunosuppression of the inflammatory reactions which play a prominent role in the pathophysiology of helminth infections (Hewlett *et al.,* 1981). A different study indicated that thiabendazole significantly augmented cellular immune responses of mice (Donskaya *et al.,* 1982a,b). Consequently, the net effect of thiabendazole on the immune system is far from clear.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

The main acute toxic effects of thiabendazole were clinical signs (abdominal pain, headaches, dizziness, nausea and vomiting), hepatotoxicity, and developmental toxicity. The principal adverse toxicological effects of thiabendazole from repetitive dosing were thyrotoxicity, hepatotoxicity, nephrotoxicity, anemia and atrial thrombosis. A statistically significant increase in thyroid follicular cell adenomas was seen in male rats; however thiabendazole was not oncogenic in mice. Thiabendazole was genotoxic. A summary of selected toxicity studies presented in this document on the effects of thiabendazole is contained in Table 12.

Acute Toxicity

The principal route of exposure for most pesticide applicators using thiabendazole, was through the skin (Formoli, 1996). Consequently, it would appear to be preferable to use the dose-response of adverse effects observed in short-term dermal toxicity studies as the basis for assessing the risks to workers from short-term exposure to thiabendazole. Such studies were not available in the database. Instead, oral dosing studies were used to estimate margins of exposure from short-term occupational and dietary exposure to thiabendazole.

As developmental toxicity may be manifested as the result of a single dose (Ogata *et al.*, 1984; Schardein, 1985; USEPA, 1991a), it is assumed, in the absence of data to the contrary, that the observed teratogenic effects were elicited from a single dose. Although a developmental endpoint for exposure to toxins is only relevant in women of child-bearing age, the assumption that all other population subgroups are as sensitive results in margins of exposure (MOEs) that protect the health of these other subgroups for other endpoints that may occur at higher dosages. The lowest NOEL from a developmental toxicity study was 10 mg/kg-day for a mean decrement (4.9%) in rat fetal weight at 40 mg/kg-day (Wise, 1990). Because the maternal NOEL was also 10 mg/kg-day for reduced food consumption, it is likely that the decrement in fetal weight was secondary to improper maternal diet, and not caused by a single dose. Other developmental toxicity studies in the mouse, rat and rabbit indicated thiabendazole caused delayed ossification and skeletal malformations during the ontogeny of the respective fetuses (Ogata *et al.*, 1984; IPTP, 1985; Hoberman, 1989). The lowest NOEL for delayed ossification and skeletal malformations in the rabbit was 24 mg/kg (Hoberman, 1989). The lowest ENEL for skeletal malformations in the mouse was 26 mg/kg (Ogata *et al.*, 1984).

Thiabendazole was originally used as a pharmaceutical in the treatment of nematode infestations (Colmore *et al.*, 1965). Consequently, there is a considerable database on the acute undesirable effects of thiabendazole in humans. The principal acute effects reported

were clinical signs and symptoms (abdominal pain, headaches, dizziness, nausea and vomiting) and cholestasis. The LOEL for dizziness from a single oral dose in two clinical trials involving a total of 49 human subjects was 25 mg/kg (Vakil *et al.*, 1966; Sabharwal *et al.*, 1966). The NOEL in a third clinical study involving 42 male subjects was 3.3 mg/kg (Colmore *et al.*, 1965). The question of developmental anomalies amongst humans treated with thiabendazole was not addressed in any of the published papers, or in the data obtained from the Food and Drug Administration. This raises the question of whether clinical signs and symptoms, observed in human studies, should be used as the regulatory endpoint for gauging the risks of short-term occupational and dietary exposure, when a more serious toxicological effect (teratogenicity) can be caused by a single dose of thiabendazole (Ogata *et al.*, 1984).

The lowest NOEL and ENEL for teratogenicity in the rabbit (Hoberman, 1989) and mouse (Ogata *et al.*, 1984) were 24 mg/kg and 26 mg/kg, respectively. If it is assumed that humans are 10 times more sensitive to thiabendazole than the laboratory animals (Davidson *et al.*, 1986; Dourson and Stara, 1983,1985; USEPA, 1986a), the extrapolated "human equivalent" NOEL or ENEL would be 2.4 to 2.6 mg/kg, respectively. Taking into account the uncertainties involved in this cross species extrapolation, these values are probably not different from the demonstrated NOEL of 3.3 mg/kg for clinical signs and changes in blood chemistry from human studies (Colmore *et al.*, 1965; Sabharwal *et al.*, 1966; Vakil *et al.*, 1966). Consequently, the human NOEL (3.3 mg/kg) for clinical signs, symptoms, and changes in blood chemistry was used as the critical acute NOEL to assess the margins of exposure for potential acute occupational and dietary exposures to thiabendazole.

USEPA's draft Re-registration Eligibility Document (RED) for thiabendazole lists the acute reference dose (RfD) as 0.1 mg/kg, based on a critical NOEL of 10 mg/kg for reduced maternal weight gain and food consumption and decreased fetal weight in a rat developmental toxicity study (USEPA, 1999).

Subchronic Toxicity

No seasonal use scenarios were identified in the exposure assessment (Formoli, 1996); therefore, critical subchronic NOELs were not developed for thiabendazole.

Chronic Toxicity

Repetitive dosing with thiabendazole was associated with hepato/biliary toxicity, thyrotoxicity, nephrotoxicity, anemia and atrial thrombosis in laboratory animals. Chronic dietary exposure of mice to thiabendazole at 278 mg/kg-day (males) or 289 mg/kg-day (females) led to a significantly increased incidence of atrial thrombosis and death, with a 2-year NOEL of 92 mg/kg-day (Bagdon *et al*., 1980). The development of thrombi can occur as a result of elevated blood platelet counts (Smith, 1996; Ramos *et al.,* 1996). Although not reported in the mouse, such platelet elevations were seen in both rats and dogs, concomitant with reduced hematocrits, hemoglobin, and red blood cell counts. In dogs, the 2-year NOEL for mild anemia was either 50 mg/kg-day (Woodard and Cronin, 1964), or 40 mg/kg-day (Lankas, 1993), depending upon the dose selection in the study. Similarly, in rats the 2-year NOEL for significantly reduced levels of hemoglobin was 50 mg/kg-day.

Hepato/biliary toxicity, thyrotoxicity, and nephrotoxicity were noted at lower dosages than the anemia. In one dog study (Woodard and Cronin, 1964), moderate inflammatory liver changes, depletion of liver glycogen, and inspissated bile were noted at 125 mg/kg-day. The hepatotoxicity at the middle dose (50 mg/kg-day) amounted to some depletion of liver glycogen and inspissated material in one dog, with a NOEL of 20 mg/kg-day. In a later chronic toxicity

study in dogs (Lankas, 1993), the LOEL for liver failure (one dog), vacuolation of the bile duct and distal tubules of the kidney, and uroepithelial cytoplasmic inclusions was 40 mg/kg-day, with a NOEL of 10 mg/kg-day. In rats, the 2-year LOEL for hepatic microgranulomas, and nephritic transition cell hyperplasia was 50 mg/kg-day, with a NOEL of 25 mg/kg-day (Fuji *et al.*, 1991). In a second rat study, the 2-year LOEL for hepatic centrilobular hypertrophy was 30 mg/kg-day, with a NOEL of 10 mg/kg-day (Wolfe and Squibb, 1994). Hepatic centrilobular hypertrophy is not an adverse effect in itself, merely an indication of hepatic stimulation (Greaves and Faccini, 1984). The critical chronic NOEL chosen was 10 mg/kg-day for hepato/biliary toxicity in dogs (Lankas, 1993), and centrilobular hypertrophy in rats (Wolfe and Squibb, 1994).

USEPA's RED for thiabendazole lists the chronic RfD as 0.1 mg/kg-day, based on a critical NOEL of 10 mg/kg-day for reduced body weight gain and hepatic hypertrophy in a chronic rat toxicity study (USEPA, 1999).

Oncogenicity

The weight of evidence in support of using a linearized model to assess the risks from the oncogenic potential of thiabendazole is equivocal. All of the submitted genotoxicity tests for thiabendazole were negative. However, other, published genotoxicity studies (De Pargament *et al.,* 1987; Zeiger *et al.,* 1988; Ohuchida *et al.,* 1989; Adler *et al.,* 1991; and Mailhes *et al.,* 1997) indicated that thiabendazole caused non-disjunction of chromosomes *in vitro* and *in vivo*. Spindle disruption was to be expected from a compound which exerts fungicide properties through disruption of microtubule formation (Davidse and Flache, 1978). Thiabendazole was not oncogenic in mice (Bagdon *et al.*, 1980). In two different published chronic rat studies using F344 rats, there was significant increase in adenomas of the preputial gland, and a significant increase in clitoral gland tumors in one of the studies at the high dose (200 mg/kg-day) (Hayashida *et al.,* 1985b; Fuji *et al.,* 1991). However, this dose caused excessive toxicity, as body weight was suppressed 40% in both studies, and the tumors were not considered further (USEPA, 1996). No such increase in preputial or clitoral gland adenomas was seen in Sprague-Dawley rats (Wolfe and Squibb, 1994), although the highest dose tested in the latter study was only 92 mg/kg-day. No other compound-related tumors were reported in the F344 rats. There was a significant ($P<0.05$), dose-related increase in thyroid follicular cell adenomas in male Sprague-Dawley rats, but not female rats (Wolfe and Squibb, 1994). There was one incidence of a thyroid follicular cell carcinoma in the high dose group, but there was also a thyroid follicular cell carcinoma in the controls. The combined incidence of adenomas and carcinomas was significantly greater than the controls at the two high doses in male rats. Thus, there is no question that thiabendazole induces tumors of the thyroid follicular cells in rats. The question is how to address the human risk from these tumors.

Ordinarily a linear approach has been used for assessing the oncogenic risks of a chemical (USEPA, 1986b; USEPA, 1996). However, the current USEPA policy on the assessment of risks for thyroid folicular cell tumors is to apply a non-linear approach when certain criteria are met (USEPA, 1998). "Non-linear thyroid cancer dose-response considerations are applied to chemicals that reduce thyroid hormone levels, increase TSH and thyroid cell division, and are judged to lack mutagenic activity" (Hill *et al.,* 1998). There is some evidence that the oncogenic activity of thiabendazole in causing thyroid tumors may arise from disruption of the hormonal axis between the pituitary and the thyroid.

The registrant suggested the development of thyroid adenomas was secondary to hepatotoxicity (Lankas, 1995). The expressed hypothesis was that an increased clearance of T3 and T4 by the over-stimulated liver would lead to a compensatory increase in the output of

TSH. The chronic stimulation of the thyroid follicular cells by elevated levels of TSH would, then, result in thyroid follicular cell hyperplasia and adenomas. An experiment was conducted to try to prove the hypothesis. In a 14 week subchronic, rat toxicity study, thiabendazole at 90 and 270 mg/kg-day caused a significant elevation of TSH and a concomitant hyperplasia of the thyroid follicular cells (Lankas, 1995). Although neither measured serum concentrations of T3 nor T4 seemed to be affected, there was a significantly increased clearance of radiolabeled iodine at a dose of 270 mg/kg-day. This suggests that more thyroid hormone needed to be produced to maintain equilibrium of T3 and T4 in the blood. Serum levels of thyroid stimulating hormone (TSH) were significantly elevated at the two highest doses. This, coupled with the increased incidence of thyroid follicular cell diffuse hyperplasia, suggests that the thyroid was indeed being hyperstimulated. Hyperstimulation of the thyroid was also consistent with the notably significant increased relative thyroid weight. All effects disappeared following a 13 week recovery period. Reversibility of the effects was another criterion set forth by USEPA (USEPA, 1998).

In summary, the weight of evidence does not indicate that the oncogenic potential of thiabendazole should be considered for linear response analysis. 1) Thiabendazole was genotoxic, but the genotoxic effects of thiabendazole were likely related to spindle disruption. Spindle inhibitors are known to have a threshold (Elhajouji *et al.,* 1997, 1998). 2) The thyroid follicular cell tumors produced in response to thiabendazole were likely due to disruption of thyroid hormonal function, as demonstrated in the subchronic rat study (Lankas, 1995). The results of that study were consistent with the USEPA Risk Assessment Forum requirements for use of a non-linear approach for risk assessment of thyroid follicular tumors (USEPA, 1998; Hard, 1998; Hurley *et al.,* 1998; Hill *et al.,* 1998). In keeping with current scientific thought (Lima and Van der Laan, 2000) and USEPA policy on the assessment of risks for thyroid follicular cell tumors (USEPA, 1998), a regulatory NOEL which takes into account hepatic catabolism of thyroid hormones would likely protect against the possible production of thyroid tumors by thiabendazole. The critical chronic NOEL, 10 mg/kg-day for hepato/biliary toxicity in dogs (Lankas, 1993), and hepatic centrilobular hypertrophy in rats (Wolfe and Squibb, 1994), provides this consideration.

It should be noted that there was a thyroid follicular cell tumor in rats at the dose (10 mg/kg-day) which is being set forth as the critical chronic NOEL. However, as one of the control males developed a thyroid follicular cell tumor, the single incidence of a thyroid tumor in male rats at 10 mg/kg-day is considered baseline, and not chemically related. This is consistent with published findings on the incidence of thyroid follicular cell tumors in male Sprague-Dawley rats, which ranges from 0-8.6% with a mean rate of 3.9% (Chandra *et al.,* 1992; McMartin *et al.,* 1992).

Table 12 - Summary of Selected Thiabendazole Toxicology Studies

Study	Species	Route	Effect	LOEL (mg/kg-day)	NOEL (mg/kg-day)	Genotox.	Ref.[a]
Subchronic (14 wk)	rat	gavage	hepatotoxicity, hemopoietic effects	100	25		1
Subchronic (14 wk)	rat	diet	hepatotoxicity, thyrotoxicity	40	10		2
Subchronic (90 d)	dog	capsule	emesis	75	35		3
Subchronic (1d)	human	oral	clinical signs, blood chemistry	25	-		4,5
Subchronic (1d)	human	oral	clinical signs, blood chemistry	-	3.3		6
Chronic (2 yr)	rat	diet	thyroid adenomas, hepatic centrilobular hypertrophy	30	10		7*
Chronic (2 yr)	rat	diet	hepatotoxicity	100	50		8
Chronic (2 yr)	rat	diet	hepatotoxicity, nephrotoxicity	50	25		9
Chronic (1 yr)	dog	capsule	hepato/biliary toxicity	40	10		10*
Chronic (2 yr)	dog	capsule	hepatotoxicity, wt. loss, lacrimation	50	20		11
Chronic (2 yr)	dog	capsule	hepatotoxicity, bone marrow hemosiderosis	100	20		12
Oncogenicity (2 yr)	mouse	diet	atrial thrombosis, death	278	92		13*
Reproduction	rat	diet	decr. parental wt. gain	30	10		14*
Reproduction	mouse	diet	reduced litter size, weanling wt.	75	15		15
Developmental	rat	gavage	decr. fetal wt. gain	40	10		16*
Developmental	rat	diet	retardation of ossification	10	5		17
Developmental	rabbit	gavage	fetal resorption, hydrocephaly	120	24		18*
Developmental	mouse	gavage	skeletal fusion	30	26[+]		19

a/ References- 1. Kangas and Lankas, 1990; 2. Myers and Lankas, 1990; 3. Batham and Lankas, 1990; 4. Bandisode *et al.*, 1966; 5. Sabharwal *et al.*, 1966; 6. Colmore *et al.*, 1965; 7. Wolfe and Squib, 1994; 8. Hayashida *et al.*,, 1985a; 9. Fuji *et al.*, 1991; 10. Lankas, 1993; 11. Woodard and Cronin, 1964; 12. Nessel, 1981a; 13. Bagdon *et al.*, 1980; 14. Lankas and Wise, 1991; 15. Nessel, 1981b; 16. Wise, 1990; 17. IPTP, 1985; 18. Hoberman, 1989; 19. Ogata *et al.*, 1984.

\+ Estimated no effect level (equivalent to an ED01) calculated by probit analysis by the author.

* Study acceptable to DPR under TSCA or FIFRA guideline requirements.

B. EXPOSURE ASSESSMENT

1. Occupational Exposure

Occupational exposures to thiabendazole were calculated by the Worker Health and Safety Branch of DPR. It was concluded that the primary route of occupational exposure to thiabendazole was via the skin, and to a much lesser extent through inhalation (Formoli, 1996). The principal occupational exposures, based on label-approved uses and sales of thiabendazole, were sorting and packing treated fruit, mixer/loader/applicators involved in treating mushrooms, and professional painters handling paint products mixed with thiabendazole. Most product labels require wearing waterproof gloves and protective clothing when applying the formulation. Ready to use dust formulations require a respirator approved by MSHA/NIOSH, goggles, and rubber gloves. The arithmetic mean exposure estimates for the various occupational categories are summarized in Table 13. Exposures for sorters and packers were based on surrogate data from studies involving ortho-phenylphenol (Formoli, 1995). Surrogate data for painter exposures was derived from a study involving paint containing chlorothalonil (Thongsinthusak, 1995). It was assumed that thiabendazole would be applied at the maximum rate in the previous two scenarios. Applications of thiabendazole at the maximum label rate may cause mushroom crop losses (Bautista, 1995), so a lower rate is used in treating mushroom farms. An exposure study using application of cyromazine in poultry houses (Haskell *et al.*, 1993) was used as the surrogate data for bodily exposure of workers treating mushroom crops.

Table 13. Mean ± standard deviation of occupational exposures to thiabendazole[a]

Occupational Category	ADD[b] (µg/kg-day)	AADD[c] (µg/kg-day)
Sorter (pears; n=15)	99.7±54.5	65.6
Sorter (citrus; n=15)	57.2±53.7	37.6
Packer (citrus; n=15)	15.8±12.4	10.4
Packer (pears;n=15)	65.4±19.2	43.0
Interior Painter (brush application; n=4)	152.3±0.1	27.1
Interior Painter (spray application; n=4)	98.0±0.1	17.4
Exterior Painter (spray application; n=4)	47.0±0.1	8.4
Mixer/loader/applicator (mushrooms)	20.7	5.9

a/ Arithmetic mean data derived from Tables 2-5, Formoli, 1996. Assumes maximum application rates for packers, painters and sorters, body weights of 65.1 kg for female workers, and 75.9 kg for male workers.

b/ Absorbed Daily Dosage (ADD) for sorters and packers was based on surrogate data from a study involving ortho-phenylphenol (Formoli, 1995), and the ADDs for painters was based on surrogate data from chlorothalonil-containing paints (Thongsinthusak *et al.*, 1993: Thongsinthusak, 1995). The ADD for mixer/loader/applicators was based on surrogate data from cyromazine applications (Haskell *et al*., 1993).

c/ Annual Average Daily Dosage (AADD) assumes 240 days a year for post harvest applications, 104 days a year for mushroom applications, and 130 days a year for painters.

The approximate 95% confidence limit on the Absorbed Daily Dosage (arithmetic mean plus two standard deviations) ranged from 20.7 µg/kg-day for mixer/loader/applicators working with mushrooms to 209 µg/kg-day for sorters of pears. The Annual Average Daily Dosage (AADD) assumes 240 days a year for post harvest applications; 104 days a year for mushroom applications; and 130 days a year for painters. There were no non-occupational exposures to thiabendazole, except through the diet.

2. Dietary Exposure

The Department of Pesticide Regulation (DPR) evaluates the risk of human exposure to an active ingredient in the diet using two processes: 1) use of residue levels detected in foods to evaluate the risk from total exposure, and 2) use of tolerance levels to evaluate the risk from exposure to individual commodities (see Tolerance Assessment). For the evaluation of risk to detected residue levels, the total exposure in the diet is determined for all label-approved raw agricultural commodities (RACs), processed forms, and animal products (meat and milk) that have established USEPA tolerances. The potential exposure from residues in the water and certain commodities without tolerances is also assessed in some cases. Tolerances may be established for the parent compound and associated metabolites. DPR considers these metabolites and other degradation products that may be of toxicological concern in the dietary assessment.

Consumption Data

The U.S. Department of Agriculture directs the Nationwide Food Consumption Survey (NCFS) and the Continuing Survey of Food Intakes by Individuals (CSFII). The NCFS is a geographically stratified probability sampling of U.S. Households and is conducted every 10 years (1977-78 and 1987-88). The CSFII is an annual survey which reflects the current consumption pattern and has a greater focus on consumption data for vulnerable populations subgroups (*e.g.*, infants and children). The consumption analysis used the three-year data (1989-1990, 1990-1991, and 1991-1992) from the CSFII because they reflected current consumption patterns (USDA, 1989-1991).

Residue Data

The residue data for a dietary exposure assessment are based on DPR and federal monitoring programs, field trials, and survey studies. In the absence of data, surrogate data from the same crop group, as defined by USEPA, or USEPA tolerances are used. Residue levels that exceed established tolerances are not used in the dietary exposure assessments. Over-tolerance incidents are separately investigated by the DPR Pesticide Enforcement Branch. The potential risk from consuming commodities with residues over tolerance levels is evaluated by the Medical Toxicology Branch using an expedited acute risk assessment process.

DPR has two major sampling programs: priority pesticide and marketplace surveillance. Samples for the priority pesticide program are collected from fields known to have been treated with the specific pesticides. For the marketplace surveillance program, samples are collected at the wholesale and retail outlets, and at the point of entry for imported foods. The sampling strategies for both priority pesticide and marketplace surveillance are similar and are weighted toward such factors as pattern of pesticide use; relative number and volume of pesticides typically used to produce a commodity; relative dietary importance of the commodity; past

monitoring results; and extent of local pesticide use. (DPR had two additional monitoring programs prior to 1991: The preharvest monitoring program routinely examined the levels of pesticides on raw agricultural commodities in the field at any time during the growth cycle. Commodities destined for processing were collected in the field no more than 3 days prior to harvest, at harvest, or post-harvest before processing.)

The U. S. Food and Drug Administration (FDA) has three monitoring programs for determining residues in food: (1) regulatory monitoring, (2) total diet study, and (3) incidence/level monitoring. For regulatory monitoring, surveillance samples are collected from individual lots of domestic and imported foods at the source of production or at the wholesale level. In contrast to the regulatory monitoring program, the total diet study monitors residue levels in the form that a commodity is commonly eaten or found in a prepared meal. The incidence/level monitoring program is designed to address specific concerns about pesticide residues in particular foods.

The U. S. Department of Agriculture (USDA) is responsible for the Pesticide Data Program (PDP), a nationwide cooperative monitoring program. The PDP is designed to collect objective, comprehensive pesticide residue data for risk assessments. Several states, including California, collect samples at produce markets and chain store distribution centers close to the consumer level. The pesticide and produce combinations are selected based on the toxicity of the pesticide as well as the need for residue data to determine exposure. In addition, USDA is responsible for the National Residue Program, which provides data for potential pesticide residues in meat and poultry. These residues in farm animals can occur from direct application, or consumption of commodities or by-products in their feed.

Analysis for thiabendazole was not included in DPR surveillance programs for raw agricultural commodities (RACs) from 1987-1995. Data came from the FDA monitoring programs, USDA's PDP program, field studies, and tolerances (Appendix B).

Tolerances are presently established at 40 ppm for residues of thiabendazole on mushrooms; 15 ppm on cantaloupes; 10 ppm on apples, avocados, sugar beet tops, carrots, citrus fruits, grapes, mangos, pears, potatoes, and rice straw; 5 ppm on papayas and strawberries; 3 ppm on bananas and rice; 1 ppm on hubbard squash, wheat and wheat straw; 0.4 ppm on banana pulp and milk, 0.25 ppm on sugar beets; 0.1 on dry beans, soybeans, cattle, eggs, poultry, goats, hogs, horses, and sheep; and 0.02 ppm on sweet potatoes (Code of Federal Regulations, 1995).

Acute (Daily) Exposure

Estimates of potential daily dietary exposure used the highest measured residue values at or below the tolerance for each commodity. For commodities with residues at or below detection limit, a value equal to the MDL is assigned to each commodity. When the residue values are derived from monitoring programs, the assumption is that the data represent high end residue levels in the diet. The use of the data does not account for the potential change in residue levels due to (1) washing and peeling, and (2) food preparation and processing (e.g., cooking and canning).

Daily dietary exposure analyses were conducted using the Exposure-4™ software program developed by Technical Assessment Systems, Inc (TAS). The Exposure-4™ software program estimates the distribution of user-day (consumer-day) exposures for the overall U.S.

population and specific population subgroups (TAS, 1996a). A user-day is any day in which at least one food from the specific commodity list is consumed. The consumption analysis uses individual food consumption data as reported in the 1989-1991 USDA Continuing Surveys of Food Intake of Individuals (USDA, 1989-91). Potential daily ingestion of thiabendazole for all labeled uses, based on the 95th percentile of user-day exposure for all population subgroups, ranged from 27 to 81 µg/kg-day (Table 14). Children 1 to 6 years of age had the highest potential daily dietary exposure to thiabendazole.

Chronic (Annual) Exposure

Estimates of potential annual dietary exposure used the average of measured and "below the detection limit" residue values for each commodity. The default procedure assumed that "below detection limit" residues were equal to one half (50%) of the detection limit for each RAC. The following assumptions were used to estimate potential chronic dietary exposures from measured residues: a) the residue level on an RAC does not change over time, b) residues are not reduced by washing the RAC, d) processing changes the residues to a level equivalent to the RAC residue level multiplied by a concentration factor, and d) exposures to a commodity at all reported residue levels do occur, i.e. a commodity with the average calculated residue is consumed every day at an annual average level (dosage). It was further assumed that 100% of all crops which had a tolerance for thiabendazole were actually treated with the compound.

The potential annual dietary exposure was calculated using the Exposure-1™ software (TAS, 1996b). The food consumption data for the annual analysis were also derived from the USDA Continuing Surveys of Food Intake of Individuals (USDA, 1989-91). Mean daily dietary exposure for all population subgroups ranged from 1.3 to 4.5 µg/kg-day (Table 14). Children one to six years of age had the highest potential annual dietary exposure to thiabendazole.

Table 14. Potential daily and annual dietary exposures to thiabendazole residues

Population Subgroup	Exposure Dosage (µg/kg-day)	
	Daily[a]	Annual[b]
U.S. Pop. (All Seasons)	40	2.3
Western Region	41	2.7
Pacific Region	43	2.6
Nursing Infants (<1 yr)	61	1.6
Non-Nursing Infants (<1 yr)	66	4.3
All Infants	67	3.5
Children (1-6 yrs)	81	4.5
Children (7-12 yrs)	53	2.8
Female (13+ yrs/pregnant/not nursing)	29	1.6
Female (13+ yrs/nursing)	47	2.6
Females (13-19 yrs/not pregnant/not nursing)	27	1.6
Female (20+ yrs/not pregnant/not nursing)	31	2.1
Females (13-50 yrs)	29	1.9
Males (13-19 yrs)	28	1.3
Males (20+ yrs)	29	1.9
Seniors (55+ yrs)	34	2.3
Hispanics	41	2.0
Non-Hispanic Whites	40	2.4
Non-Hispanic Blacks	33	1.6
Non-Hispanic Other	51	3.2

a/ Calculated from highest measured residues, less than tolerance (Appendix B). Based on the upper 95th percentile for user-day exposures in all population subgroups.
b/ Calculated using the arithmetic mean of measured residues.

3. Combined Occupational and Dietary Exposure

The combined exposure levels from occupational and dietary sources are listed in Tables 15 and 16 for daily and annual conditions, respectively. Occupational exposure is the major source of exposure to thiabendazole for workers, but there is also a dietary contribution. In order to estimate the total exposure to thiabendazole from all sources, the dietary exposure of workers was assumed to be equivalent to that of male adults older than 20 years of age. This population subgroup was selected because it matched the profile of most of the agricultural workers and painters in Appendix A.

The potential combined daily exposure to thiabendazole ranged from 45 µg/kg-day for packers of citrus produce, to 181 µg/kg-day for interior painters using a brush application (Table 15). The theoretical, combined daily exposure of the 95% confidence limit on the ADD ranged from 50 µg/kg-day for mixer/loader/applicators working with mushrooms to 238 µg/kg-day for sorters of pears. Under annual exposure conditions the mean potential combined exposures ranged from 8 µg/kg-day (mixer/loader/applicators for mushrooms) to 67 µg/kg-day (pear sorters) (Table 16).

Table 15 - Potential daily occupational, dietary, and combined exposure to thiabendazole

Occupational Category	Occupational ADD[a] (µg/kg-day)	Dietary[b] ADD (µg/kg-day)	Combined ADD (µg/kg-day)
Sorter (pears)	100	29	129
Sorter (citrus)	57	29	86
Packer (citrus)	16	29	45
Packer (pears)	65	29	94
Interior Painter (brush application)	152	29	181
Interior Painter (spray application)	98	29	127
Exterior Painter (spray application)	47	29	76
Mixer/loader/applicator (mushrooms)	21	29	50

a/ Absorbed Daily Dosage (ADD)- mean values from Table 13 were rounded to the nearest whole integer.

b/ The dietary exposure level for workers was the 95th percentile of dietary exposure in male adults 20 years of age and older (Table 14), as this population subgroup matched the profile of most of the agricultural workers and painters.

Table 16 - Potential annual occupational, dietary, and combined exposure to thiabendazole

Occupational Category	Occupational AADD[a] (µg/kg-day)	Dietary AADD (µg/kg-day)	Combined AADD (µg/kg-day)
Sorter (pears)	66	1.9	67
Sorter (citrus)	38	1.9	39
Packer (citrus)	10	1.9	12
Packer (pears)	43	1.9	45
Interior Painter (brush application)	27	1.9	29
Interior Painter (spray application)	17	1.9	19
Exterior Painter (spray application)	8	1.9	10
Mixer/loader/applicator (mushrooms)	6	1.9	8

a/ Annual Average Daily Dosage (AADD)

C. RISK CHARACTERIZATION

The clinical signs and hepatotoxicity observed in both humans and laboratory animals that have been exposed to thiabendazole are assumed to have a biological threshold. Exposure below a certain level is not expected to cause adverse effects. The Margin of Exposure (MOE) for exposure to thiabendazole was calculated as the ratio of an appropriate NOEL established in either human, or laboratory animal studies to the potential exposure dosage estimated for the human population. When the critical NOEL for an adverse effect is derived from a laboratory animal study, a calculated MOE of 100 is generally considered to be adequate for protection against potential chronic toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for intraspecies variability, as well as an uncertainty factor of 10 for inter-species variability. This latter uncertainty factor assumes that humans are 10 times more sensitive to the chronic effects of a toxin than are laboratory animals (Davidson *et al.*, 1986; Dourson and Stara, 1983,1985; USEPA, 1986a). If the critical NOEL is from a human study, a benchmark of 10 is used, incorporating a single uncertainty factor which assumes there is only a 10-fold difference between the least sensitive and the most susceptible human.

$$\text{Margin of Exposure} = \frac{\text{NOEL}}{\text{Exposure Dosage}}$$

1. Occupational Exposure

The margins of exposure for potential, mean, daily exposure, based on a critical NOEL of 3.3 mg/kg-day for clinical signs in humans, ranged from 22 for interior painters using a brush to 209 for packers of citrus fruit (Table 17). Considering the 95% confidence limit (arithmetic mean plus two standard deviations) as an upper limit of exposure for each work task, the MOEs ranged from 16, for sorters working with citrus, to 159 for mixer/loader/applicators working with mushrooms. MOEs for annual occupational exposure to thiabendazole ranged from 152 for sorters of pears to 1,695 for mixer/loader/applicators working with mushrooms.

Table 17. Margins of Exposure for potential daily, and annual occupational exposures to thiabendazole.

Occupational Category	MOE[a] (daily)	MOE[b] (annual)
Sorter (pears)	33	152
Sorter (citrus)	58	266
Packer (citrus)	209	962
Packer (pears)	50	233
Interior Painter (brush application)	22	369
Interior Painter (spray application)	34	575
Exterior Painter (spray application)	70	1,190
Mixer/loader/applicator (mushrooms)	159	1,695

a/ Based on a critical NOEL = 3.3 mg/kg-day for clinical signs in a human study (Colmore *et al.*, 1965). MOE = NOEL (3,300 µg/kg-day) / ADD

b/ Based on a critical NOEL = 10 mg/kg-day for hepato/biliary toxicity in dogs (Lankas, 1993), and centrilobular hypertrophy in rats (Wolfe and Squibb, 1994).
MOE = NOEL (10,000 µg/kg-day) / AADD

2. Dietary Exposure

Daily Exposure

The MOEs for potential daily dietary exposure to thiabendazole, based on an acute NOEL of 3.3 mg/kg for clinical signs in humans, ranged from 41 for children (1-6 yrs) to 123 for females (13-19 yrs/not pregnant/ not nursing) (Table 18).

Annual Exposure

The MOEs for annual dietary risk from the annualized daily dosage of thiabendazole, based on a NOEL of 10 mg/kg-day for hepato/biliary toxicity in dogs and centrilobular hypertropy in rats, ranged from 2,200 for children (1-6 yrs) to 7,700 for males (13-19 yrs) (Table 18).

3. Combined Dietary and Occupational Exposure

MOEs for potential combined daily exposure to thiabendazole ranged from 18, for interior painters using a brush application, to 73 for packers of citrus produce (Table 19). If the theoretical combined dietary and daily exposure of the 95th percentile of workers is considered, the MOEs range from 14 to 66. MOEs for potential combined annual exposure ranged from 149 for pear sorters, to 1,300 for mixer/loader/applicators working with mushrooms.

Table 18. Margins of Exposure for potential daily and annual dietary exposures to thiabendazole residues.

Population Subgroup	Margin of Exposure	
	Daily[a]	Annual[b,c]
U.S. Pop. (All Seasons)	83	4,300
Western Region	77	3,700
Pacific Region	77	3,800
Nursing Infants (<1 yr)	54	6,300
Non-Nursing Infants (<1 yr)	50	2,300
All Infants	50	2,800
Children (1-6 yrs)	41	2,200
Children (7-12 yrs)	62	3,600
Female (13+ yrs/pregnant/not nursing)	114	6,300
Female (13+ yrs/nursing)	70	3,800
Females (13-19 yrs/not pregnant/not nursing)	123	6,300
Female (20+ yrs/not pregnant/not nursing)	107	4,800
Females (13-50 yrs)	115	5,300
Males (13-19 yrs)	120	7,700
Males (20+ yrs)	116	5,300
Seniors (55+ yrs)	98	4,300
Hispanics	80	5,000
Non-Hispanic Whites	82	4,200
Non-Hispanic Blacks	101	5,300
Non-Hispanic Other	65	3,100

a/ Based on NOEL = 3.3 mg/kg-day for clinical signs in a human study (Colmore *et al.*, 1965).

$$\text{MOE} = \frac{\text{NOEL (3,300 µg/kg-day)}}{\text{ADD}}$$

b/ Based on a NOEL = 10 mg/kg-day for hepato/biliary toxicity in dogs (Lankas, 1993), and centrilobular hypertrophy in rats (Wolfe and Squibb, 1994).

$$\text{MOE} = \frac{\text{NOEL (10,000 µg/kg-day)}}{\text{AADD}}$$

c/ Rounded to nearest 100.

Table 19. Margins of exposure for potential daily, and annual combined occupational and dietary exposures to thiabendazole.

Occupational Category	MOE[a] (daily)	MOE[b] (annual)
Sorter (pears)	26	149
Sorter (citrus)	38	256
Packer (citrus)	73	833
Packer (pears)	35	222
Interior Painter (brush application)	18	345
Interior Painter (spray application)	26	526
Exterior Painter (spray application)	43	1,000
Mixer/loader/applicator (mushrooms)	66	1,300

a/ Based on NOEL = 3.3 mg/kg-day for clinical signs in a human study (Colmore *et al.*, 1965).

$$MOE = \frac{NOEL\ (3{,}300\ \mu g/kg\text{-}day)}{ADD}$$

b/ Based on a NOEL = 10 mg/kg-day for hepato/biliary toxicity in dogs (Lankas, 1993), and centrilobular hypertrophy in rats (Wolfe and Squibb, 1994).

$$MOE = \frac{NOEL\ (10{,}000\ \mu g/kg\text{-}day)}{AADD}$$

V. RISK APPRAISAL

Risk assessment is a process used to evaluate the potential for exposure and the likelihood that the toxic effects of a substance may occur in humans under the specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain default assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization, which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar types of uncertainty. However, the degree or magnitude of the uncertainty varies depending on the availability of the data and the exposure scenarios being assessed. Risk, the probability of a compound causing an adverse health effect, is a product of the potential exposure and the toxicity of a compound. Estimation of both of these aspects involves varying degrees of uncertainty, which can affect the accuracy of the risk characterization. Overestimates of potential exposure or toxicity will lead to excessive projections of risk, while under valuation of these aspects would result in underestimates of risk.

A. TOXICOLOGY

In the absence of scientific evidence to the contrary, effects reported in laboratory studies are expected to occur in humans at similar dosages. Specific areas of uncertainty associated with this risk assessment for thiabendazole are delineated in the following discussion.

Acute Toxicity

The acute oral LOEL for thiabendazole was 25 mg/kg, resulting in clinical symptoms (dizziness) in some patients (Colmore, *et al*., 1965). The next lower dose tested was 3.3 mg/kg, eight fold less than the LOEL. The actual NOEL may be somewhat higher than 3.3 mg/kg. It should also be noted that the NOEL used for assessing potential short-term exposures to thiabendazole is based on an oral study, while the principal route of occupational exposure to humans is dermal. Generally speaking, the pharmacokinetics of compounds absorbed through the skin are very different from those same compounds absorbed through the gut (Wester and Maibach, 1983). For a given single day's dosage of thiabendazole, peak blood levels of thiabendazole, derived from dermal exposure during several hours, would be substantially less than levels arising from a single bolus oral dose. This is especially true for the liver as a target organ, because orally ingested materials pass through the hepatic portal system. As the critical acute NOEL is for clinical signs, symptoms and changes in blood chemistry stemming from hepatotoxicity/cholestasis, the margins of exposure are likely to be greater for workers than those that were calculated. In a similar fashion, blood levels arising from consumption of contaminated food during a 24 hour period are likely to be less than those from a single, bolus dose as was given in the test regime. Consequently, MOEs for acute dietary exposure are also likely to be greater than those calculated.

Chronic Toxicity/ Oncogenicity

The toxic effects of thiabendazole due to repetitive dosing caused the selection of a regulatory endpoint for chronic exposure to be a complicated issue. Several factors had to be taken into consideration. The principal target organs in all species were the liver and the biliary system. Hepato/biliary toxicity, principally cholestasis, was manifest in all species examined, including humans. Because the production of thyroid adenomas in male rats was hypothesized to be secondary to hepatotoxicity (Lankas, 1995), it was important to select a regulatory NOEL below a level at which liver effects were noted. In the rat, the LOEL for an observable adaptive response (centrilobular hypertrophy) associated with increased liver metabolism was 30 mg/kg-day, with a NOEL of 10 mg/kg-day (Wolfe and Squibb, 1994). At this dosage in rats, there were no indications of alterations in blood thyroid hormone levels, thyroid weight, or liver weight seen at higher dose levels (90 mg/kg-day) at the end of the 30 day mechanistic study (Lankas, 1995). In one chronic toxicity dog study, depletion of liver glycogen and inspissation of material in the gall bladder were observed at 50 mg/kg-day (Woodard and Cronin, 1964). In a second, more recent chronic toxicity dog study, liver failure in one animal was reported at 40 mg/kg-day, with a NOEL of 10 mg/kg-day (Lankas, 1993). Consequently, the critical regulatory NOEL selected for chronic exposure to thiabendazole was 10 mg/kg-day. It should be noted that in the latter dog study the NOEL for thyroid toxicity (hypertrophy of the thyroid at 160 mg/kg-day) was 40 mg/kg-day (Lankas, 1993). Thus, the regulatory NOEL should be considered health protective for both hepato/biliary effects and thyroid toxicity.

The use of a non-linear approach for assessing the risks of thyroid follicular cell tumors in rats was not without some degree of controversy. The toxicity data for thiabendazole were not unequivocal in support of a non-linear approach as recommended by USEPA for chemicals that reduce thyroid hormone levels, increase TSH and thyroid cell division, and lack mutagenic activity. Thyroid hormone levels in the rat were not reduced by thiabendazole (Lankas, 1995), but the increased clearance of iodinated compounds indicated an increased turnover rate for T3 and T4. The net effect of this was to cause TSH levels to be elevated, which resulted in a

stimulation of the thyroid. Proof of the hormonal thyroid stimulation was provided by the observed thyroid follicular cell hyperplasia (Lankas, 1995).

Thiabendazole does not appear to lack mutagenic activity. A positive response in *Salmonella typhimurium* strain 98 was reported in a published summary of mutagenicity tests for 300 chemicals (Zeiger *et al.,* 1988). This would indicate some degree of mutagenicity for thiabendazole. However, three other studies, with detailed information, using the same strain (TA98) did not report mutations (Shirasu *et al.,* no date-c; Merck, 1969, 1977). Thus, the mutagenicity issue is somewhat unclear. All other genotoxic effects involved spindle disruption (Mailhes *et al.,* 1997; Pargament *et al.,* 1988), which is known to have a threshold (Elhajouji *et al.,* 1997, 1998). The USEPA document on the Assessment of Thyroid Follicular Cell Tumors states: “A linear dose-response procedure should be assumed when the mode of action underlying thyroid tumors is judged to involve mutagenicity alone” (USEPA, 1998: p3 item b). Apparently, an epigenetic mechanism for generating thyroid tumors does exist. Therefore, despite equivocal evidence of mutagenicity, a non-linear approach to risk assessment was used.

At least three authors claim that chemical induction of thyroid follicular cell adenomas in male rats may have no relevance to possible oncogenicity in humans (McClain, 1992; MacDonald *et al*., 1994; Alison *et al*., 1994). They suggest that rodent thyroid adenomas are unique products of the stimulatory effect of elevated levels of thyroid stimulating hormone (TSH). Because epidemiological data in humans do not indicate clear associations between goiter, produced by a variety of mechanisms, and thyroid cancer (Hill *et al*., 1989), the authors essayed that the relative susceptibility of rodents and humans to thyroid neoplasia, secondary to hormone imbalance, could be assessed by comparing humans in iodine deficient areas of endemic goiter to rats in these same areas, or rats treated with iodine deficient diets. The authors pointed out that endemic goiter affects millions of individuals, but extensive epidemiological studies have not established a clear etiological relationship to thyroid gland neoplasia in humans. In contrast, rodents sampled in areas of endemic human goiter, or those treated with iodine deficient diets have exhibited a high incidence of thyroid gland neoplasia (McClain, 1992). While these epidemiological data are suggestive, the negative correlations do not constitute unequivocal proof that chemically-induced stimulation of thyroid hypertrophy cannot lead to tumor formation in humans.

B. EXPOSURE

Occupational

No dermal absorption data for thiabendazole were available. Consequently, it was assumed that dermal absorption would be 100% (Formoli, 1996). This assumption probably results in an overestimate of the occupational exposure, as the range of measured dermal absorption of pesticides in humans was <1% to nearly 74% (Wester and Maibach, 1993; Thongsinthusak, 1996). Because exposures for work tasks associated with applications of thiabendazole came from surrogate data, these data carry a greater degree of uncertainty than would data derived from actual measurements using thiabendazole. Additional uncertainty arises from the fact that 10% of the dermal patches analyzed in the occupational exposure studies involving surrogate pesticides contained non-detectable levels of residues. However, it is unclear whether this results in an over- or under-estimate of exposure.

Dietary

Some practices, such as the sampling of RACs as composites, could lead to underestimates of potential daily dietary exposure. In general, though, sampling procedures, default assumptions for non-detectable residue levels, assumptions on the fate of residues on commodities, and assumptions regarding the percentage of crops treated with thiabendazole are likely to contribute to an overestimation of the potential dietary exposure. Specifically, it was assumed that 100% of the various crops were treated with thiabendazole. In the absence of chemical-specific data, it was assumed that residues of thiabendazole would be found in fruit juices, even though there were processing studies indicating other fungicides were not present in juice. The consumption data contained in the USDA survey may not be an accurate representation of actual dietary consumption by each of the population subgroups. Coding and reporting errors, response and sampling bias, and variation in culinary habits over the sampling period resulted in uncertainties in consumption data which can lead to either over- or underestimates of exposure (Bingham, 1991).

The probability of the dietary contribution to the daily exposure of an individual in a given population subgroup is a product of the probabilities that 1) an individual would consume a sufficient amount of the commodities to be in the 95th percentile of daily dietary exposure dosages and 2) the commodities would all contain the maximum residue levels. Clearly, this is an overestimate of daily dietary exposure.

Combined Dietary/Occupational

The potential combined daily dietary and occupational exposures indicated in Table 14 are probably over-estimations of the actual exposures, as it is improbable that all of the assumptions made in the calculation of combined exposure dosage would be met. It is unlikely that the agricultural workers engaged in thiabendazole application would also be in the 95th percentile of consumption of commodities, each commodity contaminated with maximum thiabendazole residues. It is highly unlikely that the 95th percentile of occupationally exposed workers would also be in the 95th percentile of dietary consumption.

C. RISK CHARACTERIZATION

When the critical NOEL for an adverse effect is derived from a laboratory animal study, a calculated MOE of 100 is generally considered to be adequate for protection against potential chronic toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for intraspecies variability, as well as an uncertainty factor of 10 for inter-species variability. This latter uncertainty factor assumes that humans are 10 times more sensitive to the chronic effects of a toxin than are laboratory animals (Davidson *et al.*, 1986; Dourson and Stara, 1983,1985; USEPA, 1986a). If the critical NOEL is from a human study, a benchmark of 10 is used, incorporating a single uncertainty factor which assumes there is only a 10-fold difference between the least sensitive and the most susceptible human.

D. FEDERAL FOOD QUALITY PROTECTION ACT

The Federal Food Quality Protection Act of 1996 (FQPA) requires USEPA to set health-based tolerances using an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data with respect to exposure and toxicity to infants and children. A different safety factor may be used only if, on the basis of

reliable data, such a factor will be safe for infants and children. In addition, USEPA must consider available information on: 1) aggregate exposure from all non-occupational sources; 2) effects of cumulative exposure to the pesticide and other substances with mechanisms of toxicity in common; 3) the effects of *in utero* exposure; and 4) the potential for endocrine disrupting effects.

Pre-/Post-Natal Sensitivity

FQPA requires USEPA to set health-based tolerances using an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data with respect to exposure and toxicity to infants and children. As discussed in the Hazard Identification portion of this document, thiabendazole has adverse pre-natal effects. The compound was associated with a wide spectrum of developmental toxicity in three species of laboratory animals (mouse, rat and rabbit), ranging from the induction of major malformations to fetal resorption (abortion). The lowest NOEL for this type of developmental toxicity was 24 mg/kg-day based on fetal resorption and hydrocephaly in rabbits (Hoberman, 1989). Consequently, an additional uncertainty factor should probably be considered by USEPA.

Endocrine Effects

Thiabendazole has not been shown to adversely affect reproduction. However, there is evidence to suggest that it causes an elevation of thyroid stimulating hormone (TSH), resulting in hypertrophy of the thyroid gland. Consequently, thiabendazole may be subject to the provisions of FQPA dealing with “endocrine disrupters”, and as such an additional uncertainty factor may be appropriate.

Multiple Chemical (Cumulative) Exposure

Thiabendazole is a benzimidazole fungicide. It is unclear at this time if thiabendazole has any cumulative (i.e., combined) toxicity due to a common mechanism of toxicity with other benzimidazoles or any other chemicals. Given the uncertainty about any potential combined toxicity, this risk assessment only addressed those factors which are specific to the toxicity of thiabendazole.

Aggregate Exposure

Thiabendazole is unlikely to become a groundwater contaminant because of low water solubility and immobility in soil. Thiabendazole did not have any non-occupational residential exposures, other than dietary. Aggregate daily occupational and dietary MOEs ranged from 18 to 73, and aggregate annual MOEs ranged from 116 to 975. Exposure to thiabendazole through the dietary route, no matter what the tolerance on any given commodity, would not be increased for the general public from non-dietary sources.

VI. TOLERANCE ASSESSMENT

A. BACKGROUND

USEPA is responsible under the Federal Food, Drug, and Cosmetic Act (FFDCA) for setting tolerances for pesticide residues in raw agricultural commodities (Section 408 of FFDCA) and processed commodities (Section 409 of FFDCA). A tolerance is the legal maximum residue concentration of a pesticide which is allowed on a raw agricultural commodity or processed food. The tolerances are established at levels necessary for the maximum application rate and frequency, and not expected to produce deleterious health effects in humans from chronic dietary exposure (USEPA, 1991b). The data requirements for tolerances include: (1) residue chemistry, (2) environmental fate, (3) toxicology, (4) product performance such as efficacy, and (5) product chemistry (Code of Federal Regulations, 1996). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications and formulations proposed (USEPA, 1982).

In 1996, the Food Quality Protection Act (FQPA) amended the overall regulation of pesticide residues under FIFRA and FFDCA (USEPA, 1997b,c). One major change was the removal of the Delaney Clause that prohibited residues of cancer-causing pesticides in processed foods. The tolerances must be health-based and the same standards are used to establish tolerances for both the raw agricultural commodities and their processed forms. FQPA required an explicit finding that tolerances are safe for children. USEPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data unless USEPA determined, based on reliable data, that a different margin would be safe. In addition, the evaluations of the tolerance must take into account: (1) aggregate exposure from all non-occupational sources, (2) effects from cumulative exposure to the pesticide and other substances with common mechanisms of toxicity, (3) effects of *in utero* exposure; and (4) potential for endocrine disrupting effects. (Discussion of these issues specific to thiabendazole is in the Risk Appraisal section.)

Under FQPA, USEPA is also required to reassess all existing tolerances and exemptions from tolerances for both active and inert ingredients by 2006 (USEPA, 1997d). Previously, USEPA reassessed tolerances as part of its reregistration and Special Review processes. In the evaluation of tolerances, the USEPA uses a tiered approach and the assessment includes all label-use commodities.

In California, USEPA established tolerances are evaluated under the mandate of Assembly Bill 2161, generally referred to as the Food Safety Act (Bronzan and Jones, 1989). The Act requires DPR to conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides. In these assessments, the tolerance for each specific commodity is evaluated individually and is discussed in the following sections. For a pesticide registered for use on a large number of commodities, tolerance assessments are conducted for only a group of selected fruits and vegetables. Generally, commodities are selected from all the uses based on the potential for high levels of exposure.

B. ACUTE EXPOSURE

An acute exposure assessment using the residue level equal to the tolerance is conducted for each individual label-approved commodity. The TAS Exposure-4® software program and the individual food consumption data as reported in the 1989-1991 USDA Continuing Surveys of Food Intake of Individuals (USDA, 1989-91) are used in this assessment. The acute tolerance assessment does not routinely address multiple commodities at the tolerance levels as the probability of consuming multiple commodities at the tolerance decreases as the number of commodities included in the assessment increases. Therefore, residue levels for thiabendazole were set equal to the tolerance, and the MOE, based on the upper 95th percentile for user-day exposures for each population subgroup was examined for the most highly consumed commodities (FDA, 1991). The MOEs for population subgroups theoretically exposed to tolerance levels of thiabendazole residues on label-approved commodities are presented in Table 20. Only the tolerances on the most frequently consumed commodities were examined, as it is assumed that the MOEs for lesser consumed commodities would be as great or greater.

The MOEs were over 10 for all population subgroups theoretically exposed to tolerance levels of residue on: avocados, bananas, dry beans, sugar beets, cantaloupes, carrots, citrus, grapes, mangos, mushrooms, papayas, pears, potatoes, rice, soybeans, strawberries, sweet potatoes, Hubbard squash, wheat, meat, milk, and eggs. MOEs were 9 or less for at least two, but not all population subgroups (with sufficient consumption data) for theoretical exposure to tolerance levels of residues on apples.

C. ANNUAL EXPOSURE

An annual exposure assessment using residues equal to the established tolerances for individual or combinations of commodities has not been conducted because it is highly improbable that an individual would chronically consume single or multiple commodities with pesticide residues at the tolerance levels. Support for this conclusion comes from FDA and DPR (formerly California Department of Food and Agriculture) pesticide monitoring programs which indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (CDFA, 1990).

Table 20 - MOE for theoretical daily dietary exposure to tolerance levels of thiabendazole residues for the most highly consumed commodities[a]

Agricultural Commodity	Tolerance (ppm)	Margin of Exposure (Range)[b]
Apples	10	4 - 83
Avocados	10	100 - 814
Bananas	3	332 - 2,000
Beans (dry)	0.1	852 - 3,000
Cantaloupe	15	42 - 270
Carrots	10	1,000 - 14,000
Citrus	10	242 - 8,000
Grapes	10	11 - 146
Milk	0.4	319 - 3,000
Mushrooms	40	162 - 632
Pears	10	12 - 234
Potatoes	10	4,000 - 10,000
Rice	3	108 - 394
Strawberries	5	262 - 30,000

a/ Based on the 95th percentile of user-days for all population subgroups.

b/ Based on NOEL = 3.3 mg/kg-day for clinical signs in a human study (Colmore *et al.*, 1965).

$$\text{MOE} = \frac{\text{NOEL (3300 µg/kg-day)}}{\text{ADD}}$$

VII. CONCLUSIONS

Margins of exposure for potential daily and annual exposures to workers associated with handling and application of thiabendazole, and to the general public exposed via dietary consumption were greater than the values conventionally recommended to protect people from the toxic effects of a chemical.

The USEPA tolerance for thiabendazole on apples does not provide a margin of exposure greater than the value conventionally recommended to protect people from the toxic effects of a chemical for theoretical daily dietary exposure to one or more population subgroups if commodities are consumed with residues at the tolerance level. Thiabendazole has adverse pre-natal effects and causes disruption of endocrine levels associated with overall metabolism; effects which should be taken into consideration when USEPA reviews the tolerance levels under the Food Quality Protection Act.

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IX. APPENDICES

APPENDIX A

EXPOSURE ASSESSMENT

ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA TO THE PESTICIDE PRODUCTS THAT CONTAIN

THIABENDAZOLE

BY

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HS-1727 May 8, 1996

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ABSTRACT

Thiabendazole (TBZ) is a fungicide that is used for postharvest application to fruit and vegetables. It can also be mixed with paint to inhibit the growth of mildew. During 1982 to 1992, a total of 17 human illness/injury cases associated with exposure to TBZ were reported in California. Most of these cases were skin rashes that occurred following handling treated fruit in packing facilities. When given orally, TBZ is rapidly absorbed and almost completely metabolized by humans. The two major metabolites are the glucuronide and the sulfate ester of 5-hydroxy thiabendazole. TBZ was used for several years as a human anthelmintic in the U.S., and is still used for this purpose in some countries. No dermal absorption study is available to indicate the dermal absorption rate. Therefore, a dermal absorption of 100% was assumed to estimate human exposure in terms of absorbed dosage. There were no worker exposure studies for TBZ. Surrogate data and the pesticide handler exposure data base (PHED) version 1.1, were used to estimate exposure to workers potentially exposed to TBZ. The estimated absorbed daily dosage (ADD) for packers and sorters handling treated fruit and painters applying paints mixed with TBZ ranged from 16 to 100 µg/kg/day.

This exposure assessment document was prepared because animal toxicology studies have shown that TBZ may be a teratogen. It will be a part of the risk characterization document for TBZ.

Department of Pesticide Regulation
Worker Health and Safety Branch

Human Exposure Assessment

Thiabendazole

May 8, 1996

INTRODUCTION

Thiabendazole (TBZ) was originally introduced as an anthelmintic in humans and veterinary medicine and later as an agricultural fungicide. In California, TBZ is currently registered as a fungicide for postharvest application to fruits and vegetables. In 1984, the California Senate Bill 950 (SB 950) or the Birth Defect Prevention Act was signed into law. SB 950 requires the Department of Pesticide Regulation (DPR) to evaluate the mandatory health effects studies of pesticides. TBZ is on the list of the first 200 pesticides to be reviewed under SB 950. DPR is currently preparing a risk characterization document for TBZ because animal toxicity studies have shown that it may be a teratogen. Human exposure assessment is essential for the assessment of risk to those that are potentially exposed and is an integral part of the risk assessment process. This human exposure assessment document was prepared to be incorporated into the risk characterization document for TBZ. It will also serve as a basis for developing mitigation strategies if exposure is found to cause excessive theoretical risk.

CHEMICAL/PHYSICAL PROPERTIES

TBZ (CAS #148-79-8) is the common name for 2-(4-thiazolyl)-benzimidazole. Its empirical formula is $C_{10}H_7N_3S$ with the molecular weight of 201.25. TBZ is a white crystalline powder that melts at approximately 300 ^oC. It is soluble in most organic solvents but essentially insoluble (30 ppm) in water at room temperature. It quickly photodecomposes in water with a half life ($t_{1/2}$) of less than 24 minutes but slowly decomposes in the soil and air. It has a $t_{1/2}$ of 128 days in the air @ 30 ^oC (Merck, 1986). It has a vapor pressure of approximately 4×10^{-9} mm Hg @ 25 ^oC (Merck, 1987). Octanol/water partition coefficient (K_{ow}) is 285 @ 25 ^oC (Merck, 1986).

USAGE

TBZ is a fungicide that is registered in California for postharvest application to fruits and vegetables such as citrus, apples, pears, potatoes, carrots, and mushrooms. It can also be mixed with paint to inhibit the growth of mildew. The total uses in California for 1991, 1992, and 1993 are shown in Table 1. Based on these reports the application to citrus is the predominant use constituting more than 80% of the total use during 1992 and 1993. Apples and mushrooms each account for approximately 5% of the total use. The balance were applied to other commodities

such as potatoes, carrots, and outdoor or greenhouse grown flower bulbs. The use in paint was not included in these use reports. The total sales in California for 1991, 1992, and 1993 were approximately 14,900, 36,650, and 28,090 lb, respectively (DPR, 1993a, DPR, 1994a, DPR, 1995a). The use in paint products is partly the reason for the difference between the sale and use figures, as the use in paint products does not require reporting. TBZ hypophosphite salt use was very limited (6 lb in 1992).

Table 1. Report of Thiabendazole Use in California During 1991 to 1993

	1991[a]		1992 [b]		1993 [c]	
Uses	Pounds	Percent	Pounds	Percent	Pounds	Percent
Citrus	5,760	53	22,330	88	14,870	80
Apples	350	3	1,310	5	960	5
Mushrooms	840	8	1,210	5	1,270	7
Others	3850	36	480	2	1,550	8
Total	10,800	100	25,330	100	18,650	100

a - DPR, 1993
b - DPR, 1994
c - DPR, 1995

Formoli, WH&S, 1995

Citrus can be treated by using a liquid ready-to-use spray (0.1 % formulation) at a rate of one gal. for coating 8,000 lb citrus. A 98.5% dry formulation (powder) is mixed with wax to make 1,000 to 5,000 ppm a.i. suspension that is applied to citrus going into storage at one gal/8,000 to 10,000 lb of citrus, using spray or drip nozzle applicators. TBZ is also used as a slurry with water (1,000 to 2,000 ppm a.i.) for drenching citrus in bins. A 575-g bag (98.5% powder) is diluted in 150 gallons of water to treat 45 bins or approximately 225,000 lb of citrus. Apples and pears can be sprayed, dipped, waxed, or drenched at storage and before packout.

Mushrooms can be treated at the maximum application rate of 8 fl. oz/1,000 ft^2 (0.24 lb a.i./ 1,000 ft^2) of a liquid formulation during casing, fuzzing, pinning, and between breaks. Mushrooms are treated by applying in water during normal watering or by a hand spray. Carrots are treated by dipping in a 1,500 ppm suspension for 5 to 10 seconds. Ornamental bulbs are treated by dipping for 10-15 seconds. Potatoes on a conveyer line are misted with 0.42 fl. oz to 2,000 lb (3.8 lb a.i/gal.) in adequate water for coverage when entering storage. A 0.5 % dust formulation can also be used for cut seed potatoes at one lb/100 lb of cut potatoes, using dust dispensing equipment with a hopper. According to Title 3, California Code of Regulation (CCR) Section 6400(a), pesticides in the form of dust are classified as Restricted Materials and, therefore, must be used by or under the supervision of a certified applicator. The use on potatoes did not show a trend and averaged approximately 95 lb a year from 1991 through 1993.

Both powder and liquid concentrate formulations are used in paint products. The viscous liquid concentrates are available in 9- or 10-g packets. The content of one packet is mixed with one gallon of paint, stain, or wallpaper paste to inhibit the growth of mildew in these products when used indoors or outdoors.

FORMULATION

As of June 21, 1995, 24 TBZ-containing products were registered in California, including one product that contained TBZ hypophosphite salt. These products include various formulations such as wettable powders with 50% or 98.5% a.i., liquid concentrates with 42% (3.8 lb/gal) or 50% a.i., ready to use dust with 0.5% a.i., and ready to use liquid containing 0.1% a.i.

LABEL PRECAUTIONS

TBZ products are toxicity category III pesticides for oral toxicity, bearing the signal word "Caution" on their labels. The labels contain precautionary statements regarding the hazards of ingestion, inhalation, and dermal contact. Most product labels, including the one that can be used on mushrooms, require wearing waterproof gloves and protective clothing when handling. The ready to use dust formulation requires a respirator approved by MSHA/NIOSH, goggles, and rubber gloves when handling.

WORKER ILLNESSES

From 1982 through 1992, a total of 17 illness/injury cases were reported to the DPR illness surveillance program that were associated with exposure to TBZ alone or in combination with other pesticides in California (DPR, 1995b). Of the 17 cases, 6 were classified as probable and 11 as possible cause of exposure. One case involved a ground applicator with systemic illness. The remaining 16 cases were all skin rashes, mostly to hands, arms, and face, that developed following handling treated fruits in packing facilities. With the exception of one case which did not describe whether or not hospitalization occurred, none of these illness/injuries required hospitalizations.

DERMAL IRRITATION AND SENSITIZATION

There was no evidence of dermal irritation when TBZ was applied to the shaved intact skin of rabbits (Lankas, 1981). TBZ was negative in a dermal sensitization study in guinea pigs (Nessel, 1981). There are two studies related to allergic contact dermatitis in humans after exposure to TBZ in occupational settings. In the first study, 3 out of 204 workers adding TBZ to animal feed tested positive for allergic contact dermatitis (Mancuso *et al*., 1990). The second study was a case study which indicated that the allergic response to TBZ may be aggravated by solar exposure (Izu *et al*., 1993).

DISLODGEABLE FOLIAR RESIDUES

TBZ is applied post-harvest. No dislodgeable foliar residues are expected. However, dislodgeable residues from treated fruit or vegetables have the potential to expose workers handling the treated commodities. To our knowledge there are no dislodgeability studies for TBZ on fruit.

METABOLISM

TBZ was rapidly absorbed and almost completely metabolized by humans (4 males weighing 66 to 89 kg) after a single oral administration of 1g TBZ labeled with 25 μc ^{14}C (Tocco *et al*., 1966). Plasma samples were taken 1, 2, 4, 8, 24, 48, and 72 hours after dosing. Complete urine samples were collected at 0-4, 4-8, 8-12, 12-24 hours and daily thereafter for the next four days. Feces were collected each day for five days. Radiometric and fluorometric analyses showed peak plasma levels one to two hours following the administration, declining to almost zero in 24 to 48 hours after the administration. A large quantity of radioactivity (84%) was excreted in urine within the first 24 hours. Less than 1% of the dose was excreted as unchanged TBZ or unconjugated 5-hydroxy thiabendazole. Glucuronide of 5-hydroxy thiabendazole and sulfate ester of 5-hydroxy thiabendazole accounted for 25% and 13%, respectively, of the dose in urine. Approximately 50% of the dose in human urine remained unidentified. Only 4 to 9% of the administered dose was found in feces during the five-day monitoring period.

In the same study, rats dosed with 100 mg/kg excreted 92% of the dose in urine (66%) and feces (26%) within 48 hours. Rats dosed with 25 mg/kg excreted 79% in urine (49%) and feces (30%) within 48 hours. As in humans, the major metabolite excreted in the urine was the hydroxylated derivative, largely conjugated. In dogs, 35% and 46% of the administered dose were excreted in urine and feces, respectively, within 72 hours of dosing.

It appears that TBZ is rapidly metabolized and excreted after an oral administration to humans and some other mammals such as rats, and dogs. It undergoes hydroxylation at the 5-position. Since the glucuronide and the sulfate ester of 5-hydroxy thiabendazole in urine together accounted for approximately 32% of the administered dose in humans, the use of the deconjugated metabolites may be feasible for biomonitoring of occupational exposure to TBZ.

DERMAL ABSORPTION

A summary of toxicological, pharmacological, and antifungal properties of TBZ reported that a formulated product readily penetrated the intact skin when applied topically *in vitro* to the epidermis and allowed to diffuse through the skin for 40 hours (Robinson *et al*., 1969). The percent of dermal absorption was not provided in this report. In the absence of any information on dermal absorption rate, a dermal absorption of 100% will be assumed in this exposure assessment.

WORKER EXPOSURE

TBZ uses in California are limited to postharvest applications to fruit and vegetables, to mushrooms, and to paint products as a fungicide. The use on potatoes is minor and did not show a trend, averaging approximately 95 lb a year during 1991 to 1993. Therefore, the potential for exposure of farm pesticide handlers and field workers is minimum. The workers with potential exposure are the mixer/loaders handling the product for postharvest applications, packing house workers handling the treated commodities, mixer/loader/applicators treating mushrooms, and painters handling paint products mixed with TBZ.

Sorters and Packers Postharvest Application Exposure:

There are no studies available that monitored the exposure of workers handling TBZ during postharvest applications or to workers handling commodities treated with TBZ. A study that monitored the exposure of workers handling pear and citrus fruit (oranges and grapefruit) treated with ortho-phenylphenol (OPP) in packing facilities is available in the DPR library. The review of this study by the DPR (Formoli, 1995) shows that the methods of postharvest application of OPP in this study are similar to those of TBZ. The work tasks (grading and packing) that were monitored in this study are identical to the work tasks involved during handling of commodities treated with TBZ. Generally, fruit packing facilities use conveyers to move fruit through the processing activities that include cleaning, treating with fungicides, inspection, grading, and packing. The estimates of exposure from reviewing the OPP study will be used as surrogate to estimate the exposure of graders and packers handling fruit such as citrus, apples, and pears treated with TBZ. During this study, pears in bins were dipped in an OPP solution tank. The pears were then moved to the conveyer belts for washing, treating with other fungicides, waxing, drying, grading/sorting, and finally packing. The treatment solution was normally prepared using open pour mixing. The technical aspects of citrus processing were similar to those of pears, except citrus was treated by foaming or spraying OPP solution on fruit. The concentration of the dip solution for treatment of pears ranged between 1,400 and 2,400 ppm OPP. The concentration of the treatment solution applied to citrus as spray or foam ranged between 5,400 and 12,900 ppm. The label-recommended concentrations of TBZ solution for postharvest treatment of fruit and vegetables are within these ranges.

In packing facilities, sorters and packers are the two job classifications that handle treated fruit following treatment. These workers wear cotton or rubber gloves as a common practice to protect the fruit and their hands from physical damage. A total of 62 workers from 6 packing facilities, all females, participated in this study. While participants were asked not to wear gloves to simulate worst case conditions, the objective was not achieved for most pear packers and some citrus packers. Packers wore cotton gloves but the sorters did not wear gloves in the pear packing facilities tested. Only the packers in one facility (# 6) wore gloves during citrus treatment.

Inhalation exposure was monitored by collecting air samples from the breathing zone of workers, using personal air samplers equipped with a Gelman GLA 5000 polyvinyl chloride filter and an SKC 780-milligram silica gel sorbent tube. Dermal exposure was monitored using cotton T-

shirts worn under long-sleeved work shirts during the entire work shift. Both the T-shirts and work shirts were collected at the end of the work shift. Hand exposure was monitored by removing the gloves, when applicable, and collecting hand rinses when workers normally washed their hands. Hand rinses were not collected for two workers identified as alternates.

All samples were placed on dry ice and shipped to the analytical laboratory. Both field and laboratory spike samples were collected for all matrices. Field spike recoveries were generally above 90%. The results of sample analysis were corrected for average field spike recoveries that were less than 100%. Dermal dosimeters and hand washes that contained no detectable residues were assumed to contain residues at half the detection limit. Dermal exposure was calculated for a worker wearing a short-sleeved shirt by combining the residues found in the T-shirt, in the sleeves of work shirt, and in the hand washes. The exposure to body parts below the torso was considered insignificant because of the lack of any contact of those body parts with the treated fruits during packing and sorting activities.

Average clothing penetration based on residues found in T-shirts and in work shirts ranged from 12% to 40% for the sorters and from 11% to 27 % for the packers. Average clothing penetration between pear and citrus workers were not significantly different. Table 2 shows the average dermal exposure and concentration in the breathing zone of packers and sorters as grouped for the commodities they handled. In general, average dermal and potential inhalation exposure levels of sorters were higher compared to those of packers. Workers monitored in citrus facilities had lower dermal and inhalation exposure levels than those monitored in pear facilities.

Table 2. Dermal and Potential Inhalation Exposure of Sorters and Packers Handling Pears and Citrus Treated with OPP

Work Task (n)	Commodity	Breathing zone ($\mu g/m^3$)	Hands (µg)	Arms (µg)	T-shirt (µg)	Total Dermal[a] (µg)
packer (15)	pear	75	430	2,700	890	4,020 ± 1,180
packer (15)	citrus	6	500	380	100	970 ± 760
sorter (15)	pear	96	1,840	3,300	990	6,130 ± 3,350
sorter (15)	citrus	38	1,550	1,680	280	3,520 ± 3,300

a - Arithmetic mean ± standard deviation.

Formoli, WH&S, 1995

Using the OPP study as surrogate, Table 3 shows the estimated absorbed daily dosages (ADD) for packers and sorters handling fruit treated with TBZ. Considering the low vapor pressure of TBZ, inhalation exposure is considered insignificant in packers' and sorters' working areas. In the absence of a study to indicate the dermal absorption rate of TBZ, a dermal absorption rate of 100% was assumed in estimating ADD in Table 3.

Table 3. Estimated Absorbed Daily Dosage for Sorters and Packers Handling Fruit Treated with Thiabendazole

Work Task	Commodity	Dermal Exposure (µg/day)	ADD[a] (µg/kg/day)
packer	pear	4,020	65.4
packer	citrus	970	15.8
sorter	pear	6,130	99.7
sorter	citrus	3,520	57.2

a - Based on body weight of 61.5 kg (Thongsinthusak *et al*., 1993), dermal absorption of 100% (see dermal absorption section), and an 8-hour workday for a female worker.

Formoli, WH&S, 1995

Mixer/Loaders Postharvest Application Exposure

TBZ products are mixed with wax to make a 1,000 to 5,000 ppm a.i. suspension that is applied to citrus going into storage at one gal/8,000 to 10,000 lb of citrus, using spray or drip nozzle applicators. TBZ is also mixed with water (1,000 to 2,000 ppm a.i.) for drenching citrus in bins. Generally, a 575-g bag of TBZ (98.5% a.i.) is diluted in 150 gallons of water to treat 45 bins or approximately 225,000 lb of citrus. Each bin is dipped in the solution for approximately three minutes. At the above application rates, a worker may need to prepare the treatment solution only once during an eight-hour workday. Mixing/loading in most citrus packing houses is performed by the pest control operators (PCO) of TBZ suppliers (Clodt, 1995; Ball, 1995). TBZ bags are water soluble, and in most packing houses, the PCOs dump a bag in the water tank that will last for two to three days of operation. It appears that the exposure to the PCOs is minimal.

Painters Exposure:

TBZ products for use in paint are usually in 9- to 10-g packets containing 50% a.i. The content of one packet is added into one gal. of paint and mixed. The exposure during adding and mixing is assumed negligible because of the small amount of the product that can be handled and short duration of handling in a workday. However, workers are potentially exposed to TBZ in the paint during painting. There are no data available that monitored the exposure of painters to TBZ. In the absence of the a.i. specific data, two sources of surrogate data were identified. The first one is the pesticide handlers exposure database (PHED) and the second one is the review by DPR of a painter exposure monitoring study (Thongsinthusak, 1995). Both surrogates are discussed below:

The PHED version 1.1, 1995 was used to estimate exposure during application of paints containing TBZ. The following subsets were selected for the applicator file:

Dermal grade: A, B, C
Hand grade: A, B
Application method: Paint brush

A total of 15 records were found in the PHED with the above subsets. The dermal grade C was included in the selection since the selection of only grades A, B would result in zero records. The grading determines the quality of the data in terms of compliance with Subdivision U guidelines of U.S. EPA. The data in the PHED were for applicators using paint brushes painting interior walls with a paint that was premixed with a fungicide. Using the PHED as a surrogate, the estimate of dermal exposure for a painter wearing work clothing and no gloves was 288,928 µg/lb a.i. applied (see attachment I). Hand exposure constituted 96% of the total dermal exposure. A professional painter may apply as much as 40 gallons of paint in an 8-hour workday, using a commercial airless sprayer (see a painter exposure study discussed below). This level of efficiency is impossible when using a paint brush or a roller. Assuming a painter that is using a paint brush could apply as much as 4 gal. of paint which contains 5 g TBZ per gallon, the total a.i. applied would be 20 g or 0.04 lb a.i. in a workday. Based on a dermal absorption of 100% and body weight of 75.9 kg, the estimate of ADD for a worker can be calculated as follows:

ADD = (288,928 µg/lb x 0.04 lb/day)/75.9 kg = 152.3 µg/kg/day
The estimate of inhalation exposure was 277 µg/lb a.i., based on an inhalation rate of 0.84 m^3/hr (Thongsinthusak *et al*., 1993). The estimate of inhalation exposure may be conservative for TBZ which has a very low vapor pressure, but still insignificant when compared to the estimate of dermal exposure.

In a painter exposure study that was reviewed by the DPR (Thongsinthusak, 1995), three formulations of paint containing chlorothalonil were used. The paint formulations were latex-based exterior, latex-based interior, and alkyd-based exterior containing approximately 45, 18, and 27 g a.i./gal., respectively. Four workers were monitored for each paint formulation. Each worker was monitored during three replicates, generating 12 replicates for each paint formulation. Each replicate consisted of spraying 5 gal. of paint, using a commercial airless sprayer. The application period ranged from 22 to 81 minutes for each replicate. Assuming a worker could apply 5 gal. in one hour, a total of 40 gal. could be applied by a worker during an 8-hour workday.

Dermal exposure was monitored by using a whole body dosimeter that was worn beneath work clothing. Hand exposure was measured by using 100% cotton gloves worn under the protective gloves. Head exposure was monitored by using two gauze patches. To monitor inhalation exposure, air samples from the breathing zone of workers were taken by using a glass fiber filter cassette and a sorbent tube containing Chromosorb 102 that were attached to a personal air sampling pump.

The mean recoveries for the field fortified samples were above 95% for all three paint formulations, therefore, the estimates of exposure were not adjusted for recoveries. Since the data for total exposure (dermal + inhalation) are log-normally distributed, the data are expressed as geometric mean (GM) and geometric standard deviation (GSD). When wearing protective gloves, the exposure to head and neck comprised 76% of the total dermal exposure with arms and hands contributing 10% and 1%, respectively. Inhalation exposure was approximately 4% or less of total exposure for the exterior formulations (outdoor use) and 10% of the total exposure for the interior formulation (indoor use). The vapor pressure of chlorothalonil is 5.72 x 10^{-7} (Thongsinthusak, *et al*., 1993a), and therefore, the particulates generated in the air during

spraying are likely to have caused the inhalation exposure to be significant. TBZ vapor pressure is within the range of the vapor pressure of chlorothalonil. Table 4 shows the estimate of ADD for painters applying TBZ based on the estimate of dermal and inhalation exposure of painters in the review of the chlorothalonil study.

Table 4. Thiabendazole Estimate of ADD for Painters Based on Dermal and Inhalation Exposure of Painters During Application of Chlorothalonil-Containing Paints

	Latex-exterior	Latex-interior	Alkyd-exterior
Dermal exposure (µg/hr)	2,620	2,970	2,320
Inhalation exposure (µg/hr)	110	350	60
Total exposure (µg/hr)[a]	2,730 ± 1.68	3,330 ± 1.60	2,390 ± 1.61
ADD (µg/kg/day)[b]	288	351	252
ADD(µg/kg/day)[c]	32	98	47

a - Work clothing and gloves, geometric mean ± geometric standard deviation.
b - Dermal and inhalation absorption of 100%, 8-hour workday, and body weight of 75.9 kg.
c - Adjusted for TBZ concentration of 5 g a.i./gal. paint from chlorothalonil concentrations of 45 g (Latex-exterior), 18 g (Latex-interior), and 27 g (Alkyd-exterior) a.i./gal. paint.

Formoli, WH&S, 1995

Worker Exposure During Application to Mushrooms:
TBZ can be applied to mushrooms by a hand wand connected to a pressurized solution container during normal watering. The maximum application rate is 0.24 lb a.i./1,000 ft^2. There are no studies available that monitored the exposure of workers applying TBZ to mushrooms in mushroom houses. In the absence of the a.i. specific data, two sources of surrogate were identified. The first one is the PHED and the second one is the review by DPR of a worker exposure study that monitored the exposure of workers applying cyromazine to poultry houses (Haskell *et al*., 1993). Using the PHED, the following subsets were selected for the mixer/loader/applicator file:

Dermal grade: A, B, C
Hand grade: A, B, C
Location: Indoor
Application method: Low pressure hand wand
Formulation type: Liquid

There were 9 records found with the selection of the above subsets. Narrowing the subset selection to only grades A and B would result in finding zero records. The PHED estimate of dermal exposure for a mixer/loader/applicator using a low pressure hand wand for indoor application was 169.7 µg/lb a.i. handled (see attachment I). This estimate is for a clothing scenario of long-sleeved shirt, long pants, and gloves. Approximately 26% and 30% of the total dermal exposure occurred to head and legs, respectively. Inhalation exposure was estimated at

14.6 µg/lb a.i. handled, based on an inhalation rate of 14 L/minute for adult males (Thongsinthusak *et al*., 1993). The estimate of inhalation exposure may be conservative for TBZ which has a vapor pressure that is lower than that of cyromazine. According to the 1993 use report, 1,270 lb of TBZ were applied to 13,055,800 ft^2 of mushroom beds in 1,360 applications. This is equivalent to an average of approximately 0.1 lb of a.i./1,000 ft^2 or 1 lb of a.i./application (10,000 ft^2). This is consistent with the application rate of 0.06 lb a.i./1,000 ft^2 in three applications, for a total of 0.18 lb a.i./1,000 ft^2/crop as practiced by some mushroom growers (Bautista, 1995). Applications at the maximum label rate may cause crop losses. The application is made by certified applicators. They will treat two rooms or approximately 10,000 ft^2/day, one to two days a week.

Below is the estimate of exposure (ADD), assuming a worker would spray 10,000 ft^2 in a workday at the maximum application rate of 0.24 lb a.i./1,000 ft^2. This is equivalent to handling 2.4 lb a.i. in a workday. The assumption is conservative since it is apparent from the use data that applications are mostly well below the maximum label application rate. Using the PHED as a surrogate, the ADD for a mixer/loader/applicator wearing work clothing and gloves can be calculated as follows:

ADD = (169.7 µg/lb x 2.4 lb)/75.9 kg = 5.4 µg/kg/day

The review by DPR of the cyromazine study (Haskell *et al*., 1993) estimated a dermal exposure of 655 µg/lb a.i. for a mixer/loader/applicator using a hand held sprayer. Inhalation exposure was based on samples with non-detectable levels and assumed exposure at half the minimum detectable limit (MDL). The estimate of inhalation exposure was at the same range as that of the PHED. Based on 655 µg/lb a.i. dermal exposure, the ADD can be calculated as follows:

ADD = (655 µg/lb x 2.4 lb)/75.9 kg = 20.7 µg/kg/day

There is less than four fold difference between these two estimates. The later estimate of exposure is more conservative and will be used in this exposure assessment.

Table 5 is a summary of the estimates of ADD and annual average daily dosage (AADD) for workers performing various work tasked during handling TBZ-containing products or TBZ treated commodities. Since the application of TBZ to fruit and mushrooms is a year-around activity, AADDs were estimated based on the number of days a worker could be exposed. The estimate of the number of days that citrus is treated with TBZ ranges from 150 days (Ball, 1995) to 300 days (Sales, 1995) during a year. Therefore, a worker that is working five days a week (excluding vacation and holidays) could be exposed 240 days a year. The estimate of exposure for applicators of mushroom houses is one to two days a week (Bautista, 1995) or 52 to 104 days a year. In much of California, the weather is dry enough for painting approximately six to eight months in a year. Painters were assumed to be exposed to paints treated with TBZ for approximately half of this period or three months in a year.

Table 5. Summary of Thiabendazole Estimated ADD for Various Work Tasks

Work Task	ADD[a] (µg/kg/day)	AADD[b] (µg/kg/day)
Sorter (postharvest)	57.2 to 99.7	37.6 to 65.6
Packer (postharvest)	15.8 to 65.4	10.4 to 43.0
Painter (paint brush interior)	152.3	27.1
Painter (airless spray interior)	98.0	17.4
Painter (airless spray exterior)	47.0	8.4
Mixer/loader/Applicator (mushrooms)	20.7	5.9

a - Clothing: Long-sleeved shirt, long pants, and gloves (no gloves for painters using paint brush, sorters and packers wore gloves as a common practice to protect the fruit and their hands).

b - Exposure of 240 days in a year for postharvest applications, 104 days for mushroom applications, and 65 days for painters.

Formoli, WH&S, 1995

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ATTACHMENT I

PAINTER (PAINT BRUSH, INTERIOR)

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, Long sleeves, no gloves

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS PER LB AI SPRAYED Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (REAL)	Lognormal	3411.850	5871.0879	119.0746	2478.0132	14
NECK.FRONT	Lognormal	603.825	3203.5920	167.6246	785.9412	15
NECK.BACK	Other	21.736	105.4937	172.9478	39.0046	15
UPPER ARMS	Lognormal	287.508	1432.5736	215.8231	538.4358	15
CHEST	Other	350.740	7948.0003	238.3180	1051.7277	15
BACK	Other	350.740	1509.1287	206.7452	561.6448	15
FOREARMS	Lognormal	3464.956	11935.5610	152.0554	4285.5991	15
THIGHS	Other	377.416	352.0512	19.0136	343.7148	15
LOWER LEGS	Other	235.144	219.3408	19.0136	214.1469	15
FEET						0
HANDS	Lognormal	298745.098	307656.6638	46.5584	279504.4054	15
TOTAL DERM:	288928.1707	307849.013	340233.493		289802.6335	
INHALATION:	Other	276.6798	258.0898	19.0085	251.9871	15
COMBINED:	289204.8505	308125.6928	340491.5828		290054.6206	

95% C.I. on Mean: Dermal: [-1995727.507, 2676194.4932]

95% C.I. on Geo. Mean: Inhalation: [155.3757, 408.6708]

Inhalation Rate : 14 Liters/Minute
Number of Records: 15
Data File: APPLICATOR Subset Name: THIABEN.APPL

DATA ANALYSIS SECTION: FILE/SUBSET SELECTION

Name: THIABEN.APPL

MLAP.FILE APPL.FILE FLAG.FILE MIXLD.FILE

Name Found, proceeding normally...
<<Specifications >> Page 1 of 1
Subset Specifications for THIABEN.APPL

With Application Method Equal to 8 and
With Dermal Grade Uncovered Equal to “A” “B” “C” and
With Hand Grade Equal to “A” “B”
Subset originated from APPL.FILE

MIXER/LOADER/APPLICATOR (LOW PRESSURE HAND WAND, INDOOR)

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, Long sleeves, gloves

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS PER LB AI SPRAYED Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (REAL)	Lognormal	13.520	95.9689	161.5896	37.5130	9
NECK.FRONT	Lognormal	4.065	7.3967	116.9075	4.3270	9
NECK.BACK	Normal	1.144	2.7243	101.6775	1.9155	9
UPPER ARMS	Normal	15.132	29.9407	99.9395	22.7111	9
CHEST	Other	18.460	146.2600	242.8398	34.8928	9
BACK	Other	18.460	66.9372	201.2858	29.0838	9
FOREARMS	Other	6.292	6.2920	0	6.2920	9
THIGHS	Other	19.864	37.9878	115.1859	27.6737	9
LOWER LEGS	Lognormal	12.376	66.9309	164.3135	30.0241	9
FEET						0
HANDS	Other	2.0833	2.0833	0	2.0834	9
TOTAL DERM:	169.6884	111.3963	462.5218		196.5164	
INHALATION:	Other	14.5833	14.5833	0	14.5828	9
COMBINED:	184.2717	125.9796	477.1051		211.0992	

95% C.I. on Mean: Dermal: [-8383.8174, 9308.861]

95% C.I. on Geo. Mean: Inhalation: [14.5828, 14.5828]

Inhalation Rate : 14 Liters/Minute
Number of Records: 9
Data File: MIXER/LOADER/APPLICATOR Subset Name: THIABEN.MLAP

DATA ANALYSIS SECTION: File/Subset Selection

Name: THIABEN.MLAP

<<Specifications >> Page 1 of 1
Subset Specifications for THIABEN.MLAP

With Liquid Type Equal to 1 or Equal to 2 or Equal to 4 or Equal to 5
Subset originated from Thiaben.MLAP
With Dermal Grade Uncovered Equal to “A” “B” “C” and
With Hand Grade Equal to “A” “B” “C” and
With Indoor Equal to “X” and
With Application Method Equal to 7
Subset originated from MLAP.FILE

APPENDIX B

RESIDUE VALUES

Residue file name: THIBNDA Analysis date: 08-28-1996/11:36:36
NFCS87/88 DATA Adjustment factor #2 NOT used
DPR NOEL (Acute) = 3.300000 mg/kg body-wt/day
COMMENT 1: Values from FDA surveillance, field studies, or equal to the USEPA tolerances
COMMENT 2: All label-approved uses for thiabendazole

RESIDUE FILE LISTING

TAS CODE	CROP GRP SOURCE	RESIDUE (PPM)	Adj Factor			FOOD NAME	
13	01014AA , N,	0.010000	1.000	1.000	0	"GRAPES",	"FDA"
14	01014DA , N,	0.010000	4.300	1.000	0	"GRAPES-RAISINS"	"FDA"
15	01014JA , N,	0.010000	1.200	1.000	0	"GRAPES-JUICE"	"FDA"
17	01016AA , N,	1.800000	1.000	1.000	0	"STRAWBERRIES"	"FDA"
20	02001AA , K,	0.020000	1.000	1.000	0	"CITRUS CITRON"	"PDP"
22	02002AB , K,	0.770000	1.000	1.000	0	"GRAPEFRUIT-PEELED FRUIT"	"PDP"
23	02002JA , K,	0.010000	2.100	1.000	0	"GRAPEFRUIT-JUICE"	"PDP"
24	02003AA , K,	0.050000	1.000	1.000	0	"KUMQUATS",	"FS"
26	02004AB , K,	0.010000	1.000	1.000	0	"LEMONS-PEELED FRUIT"	"PDP"
27	02004HA , K,	0.010000	1.000	1.000	0	"LEMONS-PEEL"	"PDP"
28	02004JA , K,	0.010000	2.000	1.000	0	"LEMONS-JUICE"	"PDP"
30	02005AB , K,	0.050000	1.000	1.000	0	"LIMES-PEELED FRUIT"	"FS"
31	02005HA , K,	0.050000	1.000	1.000	0	"LIMES-PEEL"	"FS"
32	02005JA , K,	0.050000	2.000	1.000	0	"LIMES-JUICE"	"FS"
33	02006JC , K,	0.010000	6.700	1.000	0	"ORANGES-JUICE-CONCENTRATE"	"FDA"
34	02006AB , K,	9.100000	1.000	1.000	0	"ORANGES-PEELED FRUIT"	"PDP"
35	02006HA , K,	9.100000	1.000	1.000	0	"ORANGES-PEEL"	"PDP"
36	02006JA , K,	0.050000	1.800	1.000	0	"ORANGES-JUICE"	"FDA"
37	02007AA , K,	0.050000	1.000	1.000	0	"TANGELOS"	"FS"
38	02008AA , K,	7.400000	1.000	1.000	0	"TANGERINES"	"FDA"
39	02008JA , K,	0.050000	2.300	1.000	0	"TANGERINES-JUICE"	"FS"
52	04001AA , L,	6.100000	1.000	1.000	0	"APPLES"	"PDP"
53	04001DA , L,	6.100000	8.000	1.000	0	"APPLES-DRIED"	"PDP"
54	04001JA , L,	0.680000	1.300	1.000	0	"APPLES-JUICE/CIDER"	"FDA"
56	04003AA , L,	1.600000	1.000	1.000	0	"PEARS"	"FDA"
57	04003DA , L,	1.600000	6.250	1.000	0	"PEARS-DRIED"	"FDA"
70	06001AA , A,	10.000000	1.000	1.000	0	"AVOCADOS"	"TOL"
71	06002AA , A,	0.400000	1.000	1.000	0	"BANANAS, OTHER VARIETIES"	"PDP"
72	06002AB , A,	0.400000	1.000	1.000	0	"BANANAS"	"PDP"
73	06002DA , A,	0.400000	3.900	1.000	0	"BANANAS-DRIED"	"PDP"
80	06007AA , A,	0.700000	1.000	1.000	0	"MANGOES"	"FS"
83	06010GA , A,	5.000000	1.000	1.000	0	"PAPAYAS-GREEN"	"TOL"
84	06010AB , A,	5.000000	1.000	1.000	0	"PAPAYAS-PULP"	"TOL"
85	06010DA , A,	5.000000	1.800	1.000	0	"PAPAYAS-DRIED"	"TOL"
86	06010JA , A,	5.000000	1.500	1.000	0	"PAPAYAS-JUICE"	"TOL"
141	10002NA , J,	15.000000	1.000	1.000	0	"CANTALOUPES-NECTAR"	"TOL"
142	10002AB , J,	15.000000	1.000	1.000	0	"CANTALOUPES-PULP (MUSKMELON)"	"TOL"
150	10013AA , J,	1.000000	1.000	1.000	0	"SQUASH-SUMMER"	"TOL"
198	14003AA , B,	0.010000	1.000	1.000	0	"CARROTS"	"FDA"
208	14013AB , B,	2.700000	1.000	1.000	0	"POTATOES(WHITE)-UNSPECIFIED"	"PDP"
209	14013AC , B,	2.700000	1.000	1.000	0	"POTATOES(WHITE)-PEELED"	"PDP"
210	14013DA , B,	2.700000	6.500	1.000	0	"POTATOES(WHITE)-DRY"	"PDP"
211	14013HA , B,	2.700000	1.000	1.000	0	"POTATOES(WHITE)-PEEL ONLY"	"PDP"
227	15001AA , G,	0.070000	1.000	1.000	0	"BEANS-DRY-GREAT NORTHERN"	"FS"
228	15001AB , G,	0.070000	1.000	1.000	0	"BEANS-DRY-KIDNEY"	"FS"
229	15001AC , G,	0.070000	1.000	1.000	0	"BEANS-DRY-LIMA"	"FS"
230	15001AD , G,	0.070000	1.000	1.000	0	"BEANS-DRY-NAVY (PEA)"	"FS"
231	15001AE , G,	0.070000	1.000	1.000	0	"BEANS-DRY-OTHER"	"FS"
232	15001AF , G,	0.070000	1.000	1.000	0	"BEANS-DRY-PINTO"	"FS"
249	15022AA , G,	0.070000	1.000	1.000	0	"BEANS-DRY-BROADBEANS"	"FS"
251	15023AA , G,	0.070000	1.000	1.000	0	"BEANS-DRY-PIGEON BEANS"	"FS"
256	15030AA , G,	0.070000	1.000	1.000	0	"BEANS-DRY-HYACINTH"	"FS"
258	15031AA , G,	0.070000	1.000	1.000	0	"BEANS-DRY-BLACKEYE PEAS/COWPEA"	"FS"
259	15032AA , G,	0.070000	1.000	1.000	0	"BEANS-DRY-GARBANZO/CHICK PEA"	"FS"
261	16003AA , A,	40.000000	1.000	1.000	0	"MUSHROOMS"	"FS"
270	24004AA , O,	3.000000	1.000	1.000	0	"RICE-ROUGH (BROWN)"	"TOL"
276	24007AA , O,	0.010000	1.000	1.000	0	"WHEAT-ROUGH"	"FDA"
277	24007GA , O,	0.010000	1.000	1.000	0	"WHEAT-GERM"	"FDA"
278	24007HA , O,	0.010000	1.000	1.000	0	"WHEAT-BRAN"	"FDA"

279	24007WA , O,	0.010000	1.000	1.000	0	"WHEAT-FLOUR"		"FDA"
303	15023AA , G,	0.020000	1.000	1.000	0	"SOYBEANS-UNSPECIFIED"		"FS"
304	28023AB , G,	0.020000	1.000	1.000	0	"SOYBEANS-MATURE SEEDS DRY"		"FS"
305	28023WA , G,	0.020000	1.000	1.000	0	"SOYBEANS-FLOUR (FULL FAT)"		"FS"
306	28023WB , G,	0.020000	1.000	1.000	0	"SOYBEANS-FLOUR (LOW FAT)"		"FS"
307	28023WC , G,	0.020000	1.000	1.000	0	"SOYBEANS-FLOUR (DEFATTED)"		"FS"
315	43058AA , A,	0.010000	1.000	1.000	0	"GRAPES-WINE AND SHERRY"		"FDA"
318	50000DB , X,	0.400000	1.000	1.000	0	"MILK-NONFAT SOLIDS"		"TOL"
319	50000FA , X,	0.400000	1.000	1.000	0	"MILK-FAT SOLIDS"		"TOL"
320	50000SA , X,	0.400000	1.000	1.000	0	"MILK SUGAR (LACTOSE)"		"TOL"
321	53001BA , U,	0.100000	1.000	1.000	0	"BEEF-MEAT BYPRODUCTS"		"TOL"
322	53001BB , U,	0.100000	1.000	1.000	0	"BEEF(ORGAN MEATS)-OTHER"		"TOL"
323	53001DA , U,	0.100000	1.920	1.000	0	"BEEF-DRIED"		"TOL"
324	53001FA , U,	0.100000	1.000	1.000	0	"BEEF(BONELESS)-FAT"		"TOL"
325	53001KA , U,	0.100000	1.000	1.000	0	"BEEF(ORGAN MEATS)-KIDNEY"		"TOL"
326	53001LA , U,	0.100000	1.000	1.000	0	"BEEF(ORGAN MEATS)-LIVER"		"TOL"
327	53001MA , U,	0.100000	1.000	1.000	0	"BEEF(BONELESS)-LEAN (FAT/FREE)"		"TOL"
328	53002BA , U,	0.100000	1.000	1.000	0	"GOAT-MEAT BYPRODUCTS"		"TOL"
329	53002BB , U,	0.100000	1.000	1.000	0	"GOAT(ORGAN MEATS)-OTHER"		"TOL"
330	53002FA , U,	0.100000	1.000	1.000	0	"GOAT(BONELESS)-FAT"		"TOL"
331	53002KA , U,	0.100000	1.000	1.000	0	"GOAT(ORGAN MEATS)-KIDNEY"		"TOL"
332	53002LA , U,	0.100000	1.000	1.000	0	"GOAT(ORGAN MEATS)-LIVER"		"TOL"
333	53002MA , U,	0.100000	1.000	1.000	0	"GOAT(BONELESS)-LEAN (FAT/FREE)"		"TOL"
334	53003AA , U,	0.100000	1.000	1.000	0	"HORSE"		"TOL"
336	53005BA , U,	0.100000	1.000	1.000	0	"SHEEP-MEAT BYPRODUCTS"		"TOL"
337	53005BB , U,	0.100000	1.000	1.000	0	"SHEEP(ORGAN MEATS)-OTHER"		"TOL"
338	53005FA , U,	0.100000	1.000	1.000	0	"SHEEP(BONELESS)-FAT"		"TOL"
339	53005KA , U,	0.100000	1.000	1.000	0	"SHEEP(ORGAN MEATS)-KIDNEY"		"TOL"
340	53005LA , U,	0.100000	1.000	1.000	0	"SHEEP(ORGAN MEATS)-LIVER"		"TOL"
341	53005MA , U,	0.100000	1.000	1.000	0	"SHEEP(BONELESS)-LEAN (FAT FREE"		"TOL"
342	53006BA , U,	0.100000	1.000	1.000	0	"PORK-MEAT BYPRODUCTS"		"TOL"
343	53006BB , U,	0.100000	1.000	1.000	0	"PORK(ORGAN MEATS)-OTHER"		"TOL"
344	53006FA , U,	0.100000	1.000	1.000	0	"PORK(BONELESS)-FAT"		"TOL"
345	53006KA , U,	0.100000	1.000	1.000	0	"PORK(ORGAN MEATS)-KIDNEY"		"TOL"
346	53006LA , U,	0.100000	1.000	1.000	0	"PORK(ORGAN MEATS)-LIVER"		"TOL"
347	53006MA , U,	0.100000	1.000	1.000	0	"PORK(BONELESS)-LEAN (FAT FREE)"		"TOL"
355	55008BA , V,	0.100000	1.000	1.000	0	"TURKEY-BYPRODUCTS"		"TOL"
356	55008LA , V,	0.100000	1.000	1.000	0	"TURKEY-GIBLETS (LIVER)"		"TOL"
357	55008MA , V,	0.100000	1.000	1.000	0	"TURKEY-(BONELESS)-FAT"		"TOL"
358	55008MB , V,	0.100000	1.000	1.000	0	"TURKEY-(BONELESS)LEAN/FAT FREE"		"TOL"
359	55008MC , V,	0.100000	1.000	1.000	0	"TURKEY-UNSPECIFIED"		"TOL"
360	55013BA , V,	0.100000	1.000	1.000	0	"POULTRY-OTHER-LEAN (FAT FREE)"		"TOL"
361	55013LA , V,	0.100000	1.000	1.000	0	"POULTRY-OTHER-GIBLETS(LIVER)"		"TOL"
362	55013MA , V,	0.100000	1.000	1.000	0	"POULTRY-OTHER-FAT"		"TOL"
363	55014AA , X,	0.100000	1.000	1.000	0	"EGGS-WHOLE"		"TOL"
364	55014AB , X,	0.100000	1.000	1.000	0	"EGGS-WHITE ONLY"		"TOL"
365	55014AC , X,	0.100000	1.000	1.000	0	"EGGS-YOLK ONLY"		"TOL"
366	55015BA , V,	0.100000	1.000	1.000	0	"CHICKEN-BYPRODUCTS"		"TOL"
367	55015LA , V,	0.100000	1.000	1.000	0	"CHICKEN-GIBLETS(LIVER)"		"TOL"
368	55015MA , V,	0.100000	1.000	1.000	0	"CHICKEN (BONELESS)-FAT"		"TOL"
369	55015MB , V,	0.100000	1.000	1.000	0	"CHICKEN(BONELESS)LEAN/FAT FREE"		"TOL"
377	04001JC , L,	0.680000	3.900	1.000	0	"APPLES-JUICE-CONCENTRATE"		"FDA"
378	06002NA , A,	0.400000	1.000	1.000	0	"BANANAS-NECTAR"		"PDP"
379	25002MO , B,	0.250000	1.000	1.000	0	"BEET SUGAR-MOLASSES"		"TOL"
385	55015EL , V,	0.100000	1.000	1.000	0	"CHICKEN-GIBLETS (EXCL. LIVER)"		"TOL"
392	01014JC , N,	0.010000	3.600	1.000	0	"GRAPES-JUICE-CONCENTRATE"		"FDA"
404	04003NA , L,	1.600000	1.000	1.000	0	"PEARS-NECTAR"		"FDA"
416	01016JA , N,	1.800000	1.000	1.000	0	"STRAWBERRIES-JUICE"		"FDA"
424	56000FA , U,	0.100000	1.000	1.000	0	"VEAL-(BONELESS)-FAT"		"TOL"
425	56000MA , U,	0.100000	1.000	1.000	0	"VEAL-(BONELESS)-LEAN (FAT FREE"		"TOL"
426	56000KA , U,	0.100000	1.000	1.000	0	"VEAL-(ORGAN MEATS)-KIDNEY"		"TOL"
427	56000LA , U,	0.100000	1.000	1.000	0	"VEAL-(ORGAN MEATS)-LIVER"		"TOL"
428	56000BB , U,	0.100000	1.000	1.000	0	"VEAL-(ORGAN MEATS)-OTHER"		"TOL"
429	56000DA , U,	0.100000	1.920	1.000	0	"VEAL-DRIED"		"TOL"
430	56000BA , U,	0.100000	1.000	1.000	0	"VEAL-MEAT BYPRODUCTS"		"TOL"
437	24007OL , O,	0.010000	1.000	1.000	0	"WHEAT-GERM OIL"		"FDA"
438	20000AA , A,	6.100000	1.000	1.000	0	"WI-APPLE"		"FDA"
441	02002JC , K,	0.050000	8.260	1.000	0	"GRAPEFRUIT-JUICE-CONCENTRATE"		"FS"
442	02004JC , K,	0.010000	11.400	1.000	0	"LEMONS-JUICE-CONCENTRATE"		"FS"
443	02005JC , K,	0.050000	6.000	1.000	0	"LIMES-JUICE-CONCENTRATE"		"FS"
448	02002HA , K,	0.770000	1.000	1.000	0	"GRAPEFRUIT PEEL"		"PDP"

Chronic Exposure (EX1) Analysis for Thiabendazole
RESIDUE FILE NAME: THIBNDC ANALYSIS DATE: 08-28-1996/11:49:01

NFCS87/88 DATA ADJUSTMENT FACTOR #2 NOT USED
EPA Reference dose (RfD, chronic) = 7.800000 mg/kg body-wt/day
COMMENT 2: Chronic Dietary Exposure to Thiabendazole

RESIDUE FILE LISTING

TAS CODE	CROP GRP	RESIDUE (PPM)	ADJ. FCTRS #1	#2		FOOD NAME	SOURCE CODE
13	01014AA , N,	0.005000	1.000	1.000	0	"GRAPES",	"FDA"
14	01014DA , N,	0.005000	4.300	1.000	0	"GRAPES-RAISINS",	"FDA"
15	01014JA , N,	0.005000	1.200	1.000	0	"GRAPES-JUICE",	"FDA"
17	01016AA , N,	0.070000	1.000	1.000	0	"STRAWBERRIES",	"FDA"
20	02001AA , K,	0.020000	1.000	1.000	0	"CITRUS CITRON",	"PDP"
22	02002AB , K,	0.106000	1.000	1.000	0	"GRAPEFRUIT-PEELED FRUIT",	"PDP"
23	02002JA , K,	0.010000	2.100	1.000	0	"GRAPEFRUIT-JUICE",	"PDP"
24	02003AA , K,	0.025000	1.000	1.000	0	"KUMQUATS",	"FS"
26	02004AB , K,	0.005000	1.000	1.000	0	"LEMONS-PEELED FRUIT",	"PDP"
27	02004HA , K,	0.005000	1.000	1.000	0	"LEMONS-PEEL",	"PDP"
28	02004JA , K,	0.005000	2.000	1.000	0	"LEMONS-JUICE",	"PDP"
30	02005AB , K,	0.025000	1.000	1.000	0	"LIMES-PEELED FRUIT",	"FS"
31	02005HA , K,	0.025000	1.000	1.000	0	"LIMES-PEEL",	"FS"
32	02005JA , K,	0.025000	2.000	1.000	0	"LIMES-JUICE",	"FS"
33	02006JC , K,	0.005000	6.700	1.000	0	"ORANGES-JUICE-CONCENTRATE",	"FDA"
34	02006AB , K,	0.940000	1.000	1.000	0	"ORANGES-PEELED FRUIT",	"PDP"
35	02006HA , K,	0.940000	1.000	1.000	0	"ORANGES-PEEL",	"PDP"
36	02006JA , K,	0.020000	1.800	1.000	0	"ORANGES-JUICE",	"FDA"
37	02007AA , K,	0.025000	1.000	1.000	0	"TANGELOS",	"FS"
38	02008AA , K,	4.800000	1.000	1.000	0	"TANGERINES",	"FDA"
39	02008JA , K,	0.025000	2.300	1.000	0	"TANGERINES-JUICE",	"FS"
52	04001AA , L,	0.632000	1.000	1.000	0	"APPLES",	"PDP"
53	04001DA , L,	0.632000	8.000	1.000	0	"APPLES-DRIED",	"PDP"
54	04001JA , L,	0.181000	1.300	1.000	0	"APPLES-JUICE/CIDER",	"FDA"
56	04003AA , L,	0.240000	1.000	1.000	0	"PEARS", "FDA"	
57	04003DA , L,	0.240000	6.250	1.000	0	"PEARS-DRIED",	"FDA"
70	06001AA , A,	5.000000	1.000	1.000	0	"AVOCADOS",	"TOL"
71	06002AA , A,	0.079000	1.000	1.000	0	"BANANAS, OTHER VARIETIES",	"PDP"
72	06002AB , A,	0.079000	1.000	1.000	0	"BANANAS",	"PDP"
73	06002DA , A,	0.079000	3.900	1.000	0	"BANANAS-DRIED",	"PDP"
80	06007AA , A,	0.600000	1.000	1.000	0	"MANGOES",	"FS"
83	06010GA , A,	2.500000	1.000	1.000	0	"PAPAYAS-GREEN",	"TOL"
84	06010AB , A,	2.500000	1.000	1.000	0	"PAPAYAS-PULP",	"TOL"
85	06010DA , A,	2.500000	1.800	1.000	0	"PAPAYAS-DRIED",	"TOL"
86	06010JA , A,	2.500000	1.500	1.000	0	"PAPAYAS-JUICE",	"TOL"
141	10002NA , J,	7.500000	1.000	1.000	0	"CANTALOUPES-NECTAR",	"TOL"
142	10002AB , J,	7.500000	1.000	1.000	0	"CANTALOUPES-PULP (MUSKMELON)",	"TOL"
150	10013AA , J,	0.500000	1.000	1.000	0	"SQUASH-SUMMER",	"TOL"
198	14003AA , B,	0.005000	1.000	1.000	0	"CARROTS", "FDA	"
208	14013AB , B,	0.180000	1.000	1.000	0	"POTATOES(WHITE)-UNSPECIFIED",	"PDP"
209	14013AC , B,	0.180000	1.000	1.000	0	"POTATOES(WHITE)-PEELED",	"PDP"
210	14013DA , B,	0.180000	6.500	1.000	0	"POTATOES(WHITE)-DRY",	"PDP"
211	14013HA , B,	0.180000	1.000	1.000	0	"POTATOES(WHITE)-PEEL ONLY",	"PDP"
227	15001AA , G,	0.020000	1.000	1.000	0	"BEANS-DRY-GREAT NORTHERN",	"FS"
228	15001AB , G,	0.020000	1.000	1.000	0	"BEANS-DRY-KIDNEY",	"FS"
229	15001AC , G,	0.020000	1.000	1.000	0	"BEANS-DRY-LIMA",	"FS"
230	15001AD , G,	0.020000	1.000	1.000	0	"BEANS-DRY-NAVY (PEA)",	"FS"
231	15001AE , G,	0.020000	1.000	1.000	0	"BEANS-DRY-OTHER",	"FS"
232	15001AF , G,	0.020000	1.000	1.000	0	"BEANS-DRY-PINTO",	"FS"
249	15022AA , G,	0.020000	1.000	1.000	0	"BEANS-DRY-BROADBEANS",	"FS"
251	15023AA , G,	0.020000	1.000	1.000	0	"BEANS-DRY-PIGEON BEANS",	"FS"
256	15030AA , G,	0.020000	1.000	1.000	0	"BEANS-DRY-HYACINTH",	"FS"
258	15031AA , G,	0.020000	1.000	1.000	0	"BEANS-DRY-BLACKEYE PEAS/COWPEA",	"FS"
259	15032AA , G,	0.020000	1.000	1.000	0	"BEANS-DRY-GARBANZO/CHICK PEA",	"FS"
261	16003AA , A,	20.000000	1.000	1.000	0	"MUSHROOMS",	"FS"
270	24004AA , O,	1.500000	1.000	1.000	0	"RICE-ROUGH (BROWN)",	"TOL"
276	24007AA , O,	0.005000	1.000	1.000	0	"WHEAT-ROUGH",	"FDA"
277	24007GA , O,	0.005000	1.000	1.000	0	"WHEAT-GERM",	"FDA"
278	24007HA , O,	0.005000	1.000	1.000	0	"WHEAT-BRAN",	"FDA"
279	24007WA , O,	0.005000	1.000	1.000	0	"WHEAT-FLOUR",	"FDA"

303	15023AA , G,	0.010000	1.000	1.000	0	"SOYBEANS-UNSPECIFIED",		"FS"
304	28023AB , G,	0.010000	1.000	1.000	0	"SOYBEANS-MATURE SEEDS DRY",		"FS"
305	28023WA , G,	0.010000	1.000	1.000	0	"SOYBEANS-FLOUR (FULL FAT)",		"FS"
306	28023WB , G,	0.010000	1.000	1.000	0	"SOYBEANS-FLOUR (LOW FAT)",		"FS"
307	28023WC , G,	0.010000	1.000	1.000	0	"SOYBEANS-FLOUR (DEFATTED)",		"FS"
315	43058AA ,A,	0.010000	1.000	1.000	0	"GRAPES-WINE AND SHERRY",		"FDA"
318	50000DB , X,	0.200000	1.000	1.000	0	"MILK-NONFAT SOLIDS",		"TOL"
319	50000FA , X,	0.200000	1.000	1.000	0	"MILK-FAT SOLIDS",		"TOL"
320	50000SA , X,	0.200000	1.000	1.000	0	"MILK SUGAR (LACTOSE)",		"TOL"
321	53001BA, U,	0.050000	1.000	1.000	0	"BEEF-MEAT BYPRODUCTS",		"TOL"
322	53001BB, U,	0.050000	1.000	1.000	0	"BEEF(ORGAN MEATS)-OTHER",		"TOL"
323	53001DA, U,	0.050000	1.920	1.000	0	"BEEF-DRIED",		"TOL"
324	53001FA, U,	0.050000	1.000	1.000	0	"BEEF(BONELESS)-FAT",		"TOL"
325	53001KA, U,	0.050000	1.000	1.000	0	"BEEF(ORGAN MEATS)-KIDNEY",		"TOL"
326	53001LA, U,	0.050000	1.000	1.000	0	"BEEF(ORGAN MEATS)-LIVER",		"TOL"
327	53001MA, U,	0.050000	1.000	1.000	0	"BEEF(BONELESS)-LEAN (FAT/FREE)",		"TOL"
328	53002BA, U,	0.050000	1.000	1.000	0	"GOAT-MEAT BYPRODUCTS",		"TOL"
329	53002BB , U,	0.050000	1.000	1.000	0	"GOAT(ORGAN MEATS)-OTHER",		"TOL"
330	53002FA , U,	0.050000	1.000	1.000	0	"GOAT(BONELESS)-FAT",	"GOAT(BONELESS)-FAT",	"TOL"
331	53002KA , U,	0.050000	1.000	1.000	0	"GOAT(ORGAN MEATS)-KIDNEY",		"TOL"
332	53002LA , U,	0.050000	1.000	1.000	0	"GOAT(ORGAN MEATS)-LIVER",		"TOL"
333	53002MA , U,	0.050000	1.000	1.000	0	"GOAT(BONELESS)-LEAN (FAT/FREE)",		"TOL"
334	53003AA , U,	0.050000	1.000	1.000	0	"HORSE",		"TOL"
336	53005BA , U,	0.050000	1.000	1.000	0	"SHEEP-MEAT BYPRODUCTS",		"TOL"
337	53005BB , U,	0.050000	1.000	1.000	0	"SHEEP(ORGAN MEATS)-OTHER",		"TOL"
338	53005FA , U,	0.050000	1.000	1.000	0	"SHEEP(BONELESS)-FAT",		"TOL"
339	53005KA , U,	0.050000	1.000	1.000	0	"SHEEP(ORGAN MEATS)-KIDNEY",		"TOL"
340	53005LA , U,	0.050000	1.000	1.000	0	"SHEEP(ORGAN MEATS)-LIVER",		"TOL"
341	53005MA , U,	0.050000	1.000	1.000	0	"SHEEP(BONELESS)-LEAN (FAT FREE",		"TOL"
342	53006BA , U,	0.050000	1.000	1.000	0	"PORK-MEAT BYPRODUCTS",		"TOL"
343	53006BB , U,	0.050000	1.000	1.000	0	"PORK(ORGAN MEATS)-OTHER",		"TOL"
344	53006FA , U,	0.050000	1.000	1.000	0	"PORK(BONELESS)-FAT",		"TOL"
345	53006KA , U,	0.050000	1.000	1.000	0	"PORK(ORGAN MEATS)-KIDNEY",		"TOL"
346	53006LA , U,	0.050000	1.000	1.000	0	"PORK(ORGAN MEATS)-LIVER",		"TOL"
347	53006MA , U,	0.050000	1.000	1.000	0	"PORK(BONELESS)-LEAN (FAT FREE)",		"TOL"
355	55008BA , V,	0.050000	1.000	1.000	0	"TURKEY-BYPRODUCTS",		"TOL"
356	55008LA, V,	0.050000	1.000	1.000	0	"TURKEY-GIBLETS (LIVER)",		"TOL"
357	55008MA, V,	0.050000	1.000	1.000	0	"TURKEY-(BONELESS)-FAT",		"TOL"
358	55008MB, V,	0.050000	1.000	1.000	0	"TURKEY-(BONELESS)LEAN/FAT FREE",		"TOL"
359	55008MC, V,	0.050000	1.000	1.000	0	"TURKEY-UNSPECIFIED",		"TOL"
360	55013BA, V,	0.050000	1.000	1.000	0	"POULTRY-OTHER-LEAN (FAT FREE)",		"TOL"
361	55013LA, V,	0.050000	1.000	1.000	0	"POULTRY-OTHER-GIBLETS(LIVER)",		"TOL"
362	55013MA, V,	0.050000	1.000	1.000	0	"POULTRY-OTHER-FAT",		"TOL"
363	55014AA, X,	0.050000	1.000	1.000	0	"EGGS-WHOLE",		"TOL"
364	55014AB, X,	0.050000	1.000	1.000	0	"EGGS-WHITE ONLY",		"TOL"
365	55014AC, X,	0.050000	1.000	1.000	0	"EGGS-YOLK ONLY",		"TOL"
366	55015BA, V,	0.050000	1.000	1.000	0	"CHICKEN-BYPRODUCTS",		"TOL"
367	55015LA, V,	0.050000	1.000	1.000	0	"CHICKEN-GIBLETS(LIVER)",		"TOL"
368	55015MA, V,	0.050000	1.000	1.000	0	"CHICKEN (BONELESS)-FAT",		"TOL"
369	55015MB, V,	0.050000	1.000	1.000	0	"CHICKEN(BONELESS)LEAN/FAT FREE",		"TOL"
377	04001JC, L,	0.680000	3.900	1.000	0	"APPLES-JUICE-CONCENTRATE",		"FDA"
378	06002NA, A,	0.079000	1.000	1.000	0	"BANANAS-NECTAR",		"PDP"
379	25002MO, B,	0.250000	1.000	1.000	0	"BEET SUGAR-MOLASSES",		"TOL"
385	55015EL, V,	0.050000	1.000	1.000	0	"CHICKEN-GIBLETS (EXCL. LIVER)",		"TOL"
392	01014JC, N,	0.005000	3.600	1.000	0	"GRAPES-JUICE-CONCENTRATE",		"FDA"
404	04003NA, L,	0.240000	1.000	1.000	0	"PEARS-NECTAR",		"FDA"
416	01016JA, N,	0.070000	1.000	1.000	0	"STRAWBERRIES-JUICE",		"FDA"
424	56000FA, U,	0.050000	1.000	1.000	0	"VEAL-(BONELESS)-FAT",		"TOL"
425	56000MA, U,	0.050000	1.000	1.000	0	"VEAL-(BONELESS)-LEAN (FAT FREE",		"TOL"
426	56000KA, U,	0.050000	1.000	1.000	0	"VEAL-(ORGAN MEATS)-KIDNEY",		"TOL"
427	56000LA, U,	0.050000	1.000	1.000	0	"VEAL-(ORGAN MEATS)-LIVER",		"TOL"
428	56000BB, U,	0.050000	1.000	1.000	0	"VEAL-(ORGAN MEATS)-OTHER",		"TOL"
429	56000DA, U,	0.050000	1.920	1.000	0	"VEAL-DRIED",		"TOL"
430	56000BA, U,	0.050000	1.000	1.000	0	"VEAL-MEAT BYPRODUCTS",		"TOL"
437	24007OL, O,	0.010000	1.000	1.000	0	"WHEAT-GERM OIL",		"FDA"
438	20000AA, A,	0.181000	1.000	1.000	0	"WI-APPLE",		"FDA"
441	02002JC, K,	0.050000	8.260	1.000	0	"GRAPEFRUIT-JUICE-CONCENTRATE", "FS"		"FS"
442	02004JC, K,	0.010000	11.400	1.000	0	"LEMONS-JUICE-CONCENTRATE",		"FS"
443	02005JC, K,	0.050000	6.000	1.000	0	"LIMES-JUICE-CONCENTRATE",		"FS"
448	02002HA, K,	0.106000	1.000	1.000	0	"GRAPEFRUIT PEEL",		"PDP"

APPENDIX C

TOXICOLOGICAL SUMMARY

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
THIABENDAZOLE

Chemical Code # 587, Tolerance # 242
SB 950 # 341

August 14, 1987
Revised 9/21/89, 12/11/89, 12/20/90, 4/28/92, 6/26/92, 7/22/92, 12/22/92, 1/31/95, 5/18/95, 9/28/95, 1/19/96, 3/7/97 and 12/5/97

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect indicated
Oncogenicity, mouse:	No data gap, possible adverse effect [chronic effect, not oncogenicity]
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Teratology, mouse	No data gap, possible adverse effect[a]
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

All relevant record numbers indexed as of 3/7/97 have been examined. This includes all records up to Record No. 140365 (Document No. 242-089). Some record numbers for this material are of the series 900,000+. Aldous, 3/7/97.
File name: T971205
Present revision by: Aldous, 3/7/97.
Past updates by: Kellner, 4/28/92 and 6/26/92; Gee, 7/22/92; Kellner, 12/22/92 and 1/31/95; Aldous, 5/18/95, 9/28/95, 1/19/96, 3/7/97 and Gee, 12/5/97.
The chemical grouping includes thiabendazole hypophosphite salt (chemical code # 1952, tolerance # 50807). See Thiabendazole (chemical code # 587, tolerance # 242) for reviews.
[a] This is the only change from the pervious revision. No new studies have been reviewed.
These pages contain summaries only. Each individual worksheet may contain additional

effects.

In the 1-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED RAT

****242-074 129602** Wolfe, G. and Squibb, R. "Thiabendazole: 106-Week Dietary Toxicity/Carcinogenicity Study in Rats" (Hazleton Washington, Inc. (HWA), Vienna, Virginia, Merck Report #TT 90-9009, HWA Project 284-172, 9/29/93). Thiabendazole technical (lot No. L-585, 216-000S159, purity of 98.9%) was administered in the feed to 50 Sprague-Dawley Crl:CD*BR rats/sex/dose at 0, 10, 30 and 90 mg/kg/day for 104 weeks. Body weights and food consumption were decreased in the mid- and high-dose males and high-dose females at most intervals tested. Erythrocyte, hemoglobin and hematocrit levels were decreased in mid- and high-dose rats. Total cholesterol was increased in high-dose rats. Higher liver-to-body weight ratios for high-dose males and higher thyroid/parathyroid-to-body-weight ratio for the high-dose females compared to control were reported. NOEL for systemic toxicity = 10 mg/kg/day. **Possible Adverse Effect:** Liver centrilobular hypertrophy in mid- and high-dose males; benign thyroid adenomas (possible mechanism: liver metabolic enzyme induction, leading to increased thyroxine clearance and thyroid stimulating hormone (TSH) levels). Initially classified unacceptable, but upgradeable with submission of data from test compound/dosing mixture analyses. Requested data were provided (Record No. 137480, below). Study is now classified **Acceptable**. Kellner, 1/13/95; Aldous, 9/21/95.

242-085 137480 McKeon, J. F. [untitled report of dosing material analysis for cited study]. Analyses were submitted to support rat combined study: Document No. 242-074, Record No. 129602 (rat chronic/oncogenicity study). Analyses were performed by Merck & Co., Inc. Cover letter with submission was dated May 3, 1995. Stability of technical material was confirmed after study termination (purity of 98.7%). Assay results over the course of the study were within 20% of target in all cases, and generally within a few percent of expected concentrations. Information allows an upgrade of study to **Acceptable** status. Aldous, 9/28/95.

242-070 121292 This supplemental submission is a FIFRA Section 6(a)(2) Adverse Effects Disclosure for Combined (Chronic/Oncogenicity) Rat study -074:129602 concerning increased incidence of benign thyroid adenomas in the 30 and 90 mg/kg/day dose groups. The author stated that increased thyroid adenomas may be the result of a species specific mechanism in which thiabendazole affects the thyroid in the rat indirectly (i.e., alteration of thyroxine clearance via increased hepatic metabolism causing prolonged increase in TSH levels and thyroid follicular cell hyperplasia). No Worksheet. Kellner, 1/27/95.

CHRONIC TOXICITY, RAT

See the acceptable rat chronic/oncogenicity study under "combined" studies, above. Note, in addition to laboratory animal studies presented in this summary, the extensive testing and use of thiabendazole in substantial dosages in man and domestic animals as an anthelmintic (see reviews in Vol. 242-012). Aldous, 9/25/95.

** 242-026 036977 (see also related chronic study 242-027 036978) "Safety evaluation by dietary feeding to rats for 104 weeks", Woodard Research Corp.
12/8/65. Thiabendazole, lot no. L-585216-0-40 (estimated purity 99.1%), was fed in the diet for 2 years to 35/sex/group at 0, 80 or 120 mg/kg. NOEL (considering information from both related chronic studies) = 40 mg/kg/day. **Acceptable only in fulfillment of chronic effects data requirement--a rat oncogenicity study is still required.** Insufficient numbers of animals subjected histopathology, several required tissues not examined, misc. other deficiencies preclude acceptance for oncogenicity data requirement. DPR reviews by J. Remsen (Gee), 8-22-85 and 1-28-86 did not accept study for chronic or oncogenicity data requirements: re-examined by C. Aldous on 8/12/87 in light of new data and in consideration of the overall chronic effects data base, and accepted for chronic effects data requirement.

EPA one-liner: No core grade. Systemic NOEL < 80 mg/kg (LDT; growth depression, decreased adrenal weights and increased mortality) Oncogenic NOEL > 120 mg/kg (HDT)

242-012 033541 2-paragraph summary of 026 036977, above. (Review by J. Remsen (Gee), 8/22/85)

242-002 051499 Food consumption data for 026 036977.

242-027 036978 "Safety Evaluation by Oral Administration to Dogs and Rats for 104 Weeks." (Woodard Research Corp., 4-8-64) Thiabendazole, purity 99.1% [from Vol. 002, cover memo and Table 1], was administered in the diet to CD rats for 2 years to 35/sex/group at 0, 10, 40 or 160 mg/kg. Apparent NOEL = 40 mg/kg (decreased body weight) **Unacceptable as an individual study, but contributes to fulfillment of rat chronic effects data requirement (see one-liner for study 026 036977).** As in study 026 036977, there were insufficient numbers of animals subjected histopathology, several required tissues not examined, misc. other deficiencies. DPR reviews by J. Remsen (Gee), 8-22-85 and 1-29-86. Re-examination of data by C. Aldous, 8/12/87.
EPA one-liner: No core grade. Systemic NOEL = 10 mg/kg.

242-012 033540 2-paragraph summary of 026 036978, above. (Review by J. Remsen (Gee), 8/21/85)

242-003 051504 Contains no new rat chronic data. Sections D and E include data on a 6-month rat subchronic study. Section G is a duplicate of the entire contents of Vol. 027 (differs only in the placement of one page).

SUBCHRONIC RAT

242-056 087980 Kangas, L., "Thiabendazole: A Fourteen-Week Oral Toxicity Study in the Albino Rat". (Bio-Research Laboratories. Ltd., Laboratory Project I.D. 84114, Study No. TT#89-

9014, 1/22/90). Thiabendazole, purity not given, administered by gavage at concentrations of 0 (0.5% aqueous methylcellulose), 25, 100, or 400 mg/kg/day to 20 albino rats/sex/group for 14 weeks. No DPR toxicologist's review is required for this subchronic study, however it is noted that the investigators found marked body weight gain decrements in the high dose groups, suggesting that it may be necessary to select a dose level below 400 mg/kg/day for the high dose in subsequent lifetime feeding studies. No adverse effects were noted by investigators, who placed the NOEL at 25 mg/kg/day, based on changes in hematology (i.e., reduced RBC counts, HCT, and Hb.), and on histological changes, such as lesions in stomach mucosa, thyroid follicular cell hyperplasia, and hepatocellular centrilobular hypertrophy. One-liner (without worksheet) by Kishiyama and Aldous, 12/19/90.

242-056 087981 Hill, R.N. et al., "Review: Thyroid follicular cell carcinogenesis", Fundam. Appl. Toxicol. 12:629-697 (1989). This review is a discussion of the relationship between thyroid-pituitary homeostasis and eventual development of thyroid follicular cell neoplasms. As of 12/19/90 there is no DPR "review" of this review. Aldous, 12/19/90. Note: A copy of this article was submitted in Document No. 242-085, and was considered in the review of Record No. 137482 in that document (Aldous, 9/28/95).

**** 242-060 096231** "Thiabendazole: A 14-Week Dietary Toxicity Study in Rats", (B.A. Myers and G. R. Lankas, Merck Sharp & Dohme Research Laboratories [Merck TT# 90-9002], and Hazleton Laboratories America, Inc., [HLA Study No. 284-169], 12/13/90). Thiabendazole, purity 99.4%, was administered in the feed at nominal concentrations of 0, 10, 40, 160 or 320 mg/kg/day to 10 Sprague-Dawley rats/sex/group for at least 13 weeks. Body weight and food consumption was significantly reduced for males and females in the 3 and 2 highest dose groups, respectively. Erythroid parameters were slightly reduced; cholesterol and blood urea nitrogen levels increased for the 2 highest dose groups, but these were considered secondary effects to reduced food consumption and body weight gain. Alopecia was reported to be treatment related (i.e. severity was increased) for the 2 highest dose groups, but only 2 of 10 males and females in each group showed this symptom. Liver centrilobular hypertrophy, thyroid follicular cell hypertrophy and bone marrow erythroid hyperplasia were noted under microscopic examination with a **NOEL = 10 mg/kg/day** (also for marked decreases in food consumption and body weight in males at 40 mg/kg/day and above). ACCEPTABLE. Dose levels of 10, 30, and 90 mg/kg/day established for a subsequent carcinogenicity study are justifiable. (Kishiyama, Kellner and Gee. 5/1/92).

242-085 137482, Lankas, G. R., "Fourteen-week dietary thyroxine clearance study in rats with a 14-week recovery period", Merck Research Laboratories, West Point, PA, 2/16/95. Study ID# 94-024-0. Male Crl:CD*(SD)BR rats, 35/group, were dosed with technical thiabendazole in diets for 14 weeks to achieve 0, 10, 90, or 270 mg/kg/day. Blood was sampled at weeks 2, 4, 8, and 13 to evaluate serum levels of TSH, T3 and T4. After the treatment period, 15 rats/group were necropsied, with histological examinations of livers and thyroids. At this time, an additional 5 rats/dose continued on treatment and were used for pharmacokinetic studies: thyroxine kinetic parameters such as half-life, apparent volume of distribution, and clearance were determined at 8, 22, 34, 48, and 72 hr after iv injection of 125I-thyroxine. Remaining rats were taken off treatment for 13 weeks. Serum levels of TSH, T3 and T4 were measured in these rats on recovery weeks 6 and 13. Body weights at the end of the treatment phase were reduced in 90 and 270 mg/kg/day rats by 12% and 32%, respectively. There were similar decrements in food consumption at these dose levels. Respective TSH levels between weeks 8 and 13 were 170% and 198% of control levels. There were no effects on T4 levels. T3 levels

of 270 mg/kg/day rats were slightly lower than controls, however this may have been incidental, considering lack of effects on T4 concentrations. Relative liver weights were increased at 270 mg/kg/day, and absolute and relative thyroid weights were elevated at 90 to 270 in dose-related fashion. Liver centrilobular hypertrophy and thyroid follicular cell hyperplasia commonly occurred at 90-270 mg/kg/day. Investigators noted that 125I-thyroxine clearance (units of ml/hr) was remarkably increased at 270 mg/kg/day, and that the main factor behind this change was a great increase in apparent volume of distribution at this dose. Investigators also considered this elevated clearance to be the reason for the compensatory increase in TSH. The DPR review contends that this study does not clearly demonstrate enhanced liver metabolism of thyroid hormones as the sole or primary cause for the TSH response, considering factors such as the effects of inanition on hormonal balance, and confounding effects of marked metabolic, physiological and anatomical treatment effects upon pharmacokinetic parameters. Aldous, 9/28/95.

CHRONIC TOXICITY, DOG

Studies 242-027 036979 and 242-012 033542 have been previously considered together to fill the chronic dog data requirement. Subsequently Record No. 123765 has been reviewed and classified **acceptable**. Aldous, 3/7/97.

242-072 123765 Lankas, G. R., "Thiabendazole: Fifty-three week oral toxicity study in dogs", Merck Institute for Therapeutic Research, West Point, PA. Laboratory ID: TT #91-968-0, 1/20/93. Beagles were dosed with 0, 10, 40, or 160 mg/kg/day thiabendazole (identified as L-585,216-000S159, purity approximately 99%) by gelatin capsule for 1 year. No NOEL nor NOAEL was found. Vacuolation of the gallbladder epithelium was present in dose-related degree in both sexes at all doses. The death of one 40 mg/kg/day male early in the study was considered by investigators to be a possible idiosyncratic treatment effect: there were no comparable reactions in either sex at that dose or above. [A dose of 50 mg/kg/day has been used for years routinely as an anthelmintic for dogs and other animals]. Common findings at 40 mg/kg/day included liver bile duct vacuolation and urinary bladder epithelial cytoplasmic inclusions. A noteworthy reduction in RBC parameters in high dose dogs was associated with other indications of anemia, especially bone marrow hematopoiesis at 160 mg/kg/day and splenic erythropoiesis and/or hemosiderosis at 40 and 160 mg/kg/day. No adverse effects are indicated. Study was originally classified as unacceptable, due to lack of information about test article purity and stability. Requested data were submitted as part of a rebuttal, dated 9/25/95 (see also 3/7/97 DPR rebuttal response). Study is re-classified as **acceptable. H. Green and C. Aldous, 5/18/95; Aldous, 3/7/97.

242-072 123795 Smith, P. F. et al., "Studies on the mechanism of simvastatin-induced thyroid hypertrophy and follicular cell adenoma in the rat", Toxicologic Pathology 19:197-205 (1991). This article was included in the dog chronic study report (Record No. 123765) to demonstrate how induction of hepatocellular metabolic activity can lead to increased turnover of thyroid hormones, and subsequently to thyroid follicular hypertrophy. This has been considered already with respect to thyroid changes in the rat (see previous pages, this Summary). No worksheet for this article. Aldous, 4/26/95.

242-027 036979 "Safety Evaluation by Oral Administration to Dogs and Rats for 104 Weeks." (Woodard Research Corp., 4-8-64) Thiabendazole, technical., purity 99.1%, was administered

to beagles, 3/sex/group, by capsule 5 days/week at 0, 20, 50 or 125 mg/kg. Apparent NOEL = 20 mg/kg/day ("mild lacrimation and scleral injection" noted at 50 mg/kg/day and above: salivation, rough hair coats, dry skin, reduced hemoglobin and hematocrit, seizures and some mortalities at 125 mg/kg/day (the latter two findings not necessarily direct treatment effects.) J. Remsen (Gee), 1/29/86; C. Aldous 8/6/87.
EPA one-liner: No core grade. Systemic NOEL = 50 mg/kg (decreased body weight).

242-012 033543 Very brief summary of 242-027 036979, initially reviewed by J. Remsen on 8/22/85.

242-002 051500 Individual body weights for 027 036979.

242-012 033542 "Two Year Chronic Oral Toxicity in Dogs." (Merck Sharp and Dohme Research Labs, 1-69) [Summary report]. Thiabendazole, technical. 99.1%, was given to beagles daily for 2 years at 0, 20, 100 or 200 mg/kg, 2/sex/group [doses were raised to above levels by degrees to prevent emesis of dose]. Interim sacrifices of one control and one 200 mg/kg/day male 5 months after 200 mg/kg/day treatment began. Apparent NOEL = 20 mg/kg/day (Hemosiderosis of liver and bone marrow at 100-200 mg/kg/day; reduced body weights, also reduced RBC counts, hematocrits, and hemoglobin at 200 mg/kg/day. Not an acceptable independent report, but useful data considering supplementary information, below. J. Remsen (Gee), 8-22-85; subsequent review with ancillary data by C. Aldous, 8/6/87.

242-003 051505 (Tab = "Section D", relevant pages are D-205 through D-297) provides data for study 012 033542. Data include individual food and water consumption, hematology, clinical chemistry, prothrombin time, urinary output, body weights, and organ weights. Body weights appear to be reduced in 200 mg/kg/day dogs, however there was no mortality. Males and females in the 200 mg/kg/day group appeared to have reduced RBC counts, hematocrits, and hemoglobin concentrations compared to all other groups. In tab marked "Section E" there were tables 15-19, indicating results of microscopic examination of dogs in the 1969 study, 012 033542. The only consistent apparent treatment effects were marked to moderate hemosiderosis in liver and bone marrow in 100 and 200 mg/kg/day groups (both sexes). Section G is a duplicate of the entire contents of Vol. 027 (differs only in the placement of one page). (Ancillary data only. See overall review of this study and of 027 036979, summarized above, worksheet by C. Aldous, 8/6/87).

SUBCHRONIC DOG

242-055 087979 Batham, P., "Thiabendazole. A Fourteen-Week Oral Toxicity Study in the Beagle Dog", (Bio-Research Laboratories. Ltd., Laboratory Project. I.D. 84021, Study No. TT#89-9010, 1/22/90). Thiabendazole, purity 99.4%, administered orally via gelatin capsule at concentrations of 0 (placebo capsule), 35, 75, or 150 mg/kg/day to 4 beagle dogs/sex/group for 90 days. Incidence of emesis (NOEL = 35 mg/kg/day) and salivation increased; erythrocyte parameters (RBC, Hb, and HCT) decreased. It appears that the dosage range employed in this study would be appropriate for a subsequent chronic study, should such a study be undertaken. Note that studies 242-027 036979 and 242-012 033542 together have already fulfilled the chronic dog data requirement for DPR. The information from this subchronic study is supplementary. (Kishiyama and Aldous, 12/19/90, one-liner without worksheet).

ONCOGENICITY, RAT

Journal Article (no document or record #): Fuji, T. et al. 1991. "Chronic Oral Toxicity and Carcinogenicity Study of Thiabendazole in Rats", Fd Chem. Toxic., Vol. 29, No. 11, pp. 771-775. Thiabendazole (TBZ, purity of 98.5%, obtained from Merck Sharp and Dohme International, NJ) was administered in the diet at nominal concentrations 0, 500, 1000, 2000 or 4000 ppm to 30 F344/DuCrj rats/sex/dose for 104 weeks. Body-weight gain was reduced about 20 and 40% compared to controls in the 2000 and 4000 ppm dose groups, respectively; survival of rats was enhanced with increasing dose level. Lung phagocytes (foamy cells) showed significantly increased focal or multifocal aggregation at 1000 ppm and above in females and 2000 ppm and above in males. Liver bile duct hyperplasia with periductal fibrosis increased in a dose-related manner in females but not males; hepatic microgranuloma showed dose-related increases in both sexes. Hyperplasia of renal tubule and collecting duct epithelium of the kidney was seen in high-dose males and females; hyperplasia of the epithelium of both the papilla and pelvis of the kidney was significantly higher in the 2000 and 4000 ppm dose groups of both sexes. NOEL for hyperplasia of kidney papilla and pelvis epithelium is 500 ppm (21 mg/kg/day in males, 26 mg/kg/day in females). **Possible Adverse Effect:** Preputial (male) and clitoral (female) gland adenomas were increased at the high dose, NOEL = 2000 ppm (male: 90 mg/kg/day). Not a guideline study; supplemental data only. Kellner and Gee, 5/4/92.

242-048 067761 and 242-051 074912 are based on the same study described in the preceding one-liner (Fuji, et al., 1991). Specifically, -048 067761 is a journal article (Hayashida et al., 1985. Annual Report of the Tokyo Metropolitan Research Laboratory of Public Health 36, pp. 377-389) that was published before the pathologic examinations were completed and is consequently lacking these data; it does contain weekly body weight, food and water intake, hematology, serum biochemistry and organ weight data that were not included in the 1991 paper. Study -051 074912 is an unpublished, draft version of the pathology report; it also contains additional details not found in the 1991 article (e.g. lesion counts for all examined organs are listed). Kellner and Gee, 6/29/92.

242-051; 074911; "Enhancing effect of thiabendazole by urinary bladder carcinogenesis induced by sodium o-phenylphenate in F344 rats"; T. Fuji et al. (1986), Food and Chemical Toxicology, 24(3):207-211. This is paper from the open literature. No worksheet was done (Morris, 10/13/89).

ONCOGENICITY, MOUSE

**** 242-025 036966** "Lifetime Carcinogenic Study in Mice," (Merck, Sharp & Dohme, ½/80). Thiabendazole (purity = 99.3 - 99.8%) was administered to CD-1 mice (50/sex/group) in the diet at 0 (vehicle = 1% vegetable oil in the diet), 0.006, 0.066 and 0.20% (males) or 0.006, 0.200, and 0.533% (females) [low dose groups were initiated at higher levels, but adjusted to above levels at week 7]. Animals in a group were sacrificed when survival reached 20% (81-105 weeks). **Possible adverse effect indicated: (atrial thrombosis).** NOEL = 0.006% (i.e. 60 ppm or about 5.7 to 9.9 mg/kg/day (female) or 0.066% (660 ppm or about 63-121 mg/kg/day (male), based on increased mortality in both sexes dosed at ≥ 0.20% in diet, due primarily to atrial thrombosis). Note: NOEL for males was incorrect in earlier review (see discussion in 9/21/88 review). No oncogenic effect indicated. This study was originally reviewed by J. Gee

(1/30/86) as unacceptable but upgradeable, with a possible adverse effect (apparent increase in "Type B" hepatocellular tumors in 0.533% females). Study was re-examined by C. Aldous (8/11/87) and still considered to be unacceptable, but upgradeable upon receipt of additional information to clarify the statistical and toxicological meaning of the apparent increase in hepatic "Type B" neoplasms. The requested information (046:064610, which included "blind" re-evaluation of slides by R. A. Squire) removes the concern about possible hepatocellular tumors (no treatment effect seen on secondary review). Study is upgraded to ACCEPTABLE. C. Aldous and M. Silva, 9/21/88.

EPA one-liner: Minimum. Oncogenic NOEL > 0.533% (HDT) systemic NOEL = 0.066% (lower weight gain).

242-046 064610 Additional information relating to study 025 036966. Definition of Type A and Type B hepatocellular tumors and interpretation of significance of data in the original report. Historical control data on such tumors. Report of "blind" secondary evaluation of female liver slides by R. A. Squire, who found no evidence of treatment effect on tumors. One-page EPA memo, which indicated that EPA had determined that there was no oncogenic effect (following evaluation of Squire report and independent evaluation of slides by EPA). See DPR review of 9/21/88 for details. C. Aldous, 9/21/88.

242-012 033544 Summary of 025 036966, above, reviewed by J. Remsen (Gee) 8/22/85.

342-002 051501 (Addendum to 025 036966) "Thiabendazole: Six-week pilot study in mice" [TT #77-004-0]. Merck Institute for Therapeutic Research, 8/24/77. Thiabendazole mixed in diet to provide daily doses of 0, 50, 150, 300, 600, and 900 mg/kg/day. Males had slight decrease in food consumption and body weight gain at 600 and 900 mg/kg/day. No changes in females. This study justifies the dose levels used in the primary study. D. Shimer/ C. Aldous, 7/11/87. [Note that C. Aldous requests additional information relating to the primary study.]

REPRODUCTION, RAT

** 242-028 036980 "Multigeneration Reproduction and Lactation Studies with Thiabendazole." (Food and Drug Research Labs, 12-26-67). Thiabendazole, purity approx. 98.8%, administered orally in diet (in very young rats) or by gavage (in older rats) from mating through weaning to FDRL rats at 0, 20, 40 or 80 mg/kg; 10/sex/group; NOEL > 80 mg/kg for reproduction; no effect on reproduction parameters. Originally classified as "unacceptable" in reviews of J. Remsen (Gee) [8/22/85 review of the summary of this report in 012 033547, and 1/29/86 review of final report in 028 036980]. Re-evaluated by D. Shimer/ C. Aldous on 8/10/87, and found ACCEPTABLE, on basis of additional data in 002 051502 (see below).

EPA one-liner: No core grade. Reproductive NOEL = 20 mg/kg (decreased viability index of F1A). [Note that DPR does not agree with this determination, as there is no consistent treatment effect on viability or on other reproductive parameters].

242-012 033547 Brief summary of 242-028 036980 (see above).

242-002 051502 (Addendum to Document 028 036980, above). Explanation of dosing regime (part gavage, part dietary admixture), purity information (approx. 98.8% purity, process same as in current production), individual reproduction data, hematology, clinical chemistry, and

organ weights for adults, reproduction and lactation data. These data allow upgrade of principal study to upgradeable status. D. Shimer/C. Aldous, 7/10/87,

242-066 116221, "Two-Generation Dietary Reproduction Study in Rats", (Dr. L. David Wise, Merck Institute for Therapeutic Research, Merck Research Laboratories, Merck & Co., Inc., West Point, PA. Report # TT #90-733-0, 21 May 1992). Thiabendazole (>99% purity) was administered in the diet through two generations with 1 litter per generation at nominal concentrations of 0 (control), 10, 30, and 90 mg/kg/day and with 33 and 25 Sprague-Dawley [Crl:CD*(SD) BR] rats/sex/dose for F0 and F1 parents, respectively. Prior to mating, F0 and F1 adults received treated diet for approximately 9-weeks and 14-weeks, respectively. Group mean F0 and F1 parental body weight reduction (7% to 14%) and food consumption decrease (8% to 16%) was indicated at 90 mg/kg/day. Significantly decreased pup weight gain was seen at 90 mg/kg/day. Parental NOEL = 10 mg/kg/day (reduced body weights and food consumption at 30 and 90 mg/kg/day). Reproductive NOEL = 30 mg/kg/day (reduced pup weights at 90 mg/kg/day) **No Adverse Effects. Originally unacceptable, but upgradeable [with analyses of test compound (with verification of technical grade) and dosing material]. (Green, Kellner and Gee, 11/10/92). Test compound/dosing mixture analyses (see -071:122339) have been submitted and the study is upgraded to **ACCEPTABLE.** Kellner, 1/31/95.

-071 122339 Addendum to -066 116221 "Two-Generation Dietary Reproduction Study in Rats", (Dr. L. David Wise, Merck Institute for Therapeutic Research, Merck Research Laboratories, Merck & Co., Inc., West Point, PA. Report # TT #90-733-0, 21 May 1992). Supplemental submission included information on the analysis of the test compound and results of the dietary analyses conducted during the study. Although not conducted under GLP standards (see -075:129603), these analyses were adequate to establish that the rats received their prescribed dosages; study -066:116221 is upgraded to ACCEPTABLE. Kellner, 1/31/95.

-075 129603 Addendum to -066 116221 "Two-Generation Dietary Reproduction Study in Rats", (Dr. L. David Wise, Merck Institute for Therapeutic Research, Merck Research Laboratories, Merck & Co., Inc., West Point, PA. Report # TT #90-733-0, 21 May 1992). Supplemental submission included changes inserted into to final report which were the result of a U.S. EPA GLP inspection. These additions had no effect on either the final conclusion of the report or the DPR evaluation of the study. Kellner, 1/30/95.

242-030 036981 "Thiabendazole Evaluation of Teratogenic Potential in the Rat." [Study is actually a 1-generation reproduction study]. (Woodard Research Corporation, 4-8-64) Thiabendazole, no purity stated, was given at 0 or 500 ppm in the diet for 70 days, 20/sex/group, 2 litters raised to weaning. NOEL > 500 ppm for 1 generation reproduction study. No adverse effect indicated. UNACCEPTABLE, inadequate protocol. J. Remsen (Gee), 1-29-86. Re-examined after receipt of 002 051503 (see below) by D. Shimer/C. Aldous, 7/10/87.

242-012 033546 Brief summary of the 1-generation, 2-litter reproduction study, reported more fully in 030 036981, above. This summary reviewed by J. Remsen (Gee) on 8/22/85, and found UNACCEPTABLE.

242-002 051503 (Addendum to 030 036981) New data are individual body weights of pups at birth and at 21 days. No changes in interpretation of study. Report is now complete, and study remains UNACCEPTABLE. D. Shimer/C. Aldous 7/10/87.

REPRODUCTION, MOUSE

242-012 033545 "Reproduction and Teratogenic Studies: Multigeneration Reproduction Study in the Mouse." (Merck Sharp and Dohme Research Labs, 1-69) Brief summary of a 5 generation study in which thiabendazole was administered in the diet to 25/sex/group at 0, 0.02, 0.1 or 0.5 % of diet. Reproductive effects NOEL = 0.1% in diet (reduced numbers of mice born and weaned per litter, reduction of weanling weight). (**Note**: 8/22/85 review by J. Remsen (Gee) considered reproductive effects at 0.5% in diet to be a "possible adverse health effect". This dose was shown to be well into the toxic range in the mouse oncogenicity study (242-025 036966, which found increased mortality in males dosed with 0.066% and higher concentrations in diet and in females dosed 0.200% and above, also decreased body weight gain in both sexes at 0.200% and above). Reviewer (Aldous) therefore determines that **reproductive effects at this high and parentally toxic level do not constitute a "possible adverse health effect".** (Report remains UNACCEPTABLE (no data provided). (Re-reviewed by C. Aldous, 8/14/87.)

EPA one-liner: No core grade. Reproduction NOEL = 150 mg/kg.

TERATOGENICITY, RAT

** 242-059 096230 "Thiabendazole: Oral Developmental Toxicity Study in Rats", (L. D. Wise, Merck Sharp & Dohme Research Laboratories, Project I.D. No. TT# 90-713-0, 11/16/90. Thiabendazole, purity 98.9%, was administered by gavage at concentrations of 0 (0.5% methylcellulose), 10, 40, or 80 mg/kg to 25 mated Sprague-Dawley female rats per group on days 6 through 17 of gestation. Body weights of high-dose maternal rats ranged from 1.7% to 4.8% less than control at day 8 and 14 of gestation, respectively; food consumption during dosing was reduced 11-15% and 22-28% for the mid and high dose groups, respectively. Maternal NOEL = 10 mg/kg/day, based on reduced body weight gain and food consumption. Fetal body weight was significantly lower and averaged 4.9% and 6.3% less than controls for mid and high dose males, respectively, and 4.7% lower for high dose females. **No Adverse Developmental Effects.** Developmental NOEL = 10 mg/kg/day, based on reduced fetal weights. Initially reviewed as unacceptable but upgradeable (Kishiyama, Kellner and Gee, 5/1/92). Upgraded to **acceptable** with submission of -068:117129. (Kellner and Gee, 11/3/92).

242-068 117129 [Addendum to -059:96230] Supplemental submission provided analytical method and tabulated results of dosing material analysis for upgrade of rat teratogenicity study (-059:96230) to acceptable. Kellner and Gee, 10/29/92.

242-046 064612 "Report on Prenatal Toxicity Studies in Rats with Thiabendazole," (Institut f~~ur~~ Pharmakologie, Toxikologie und Pharmazie, 8/14/85). Thiabendazole (analytical grade, no purity given; Ch. RMO 5878, Batch No. 18295 supplied by MSD) was administered in diet to mated Wistar SPF rats at 0 (vehicle = diet), 2, 15, 50 and 100 ppm during days 6-17 of gestation (presence of vaginal plug = day 0 of gestation). **Maternal NOEL** > 100 ppm (no significant effects were observed at any dose level). **Possible adverse effect indicated. Developmental NOEL =** 15 ppm (significantly lower fetal weights at 50 ppm (3.5 g) and 100 ppm (3.4 g) compared with 3.6 g in controls; significant increase in major malformations in the skeletal system at 100 ppm). NOT ACCEPTABLE (no analysis of test chemical; no analysis of dosing material was included; individual maternal food and water consumption data and fetal

visceral, skeletal, external effects and bodyweights were missing; no GLP or QA was included; an "annex" section was cited but missing from the report; historical controls should have been included with the study). Possibly upgradeable (the above mentioned missing information must be submitted to DPR). M. Silva, 9/7/88.

242-046 064611 "Thiabendazole - Review of Available Rat Teratology and Fetotoxicity Studies." In this report a number of studies are summarized, including 064611-12, 064615 and 064622. Other studies (Delatour et al.) were mentioned where one dose was tested on Sprague-Dawley rats and no developmental or maternal effects were noted at 80 mg/kg/day (gavage). Two studies performed at the Institute of Pharmacology and Toxicology in Hanover West Germany (Wistar Rats treated by gavage) were briefly described. Dose levels were: Study 1. 100, 200, 400 and 800 mg/kg/day and Study 2. 200 (15 mg/kg), 400 and 800 ppm. NOELs were not reached in the German studies and fetal effects (13% weight reduction) were observed at the lowest dose levels tested -100 mg/kg/day (maternal effects were not mentioned) in Study 1. **Both maternal and developmental effects were observed in Study 2 at 200 ppm (15 mg/kg/day)** but since a NOEL was not reached, indications of adverse effects cannot be determined. Based on the data presented in the summary, fetotoxic effects are secondary effects due to decreased weight gain in dams (maternal toxicity). It is not conclusive whether TBZ is teratogenic or selectively fetotoxic. This information is supplementary. M. Silva, 9/6/88.

242-046 064615 "Effect of Dietary Administration of Thiabendazole on Pregnant Rats and Fetal Development," (J. Food Hyg. Soc. Japan, Vol. 23, No. 6, pp. 468-473, 1982). Thiabendazole (> 98% pure) was given in diet to mated Wistar rats at 0 (vehicle = diet), 0.125 (92 mg/kg), 0.25 (154.5 mg/kg), 0.5 (223.7 mg/kg) and 1% (187.5 mg/kg, calculated to be less due to reduced food consumption in the 1% group) during days 7 to 17 of gestation (positive vaginal smear = day 0 of gestation). Maternal NOEL = 0.125% (maternal body weight gain and food consumption were significantly suppressed at ≥ 0.25%; clinical signs of toxicity, included piloerection, listlessness/general weakness were observed at ≥ 0.5%). Developmental NOEL = 0.125% (decreased body weight at ≥ 0.5%; increase in incidence of fetal death at 1%; increased skeletal variations at ≥ 0.5%; retardation of ossification at ≥ 0.25%). There was no evidence of fetal malformations attributable to thiabendazole ingested. Fetal changes were considered to be primarily induced by direct effects of thiabendazole on the fetuses as well as effects due to maternal weight loss brought on by a marked decrease in food consumption. No adverse effect indicated. This information is supplementary**.** M. Silva, 9/7/88.

242-046 064622 "Teratologic Assessment of Maleic Hydrazide and Daminozide, and Formulations of Ethoxyquin, Thiabendazole and Naled in Rats," (J. Environ. Sci., Health, B14(6), pp. 563-577, 1979). Mated (positive vaginal smear = day 1 of gestation) Wistar rats were treated by gavage with 0 (vehicle = distilled water), 125, 250 or 500 mg/kg thiabendazole (formulation = 45% a.i. & 55% unknown ingredients) during day 6-15 of gestation. Maternal NOEL $\underline{\geq}$ 500 mg/kg (no effects were observed at any dose). No adverse effect indicated. Developmental NOEL = 500 mg/kg (although an increase in the total number of anomalous fetuses/number of fetuses examined in the 500 mg/kg group was observed ($P < 0.005$), no single anomaly was significantly increased in incidence). This information is supplementary. M. Silva, 9/7/88.

Summary: The definitive studies are -046:064612 and -059:096230. In 064612, a possible adverse effect with a developmental NOEL of 15 ppm was demonstrated (significantly decreased fetal weights at 50 and 100 ppm and increased skeletal malformations at 100 ppm),

but the study was found to be unacceptable by DPR because of numerous deficiencies. A guideline-type study (-059:096230) has since been reviewed with a conclusion of no developmental effects in fetuses other than lower body weight with a NOEL of 10 mg/kg/day (equal to the maternal NOEL). This study was originally found to be unacceptable, but was upgraded to acceptable after review of supplemental submission -068:117129. This guideline study will be used to establish the NOEL for rat teratogenic effects (Kellner and Gee, 11/9/92).

TERATOLOGY, RABBIT

** 242-062 097879 "Thiabendazole: Oral Development Toxicity Study - Rabbits", (G. L. Lankas & L. D. Wise, Merck Sharp & Dohme Research Laboratories, Project ID Number TT # 90-734-0, 6/10/91). Thiabendazole (lot Number L585, 216-000S159), purity 98.9% (based on TLC) was administered by oral gavage at concentrations of 0 (0.5% methylcellulose), 50, 150, or 600 mg/kg to 18 mated female New Zealand Rabbits/group during gestation days 6 through 18. **Developmental NOEL = 150 mg/kg/day** (increased resorptions, lung lobation, incompletely ossified metacarpal and reduced fetal weight for the high dose group). Increases in incompletely ossified sternebra and talus-calcaneus were reported to be within the historical control range. **Maternal NOEL = 150 mg/kg/day** (based on decreased body weight gain and food consumption during the treatment period). The "possible adverse effects" flag was removed from the rabbit developmental toxicity test because **no adverse developmental effects** were seen below maternally toxic doses. Initially reviewed as unacceptable but upgradeable (Kishiyama, Kellner and Gee, 5/1/92); study was upgraded to **Acceptable** with submission of -068:117130. (Kellner and Gee, 11/3/92).

242-068 117130 [Addendum to -062:97879] Supplemental submission provided analytical method and tabulated results of dosing material analysis for the upgrade of a rabbit teratogenicity study (-062:97879). In addition, historical control data and information from previous studies were presented that allowed the developmental NOEL to be increased from 24 mg/kg/day (as recommended in previous rabbit study -054:90065) to 150 mg/kg/day (from study -062:97879), thus permitting removal of the "possible adverse effect" flag from the rabbit developmental toxicity test. Kellner and Gee, 10/29/92.

Note: One of the purposes of study TT #90-734-0 (-062 97879) was to clarify the relationship of thiabendazole treatment to the occurrence of fetal hydrocephaly, resorptions and abortions seen in the mid- and high-dose treatment groups (120 and 600 mg/kg/day) of study TT #89-9005 (-054 90065). In the latter study, the NOEL for developmental toxicity was 24 mg/kg/day based on whole litter resorptions and hydrocephaly; the NOEL for maternal toxicity (120 mg/kg/day) was based on decreased body weight gain and food consumption. The study indicated a **"possible adverse effect"** based on embryo-fetal toxicity in the absence of definitive maternal toxicity. In contrast, study TT #90-734-0 showed a single case of hydrocephaly at the low dose only and no definitive adverse developmental effects at 50 mg/kg/day.

A supplemental report (-068:117130) was submitted by the author to explain the differences in results between the two studies and to provide justification for a maternal and developmental NOEL of 150 mg/kg/day. For example, data were presented which showed that the frequency of skeletal malformations reported in the first study was comparable to historical control data. Further evidence was presented in the form of thiabendazole range-finding study in which 8 pregnant does received doses of either 200 or 400 mg/kg/day under the same conditions as the

first study; no evidence of adverse developmental effects was reported. These and other data allowed the developmental NOEL to be increased from 24 mg/kg/day to 150 mg/kg/day, thus permitting removal of the "possible adverse effect" flag from the rabbit developmental test.

****242-054 090065** Hoberman, A.M., "Thiabendazole: Oral Developmental Toxicity Study in Rabbits", (Argus Research Laboratories Inc., project No. 013-029; Merck & Co., Inc. study number: TT89-9005, October 27, 1989). Thiabendazole, purity 98.9%, administered by gavage at concentrations of 0 (0.5% methylcellulose), 24, 120, or 600 mg/kg/day to 18 artificially inseminated Hra: (New Zealand White) SPF rabbits/group on days 6 through 18 of gestation. Maternal toxicity NOEL = 120 mg/kg/day (marked body weight gain decrements, marked decrease in food consumption during treatment). Developmental toxicity NOEL = 24 mg/kg/day [4/18 litters with whole litter resorptions at 120 mg/kg/day: also hydrocephaly in 2 fetuses (2 litters) at 600 mg/kg/day and 1 fetus at 120 mg/kg/day]. The study technically indicates a "**possible adverse effect**", based on embryo-fetal toxicity in the absence of definitive maternal toxicity. ACCEPTABLE**.** (Kishiyama and Aldous, 12/19/90).

242-054 090066 Rangefinding study for Record #090065, above. Dosage levels selected for the above primary study are justified. No DPR worksheet for the pilot study, which is addressed in the review of the primary study. This 1-liner is by Aldous, 12/19/90.

242-030 036982 Entitled "Thiabendazole reproduction [sic] study in the rabbit" (actually a teratology study). Merck Institute for Therapeutic Research, June 29, 1966. Doses of 100, 200, 400, and 800 mg/kg/day by gavage in Methocel* suspension. No adverse effects indicated. Not complete, NOT ACCEPTABLE, upgrade unlikely (intercurrent disease, small group sizes, small numbers of fetuses subjected to skeletal examinations, etc.). Original review by J. Remsen (Gee), 1/29/86, [Not acceptable, possible upgrade indicated], subsequent review by C. Aldous considering additional information (below), 8/12/87, [NOT ACCEPTABLE, unlikely upgradeability].

242-002 (No record #, rebuttal on pp. 9-10 at front of volume). Addendum to study 030 036982. Identifies test article as purity of approx. 99.1%, comparable to currently manufactured product. Clarifies that data from 4 small studies conducted within 5 months were combined into one report. Indicates that individual data are available on request. No change in status of study indicated. Aldous (considered in 8/12/87 review, see above).

TERATOGENICITY, MOUSE

****242-089 140365** Nakatsuka, T., "Thiabendazole: Oral developmental toxicity study in mice", Banyu Pharmaceutical Co., Ltd. (Japan), 6/26/95. Study ID Number TT #94-9818. Thiabendazole, purity 99.8%, was administered via gavage at concentrations of 0 (olive oil), 25, 100 or 200 mg/kg/day to 25 Jcl:ICR mice/group during days 6 through 15 of gestation. Maternal NOEL = 25 mg/kg/day [weight gain decrements, (very marginal at 100 mg/kg/day)]. Fetal NOEL = 25 mg/kg/day (small, dose-related decrements in mean fetal weight). A "possible adverse effect" is indicated, based on incidence of cardiovascular malformations at 200 mg/kg/day. This is based on 2 high dose litters with such changes, compared to 1 fetus each in low and medium dose groups, and none in controls. Study investigators did not consider data to indicate teratogenicity. Kishiyama and Aldous, 1/19/96.

242-089 140358 Pilot study for Record No. 140365, above. Dams were dosed by gavage on gestation days 6-15 at 25, 100, 200, 400, and 800 mg/kg/day. There were modest b.w. decrements at 400 and 800 mg/kg/day, and modest reductions of the major hematology parameters at these dose levels (i.e. reduced RBC counts, Hb, and HCT). Live fetal weights were reduced statistically significantly in dose-related fashion over the dose range of 100 mg/kg/day and above. An increase in incidence of cleft palate at 800 mg/kg/day (15 fetuses, 4 litters) was attributed to treatment, possibly mediated by maternal stress. Dose levels selected for the definitive study are consistent with findings in this pilot study. Aldous, 1/19/96.

Journal Article (No Document or Record #). Ogata, A. et al. "Teratogenicity of Thiabendazole in ICR Mice". Fd. Chem. Toxic. Vol. 22, No. 7, pp. 509-520. Dept. of Toxicology, Tokyo Metropolitan Research Laboratory of Public Health, Japan. Thiabendazole (TBZ, 98.5% purity, lot no. A101) was administered in olive oil orally to pregnant mice at different stages of organogenesis (3 experiments). Experiment 1: 39 mice/dose were given daily doses of 0, 700, 1300 or 2400 mg/kg/day on days 7-15 of gestation. Experiment 2: 7-12 mice/dose were given a single dose of 2400 mg/kg on one day during days 6-15 of gestation. Experiment 3: 22-31 mice/dose received one of a range of 17 dose levels between 30 and 2400 mg/kg on day 9 of gestation.

In exp. 1, maternal deaths numbered 5/39 and 24/39 in the two highest dose groups; fetuses showed dose-related external and skeletal anomalies (e.g.. cleft palate and fusion of vertebrae). In exp. 2, at least one maternal death occurred on each treatment day; dose-related reduction deformity of the limbs was found in mice given 2400 mg/kg on one day 9-12. In exp. 3, maternal deaths occurred in doses exceeding 1389 mg/kg; increasing dosage of TBZ led to proportional increases in the number fetuses with reduction deformity of limbs and skeletal fusion. The effective dose (ED_1) for skeletal fusion of 26 mg/kg was established by probit analysis.

Although the methods, results and conclusions described in the article were scientifically sound, this study was not performed under FIFRA GLP guidelines; this data should be considered supplementary only. A key limitation of the study was that internal soft tissue examinations were not undertaken. (Kellner and Gee, 4/17/92)

GENE MUTATION

** 242-067 116350 "Thiabendazole Microbial Mutagenesis Assay", (Joseph F. Sina, Ph.D., Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., Report Numbers TT# 91-8039 and TT# 91-8042, 4 March 1992). Thiabendazole (>99.5% estimated purity by TLC) was tested with and without metabolic activation in the reversion assay using Salmonella typhimurium (TA97a, TA98, TA100, and TA1535) and Escherichia coli (WP2, WP2 uvrA, and WP2 uvrA pKM101) plated in quadruplicate with 48 hour exposure at nominal concentrations of 0, 3, 10, 30, 100, 300, 1000, 3000, and 6000 mg/plate. **Increased reversion frequency was not indicated. Acceptable**. (Green, Kellner and Gee, 11/6/92).

** 242-029 036968 and 036969 "Mutagenicity Testing on Thiabendazole in Microbial Systems." (The Institute of Environmental Toxicology, report no. 76-9814C, no date) Thiabendazole, >98.6%, was tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, TA100 and G46, E. coli strain WP2 hcr-, with and without rat liver activation at 0, 10, 100, 500,

1000 and 2500 ug/plate. No increase in mutagenicity was observed. ACCEPTABLE**. (**J. Gee, 1-28-86)

EPA one-liner: Acceptable. Negative, no increase in G46 revertants from mice exposed to TBZ.

242-029 036976 "Thiabendazole: Microbial Mutagenicity Studies (Ames Test) with Salmonella typhimurium." (Merck, 1977, report no. 76-9813C) Several lot numbers of thiabendazole were tested with S. typhimurium at 0 to 2000 ug/plate, with and without phenobarbital induced rat liver enzymes. Data demonstrate that the low level mutagenic activity in TA98 was due to an impurity in lot #F291764. No adverse effect indicated. UNACCEPTABLE. (J. Gee, 1-28-86)

EPA one-liner: Acceptable. Negative for induced revertants in all Ames strains except TA98 + phenobarbital S-9.

242-012 033551 "Mutagenic Studies: Host Mediated Assay - Salmonella typhimurium in Male ICR Mice." (Merck Sharp and Dohme Research Labs, 1-69, report no. 76-9814C) Summary report states no significant increase in mutation frequency of Salmonella strain G46. UNACCEPTABLE. (J. Gee, 8-22-85)

242-012 033662 "Mutagenic Studies: in vitro Bacterial Mutagen Tests - Reverse Mutation Tests - E coli." (Merck Sharp and Dohme research Labs, 1-69) Single sentence states no increase in E. coli revertants. UNACCEPTABLE**.** (J. Gee, 8-22-85)

242-012 033549 "Mutagenic Studies: in vitro Bacterial Mutagen Tests-Ames Tests." (Merck Sharp and Dohme Research Labs, 1-69, report no. 76-9813C) Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without Aroclor-induced rat liver activation. Paragraph states no mutagenic activity found up to 2.5 and 5.0 mg/plate. UNACCEPTABLE**.** (J. Gee, 8/22/85)

SUMMARY: There is no evidence for mutagenicity of thiabendazole in bacteria but there is a suggestion that an impurity in some lots may be weakly mutagenic in at least one strain of Salmonella - TA98 - for frameshift mutation. [DPR reviewer name not stated: may have been J. Gee on or about 1/28/86].

CHROMOSOME EFFECTS

242-078 131712, "Thiabendazole: Assay for Chromosomal Aberration in Mouse Bone Marrow", (Sheila M. Gallaway, Merck Institute for Therapeutic Research, West Point, PA., 11 July 1994). The test article is identified as thiabendazole (TBZ) with 99.8% purity. Eight, 10, or 12 male Crl:CD-1*(ICR)BR mice per group received a single dose of 0, 200, 667, and 2000 mg/kg by gavage, with mitomycin C as the positive control. Sampling was performed 6, 24, and 48 hours post-treatment. **Increased chromosomal aberrations are not indicated at the levels tested. Study was initially classified as unacceptable but upgradeable (adequate justification for 1 sex only, test article verification as technical grade). Requested data were submitted as part of a rebuttal, dated 9/25/95 (see also 3/7/97 DPR rebuttal response). Study is re-classified to **acceptable**. H. Green and J. Gee, 5/18/95; Aldous, 3/7/97.

** 242-029, 047 036971, 067211-12 "Cytogenetic Studies With Thiabendazole in Rat Bone Marrow Cells," (Institute of Environmental Toxicology, Tokyo, Japan; report no. 76-9816C, no date). Thiabendazole (purity = 98.6%) was given by oral gavage as a single dose at 0, 100, 300 or 1000 mg/kg or 5 doses at 30, 100 or 300 mg/kg (5 males/group). Animals were sacrificed at 24 hours (single dose) and 3 hours (5 doses). No increase in bone marrow chromosomal aberrations are reported. The study was originally reviewed as unacceptable (J. Gee, 11/28/86) but upgradeable with justification of use of males only instead of both sexes as required. The requested information was received at DPR (047 067211) and based on the fairly complete data base which indicated no sex differences in any of the tests, the study has been upgraded to ACCEPTABLE. (M. Silva, 9/9/88)

EPA One-liner: Acceptable. Negative for chromosome damage in rat bone marrow cells.

242-049 067759 Exact duplicate of 047:067212.

242-012 033555 Summary of 029 036971.

242-047 067213 "Selected Mutagenesis Studies on Thiabendazole," (SRI International, 3/77). Thiabendazole (purity and grade not specified) was used on human diploid fibroblast WI-38 cells in the log phase of growth at 0 (vehicle = 1% DMSO), 0.1, 1.0, 10.0, 100 and 1000 ug/ml without activation duplicate samples). No increase in chromosomal aberrations was observed at any dose level. Positive controls functioned as expected. UNACCEPTABLE (purity of test material was not provided nor was an analysis of dosing material; the test was not run with enzyme activation; only one time point was sampled; QA statement not included). Not upgradeable. (M. Silva, 9/9/88)

242-029 036970 "Cytogenetic Studies with Thiabendazole in Cultured Human Fibroblasts." (Institute of Environmental Toxicology, report no. 76-9815C, no date.) Thiabendazole, 98.6%, was tested with human embryo fibroblasts, strain #1162, for in vitro chromosomal aberrations; exposed to 0, 2, 10 or 50 ug/ml for 3 and 24 hours, no activation, no increase in aberrations. UNACCEPTABLE. An activation system must be used. (J. Gee, 1-28-86)
EPA one-liner: Acceptable. Negative - no increase in chromosome breakage in human embryonic fibroblast cultures.

242-012 033553 Summary of 029 036970.

242-012 033554 "Mutagenic Studies: Cytogenetic Studies - in vitro Studies with Human Diploid Fibroblasts." (Merck Sharp and Dohme Research Labs, 1-69) WI-38, 3 hour exposure. Summary report states a depression in mitotic index but no increase in aberrations. UNACCEPTABLE. (J. Gee, 8-22-85)

242-029, 047, 049 036972, 067211, 067760 "Dominant Lethal Studies With Thiabendazole in Mice," (Institute of Environmental Toxicology, 76-9817C, no date). Thiabendazole (purity = 98.6%) was administered by gavage to C3H/HeCr mice (15 males/group) at 0, 200 or 600 mg/kg for 5 consecutive days. No adverse effect indicated. NOEL > 600 mg/kg for dominant lethal effect. Originally reviewed as unacceptable by J. Gee, 1/28/86 (no individual data; no analysis of dosing material; no justification of dose and dosing schedule). Justification for dose selection (range-finding study: 049 067760) was submitted to DPR, however, results of the

preliminary study do not justify the final dose selection. The study remains UNACCEPTABLE and not upgradeable. (M. Silva, 9/9/88)

EPA one-liner: Not acceptable. Negative for dominant lethals in treated C3H/HeCR mice.

242-029 036974 "Thiabendazole: Mutagenicity Study in the Mouse Using the Micronucleus Test." (Merck, 6-3-77, report no. 76-8-83). Thiabendazole, lot no. F291764 (no purity stated), was administered by oral gavage to 8 (or 14 for control)/sex/group CD-1 mice at 0, 125, 250 or 500 mg/kg/day, 2 doses; sacrificed at 6 hrs; NOEL > 500 mg/kg; no effect on micronucleus in PCE's or PCE/NCE reported. UNACCEPTABLE. Doses are not justified, protocol is unacceptable, no purity stated. (J. Gee, 1-28-86)

EPA one-liner: Not Acceptable. Negative (up to 500 mg/kg) in CD-1 mice.

242-012 033552 Summary of 029 036974.

242-029 036975 "Thiabendazole: Mutagenic (Subacute Dominant Lethal) Study in the Mouse." (Merck, 1977, report no. 76-7030) Thiabendazole, lot no. F291764 (no purity stated), given by oral gavage to 10 CF_1S males per test group (20 for negative control), at 0, 125, 250 or 500 mg/kg/day in 5 daily doses; NOEL for dominant lethal > 500 mg/kg; mated over 8 weeks, 1:1, no adverse effect reported. UNACCEPTABLE. No justification of doses, no concurrent positive control or appropriate historical data, not enough females per time point. (J. Gee, 1-28-86)

EPA one-liner: Not acceptable. Negative (up to 500 mg/kg) in CF1S mice.

242-012 033557 Summary of 029 036975.

242-012 033556 "Mutagenic Studies: Dominant-Lethal Studies - C3H/HECR Mice." (Merck Sharp and Dohme Research Labs, 1-69) Summary report, 200 and 600 mg/kg given in 5 doses, **no effects noted over 6 weeks of mating**. No data. UNACCEPTABLE. (J. Gee, 8-22-85)

DNA DAMAGE

242-029 036967 "Mutagenicity Testing on Thiabendazole in Microbial Systems." (The Institute of Environmental Toxicology, 76-9813C, no date.) Thiabendazole, >98.6%, was tested with Bacillus subtilis strains H17 and M45 at 0, 2, 10, 20, 50, 100, 200, 500 and 1000 ug/disc, no metabolic activation, no adverse effect indicated. UNACCEPTABLE, not upgradeable. Metabolic activation must be used. (J. Gee, 1-28-86)

EPA one-liner: Negative. No differential toxicity between B. subtilis strains H17 and M45.

242-012 033550 Summary of 029 036967.

** 50807-006 074699, "Thiabendazole, <u>In Vitro</u> Alkaline Elution/Rat Hepatocyte Assay", (Merck Institute for Therapeutic Research, West Point, PA., Study # 89-8312, 5/19/89), Thiabendazole, MK-0360, 98.9% purity. Primary rat hepatocytes, isolated from Charles River Crl:CD*(SD) BR Sprague-Dawley rats, were exposed to 0, 0.3, 0.7, 1.0, or 1.3 mM (in 1% DMSO) for 3 hours and analyzed for DNA strand breaks by the alkaline elution method. Viability was ≥ 93 % of controls. Elution rates were less than 3 times controls indicating no adverse effect. The study is acceptable (H. Green, S. Morris, 10/13/89).

NEUROTOXICITY

Not required at this time.

APPENDIX D

RESPONSE TO EXTERNAL COMMENTS

OEHHA's Introductory Comments:

I . (OEHHA) We recommend providing further scientific support for the selection of the no-observed-adverse-effect-levels (NOAELs) used in the draft RCD. This especially applies to the chronic NOAEL, which appears to actually be a lowest-observed-adverse-effect-level (LOAEL) based on the cellular changes observed in animals at this level compared to controls.

DPR: The chronic NOEL is partly based on the lack of hepatic stimulation in the rat at that dose. Consequently, at that dose there would not be stimulated hepatic metabolism of thyroid hormones. The regulatory endpoint is also based the lack of hepato/biliary toxicity at that dose in dogs. Although OEHHA appears to consider the lowest dose tested in dogs to be a LOAEL (Lowest Observed Adverse Effect Level), the data do not support that assertion. At a dose of 10 mg/kg-day in dogs (Lankas, 1993), all of the dogs exhibited vacuolation in gall bladder epithelial cells. In general, cellular vacuolation can indicate cellular stress. However, the gall bladder is a repository of bile salts. It is not involved in the metabolic processes of the liver. The toxicologist conducting the study expressed uncertainty regarding the toxicological significance of the finding. DPR researched the topic of hepatotoxicity and could find nothing relating to gall bladder epithelial vacuolation. A veterinary pathologist here at DPR was unable to suggest the toxicological or physiological significance of the observation. As noted in the text of the RCD, Dr. Swenberg (an expert in the field hepatotoxicity) was not clear about the physiological significance. As noted in the RCD, at the doses tested there was no dose response in incidence; and all other indications of hepato/biliary effects occurred at the mid and high dose levels. As a result of all of these considerations, DPR discounted vacuolation of gall bladder epithelial cells as an adverse effect to be used as the basis for a chronic regulatory endpoint.

2. (OEHHA) We recommend reorganizing and expanding the description of human health effects from human exposure to TBZ, including a summary of the adverse effects of using TBZ as an anthelminthic drug.

DPR: The "side effects" of a single oral dose of thiabendazole in humans are adequately described in the summaries of the four studies cited in the Acute Toxicity, and Subchronic Toxicity portions of the RCD. The effects described occur at the LOEL, the dose above the NOEL which is used as the acute regulatory endpoint for the described effects. The descriptions of potential side effects delineated in various editions of Goodman and Gillman (as cited later in this critique by OEHHA) are qualitative in nature, and do not address either 1) the dose at which the effects were observed, or 2) whether the effects were the result of repetitive dosing with the anthelminthic. Simply put, the effects described in Goodman and Gillman have nothing to do with determining the regulatory endpoint for quantitative assessment of risk.

3. (OEHHA) We recommend including more discussion regarding dermal sensitization of TBZ in humans. The negative results from animal tests for dermal irritation and sensitization should be compared with the observation of skin rashes caused by TBZ in humans. The apparent contradiction in results might be related to study design or differences in susceptibility.

DPR: The discussion in the RCD is considered adequate. The three reported instances of dermal irritation in humans (illness reports) came from exposure to formulations of thiabendazole. It is not clear whether the active ingredient or the inerts in those formulations caused the irritations.

4. (OEHHA) The potential for distributing TBZ into milk should be addressed in the section on "Pharmacokinetics." We also recommend including a discussion on the toxicity of TBZ metabolites and their role in the overall toxicological response from exposure to the parent compound.

DPR: There were no specific data on the potential partitioning of thiabendazole into milk. There was some indication that this might occur in the reproductive toxicity study, but this was only by inference. A discussion of the toxicity of the metabolites of thiabendazole would have been included if there were any information. Unfortunately, there were no data.

5. (OEHHA) We recommend expanding the discussion of the oncogenic potential of TBZ by addressing the significance of the positive genotoxic effects in support of a non-threshold approach to risk assessment, and to include all sites of tumor incidences in rats. A discussion of the structure-activity relationships for oncogenic activity among benzimidazole compounds would also be informative.

DPR: The weight of evidence approach recommended by USEPA in their document "Assessment of Thyroid Follicular Cell Tumors" and its relationship to the thiabendazole data was discussed thoroughly. No additional discussion is necessary. A speculative discussion of the structure-activity relationships for oncogenic activity among benzimidazole compounds is beyond the scope of this document.

6. (OEHHA) We recommend including more discussion of the mutagenic and clastogenic effects of TBZ, including its potential for aneugenicity.

DPR: The genotoxic effects of thiabendazole were addressed adequately in the RCD. It is unlikely that there would be any potential for aneugenicity at dosages equivalent to the regulatory endpoints, at which nothing was observed to happen, let alone at the exposure levels experienced by workers or the general public. Especially since the NOEL for anueploidy in mice was an order of magnitude greater than the regulatory endpoint.

7. (OEHHA) The draft RCD concludes that children are more sensitive to TBZ exposure than adults based on pre- and post-natal and endocrine effects in animal studies. The draft RCD also states that margins of exposure (MOEs) for both daily and annual exposures to farm workers handling TBZ, and to the general public exposed via dietary consumption, were considered health protective. The draft RCD should include more discussion on whether the MOE calculations sufficiently account for the greater susceptibility of children.

DPR: The draft RCD does not conclude that children are more sensitive to TBZ exposure than adults. There are no data which support such a contention. Under FQPA, additional uncertainty factors may be used by USEPA in gauging whether a tolerance is adequately health protective. Our statement reads "… an additional uncertainty factor

should probably be considered by USEPA." This statement was based on developmental toxicity (*in utero* effects) observed in laboratory animals.

8. *(OEHHA) The draft RCD concludes that children are more sensitive to TBZ exposure than adults. In the draft RCD, tolerances were assessed quantitatively without application of an additional uncertainty factor for a greater susceptibility of children and infants to TBZ toxicity that appears to be warranted based on the toxicological data. Most of the current existing tolerances may not be health protective for children since they do not take into account their greater sensitivity to this chemical as compared with adults. This is an important issue and we feel that the incorporation of an additional uncertainty factor in the RCD to protect children and infants requires further discussion and consideration.*

DPR: This is the same point as item 7, and was answered above.

9. *(OEHHA) We recommend expanding the "Risk Characterization" section of the document to include a discussion of the uncertainties specific to the quality of the existing toxicological database. This section is also deficient in discussing other toxicological effects of TBZ for which risk assessment methodology is not yet accepted. These include the direct and indirect evidence of immunotoxicity and neurotoxicity of TBZ. The discussion on exposure issues related to more susceptible subpopulations should be expanded, including the identification of the unborn fetus, children and infants, woman of child-bearing age, and people with liver dysfunction as susceptible populations.*

DPR: The data indicating a direct effect of thiabendazole on the immune system are interesting, but there are no accepted methods for using those data in quantitative risk assessment. The references suggested by OEHHA have been incorporated into the RCD in a specific section. There were no data indicating a direct neurotoxic effect of thiabendazole. Speculation in the absence of data is unwarranted. Discussion of exposure issues in the risk appraisal section deals with the adequacy of the exposure data. Susceptible human sub-populations are addressed to the extent possible in the Hazard Identification section.

<u>General Comments</u>

1. *(OEHHA) More discussion is needed in the draft RCD to provide adequate scientific support for the selection of the no-observed-adverse-effect-level (NOAEL) of 10 mg/kg-day for chronic exposure. At this dose level there were two types of histopathological changes noted: gallbladder epithelial vacuolation and gallbladder inspissation (drying and/or thickening by the evaporation of readily vaporizable parts) (page 16). "The individual data from both sexes indicated an increase in the severity of epithelial vacuolation but not inspissation over the dose range tested." Neither of these toxicological effects was considered in the draft RCD as a NOAEL for use in risk assessment. We agree that the gallbladder inspissation may not be appropriate as a NOAEL because the individual data do not demonstrate a clear dose-response relationship. However, the individual data from both sexes indicate an increase in the severity of epithelial vacuolation. The reason given in the draft RCD (page 16, first paragraph) for discounting gallbladder epithelial vacuolation is "The physiological significance of the gall bladder epithelial vacuolation was not clear to either the study's pathologist, or Dr. Swenberg at CIIT (personal communication)." However, "vacuolation*

of the bile duct and distal tubules of the kidney" was deemed appropriate for the selection of the NOAEL (page 26, fourth paragraph). This inconsistent approach and use of the data to determine the biological significance of cellular vacuolation needs further clarification and support. (Note: Dr. Swenberg is identified as being at CIIT; however, is now on the faculty at the University of North Carolina. While it is possible that he provided his comments via personal communication while still at CIIT, more likely his affiliation should be identified as UNC.)

DPR: There is no inconsistency in approach. The physiological and toxicological significance of vacuolation of distal tubules of the kidney and the bile duct are well known (M.T. Moslen, Toxic Responses of the Liver. *and* R.S. Goldstein and R.G. Schnellmann, Toxic Responses of the Kidney *In*: Cassarett and Doull's Toxicology: The Basic Science of Poisons 5th Edition). Based on available references and the expert opinions of the study pathologist and Dr. Swenberg, the physiological significance of vacuolation of gall bladder epithelium is unclear. A discussion of the physiological significance of cell vacuolation in general would not add anything but speculation as to the toxicological significance of gall bladder epithelial vacuolation. As stated above, the physiological and toxicological significance of this observation is unclear. If OEHHA has a reference specific to this observation which could assist DPR in this regard, we would be appreciative of the help. The attribution to Dr. Swenberg's occupational location was correct with regard to when the consultation occurred.

2. *(OEHHA) We identify 10 mg/kg-day as a lowest-observed-adverse-effect-level (LOAEL) based on the occurrence of gallbladder epithelial vacuolation. Therefore, we recommend that a LOAEL of 10 mg/kg-day be used in assessing risk for chronic TBZ exposure instead of its current identification and use as a NOAEL in the draft RCD. The biological significance of cellular vacuolation is well-established. There are numerous reports of cellular vacuolation induced both in cultured mammalian cells and in experimental animals (Hirano et al., 1992; Plopper et al., 1992; Li et al., 1993; Muir et al., 1994; Reindel et al., 1994; Roy et al., 1998a; Roy et al., 1998b; Hertle et al., 1999; Kim et al., 1999). In every case referenced above, vacuolation is associated with cellular stress or cell killing. Therefore, vacuolation is often a sign of serious perturbation to cellular homeostasis.*

DPR: See responses to Introductory question 1 and General question 1.

3. *(OEHHA) Values for NOAELs from acute, subchronic, and chronic toxicity studies selected as the basis for risk assessment usually are inversely correlated with the length of exposure (i.e., the longer the exposure, the lower the value). This does not seem to be the case for TBZ as presented in the draft RCD. The NOAEL of 3.3 mg/kg-day, based on an oral human study, was selected for the evaluation of acute occupational and dietary exposures to TBZ (page 10, third paragraph), and the NOAEL of 10 mg/kg-day was selected for chronic exposure assessments (page 16, first paragraph). The latter was based on hepato/biliary toxicity in dogs and centrilobular hypertrophy in rats. If the value of 10 mg/kg-day were considered a LOAEL rather than a NOAEL per our recommendation (see comment number one above), then the values used for risk assessment would be inversely correlated with the length of exposure. If the draft RCD is not revised to include OEHHA's recommendation, then this dose-response anomaly requires a better explanation as well as a discussion of the implications for protection of worker and community health.*

DPR: The critical chronic NOEL of 10 mg/kg-day for hepato/biliary toxicity in dogs and centrilobular hypertrophy in rats would extrapolate to a NOEL of 1 mg/kg-day for humans if it is assumed that the least sensitive human is 10 times more sensitive than laboratory animals to the toxicity of thiabendazole. Thus, we have an equivalent numerical critical chronic human NOEL less than the numerical critical acute human NOEL.

Dermal irritation and sensitization

OEHHA: Dermal irritation and sensitization is addressed in Appendix A prepared by the Worker Health and Safety Branch of the Department of Pesticide Regulation (DPR, page 28). Neither dermal irritation nor sensitization was addressed in the text of the draft RCD. We recommend that the RCD section on acute toxicity (page 9) be expanded to include a discussion of the potential for dermal irritation and sensitization. An explanation should be provided for the negative results in animal tests for dermal irritation and sensitization, considering the skin rashes caused by TBZ in humans (described in paragraph 3). The latter human effects and blood changes (anemia) observed in long-term toxicity studies in rats and dogs are suggestive of a potential for TBZ to cause immunotoxicity.

DPR: The issue of dermal sensitization was addressed in the appropriate document. The thiabendazole used in laboratory animal dermal irritation and sensitization tests is reagent grade, but the thiabendazole that humans come in contact with was in a formulation. It is not possible to retrospectively determine whether it was the thiabendazole or the "inerts" that caused the "…dermatitis, conjunctivitis, or rashes". Based on the limited information available in those reports, it would be speculative to attempt to draw an association between any dermal irritation/sensitization and immunological mechanisms.

Human health effects

1. *(OEHHA) Human health effects from exposure to TBZ are described in the draft document under "Illness Reports (page 4), "Acute Toxicity" (pages 9 to 10), and "Subchronic Toxicity" (page 12). To give a more coherent discussion of human health effects, we recommend that these various descriptions of human health study results be separated from the animal studies and summarized in a separate section.*

DPR: The illness report data did not arise from intentional human testing. Those data are located in the same section of every RCD. The human acute toxicity testing studies are located in the appropriate section of the RCD. The human subchronic toxicity testing study is also located in the appropriate section of the RCD.

2. *(OEHHA) We recommend including a summary of the health effects information of TBZ when it is used as an anthelminthic (treatment for worms). Side effects frequently encountered are anorexia, nausea, vomiting, and dizziness. Less frequently, diarrhea, weariness, drowsiness, giddiness, and headache occur. Occasional fever, rashes, erythema multiforme, hallucinations, sensory disturbances and Stevens-John syndrome (severe form of skin disorder with the involvement of oral-nasal and anogenital mucosa, the eyes, and viscera; can be fatal)-have been reported. Angioneurotic edema, shock, tinnitus, convulsions, and intrahepatic cholestasis are rare complications of the therapy.*

Crystalluria with hematuria has been reported on occasion (Gilman, 1990). Side effects that are experienced rarely include tinnitus, collapse, abnormal sensation in the eyes, numbness, hyperglycemia, xanthopsia, enuresis, decrease in pulse rate and systolic blood pressure, and transitory changes in liver function (Gilman, 1980). TBZ used as an anthelminthic has been shown to produce striking effects on the immune system, apparently independent of its antiparasitic activities. It caused significant reduction of lung granulomas around Schistoma Mansom eggs, and footpad edema in response to schistosome egg antigens in unsensitized animals when given daily for eight days (Hewlett et al., 198 1). TBZ also produced a marked increase in the number of large, mitotically active lymphoblasts in the thymus cortex. In a companion study, TBZ administered together with dinitrofluorobenzene stimulated T cells in lymph nodes and spleen (Donskaya et al., 1982).

DPR: As noted above in response to these points under Introductory question 2, we would ask at what dose do these effects occur? Do these effects occur as a result of a single dose or multiple doses? What is the NOEL for these effects? The answers are not available in the Summary presentations of anecdotal data in the two editions of Goodman and Gillman's Pharamacological Basis of Therapeutics which were cited. However, a critical acute NOEL for the LOEL at which the effects noted in the human toxicity testing studies cited in the RCD is obtainable. The other cited possible effects, for which there are no dose data, are interesting, but not useful in establishing the toxicological basis for regulatory endpoints in a quantitative risk assessment.

A section on Immunotoxicity has been added to the RCD.

Oncogenicity

I . (OEHHA) We recommend that the discussion on oncogenicity be expanded in the RCD to address data in support of a non-threshold approach, including the structure-activity relationship issue for oncogenic potential among other benzimidazoles. Such a discussion should clearly describe the complexity and uncertainties related to the mechanism of oncogenic activity of TBZ. However, TBZ has also been reported to damage DNA, measured as both the induction of sister-chromatid exchanges (SCEs) (de Pargament et al., 1987) and positive results in the comet assay (Sasaki et al., 1997). It is important to emphasize that TBZ has tested positive for genotoxicity in four independent in vivo studies, namely inducing SCEs in two separate in vivo studies in male mice (de Pargament et al., 1987; Ardito et al., 1996), micronuclei in one in vivo study in CFW mice, and DNA strand breaks, as assayed by the comet test using cells from mice exposed to TBZ in vivo (Sasaki et al., 1997). Generally speaking, positive evidence of genotoxicity in vivo is given more weight than evidence solely from in vitro tests. The replication of the positive findings in the SCE assay increases confidence in these results. Increased concern over the genotoxic activity of TBZ also comes from observations of positive findings in systems testing for different genotoxic endpoints.

DPR: The complexities and uncertainties related to the mechanism of oncogenic activity of TBZ have been discussed thoroughly in both the Hazard Identification section and the Risk Appraisal section. The structure-activity relationship of other benzimidazoles as oncogens is irrelevant in this discussion. The fact that TBZ is genotoxic has been acknowledged, but all of the effects noted could be attributed to disruption of tubulin formation. The toxicological significance of SCE is unknown, and USEPA has removed

it from the required battery of genotoxicity tests. SCE can be caused by spindle disrupters, as well as low pH, increased ion concentrations, and changes in osmolarity (Brusick, 1986). A chemical's ability to produce SCEs does not make it a mutagen likely to produce oncogenic effects. Nor does the production of SCEs by thiabendazole necessarily imply that this spindle disrupter interacts directly with the DNA. SCE does indicate breaks in the chromosomes have occurred.

The meanings of the comet assay results cited by OEHHA are also unclear. The paper by Sasaki *et al.,* 1997 purports to demonstrate DNA-damaging action of thiabendazole (TBZ) in 7 mouse organs *in vivo* using a modification of the comet assay. The author says, "Because of increased sister-chromatid exchanges in mouse bone marrow cells, TBZ was assumed to have a DNA-damaging action as well as an inhibitory action on the spindle apparatus. The alkaline SCG assay [comet] detects genotoxicity as DNA fragments derived from single strand breaks and alkali-labile sites, and we have shown that the aneugen colchicine was not positive in any mouse organ (Sasaki *et al.,* 1997)." However, the comparison of the lack of effects by colchicine with TBZ was not necessarily appropriate. The technique used for the SCG assay of colchicine (in a separate published study) was different than the one was used for TBZ.

The effect of using this different technique is not entirely clear. However, in the preceding paragraph of the paper (Sasaki *et al.,* 1997) the author discounts the positive results of orthophenyl-phenol (OPP) in his SCG assay, stating: "Therefore, the DNA damage observed in five mouse organs might not have been responsible for the carcinogenicity….[as]…OPP and Na-OPP did not exert carcinogenic potential in B6C3F1 mice (Hagiwara *et al.,* 1984). Indeed, the results obtained in this paper (Sasaki *et al.,* 1997) could not be duplicated in the same strain of B6C3F1 mice using the standard comet assay (Brendler-Schwaab, 2000). Because of the uncertainty of the meaning of the comet assay in the Sasaki paper, it was not included in the RCD.

2. *[OEHHA] TBZ induces adenomas of the thyroid follicular cells in male but not female Sprague-Dawley rats. It is not oncogenic in mice. Some evidence supports that the development of the tumors is secondary to hepatotoxicity. With regard to the discussion of the thyroid tumors observed in the Sprague-Dawley rats, it is helpful to refer directly to the U.S. Environmental Protection Agency's (U.S. EPA) science policy guidance on thyroid follicular cell tumors (Assessment on Thyroid Follicular Cell Tumors, U.S. EPA, 1998). In this science policy document, U.S. EPA uses the term "mutagenic" in a broad sense. Examples taken from U.S. EPA's document include: "Mutagenic influences are evaluated by short-term tests for gene and structural chromosome mutations and other tests" (page 3); "Tumors seeming to arise from relevant mutagenic influences (e.g., gene mutations and structural chromosomal aberrations)" (page 17); and "Finally, careful review is warranted when both antithyroid and other determinants seem to apply to the observed thyroid tumors, such as when there are certain mutagenic influences (e.g., structural chromosome aberrations)." (page 28). Clearly, TBZ should be regarded as having mutagenic effects, for the purposes of determining which dose-response methodology is appropriate for evaluating the thyroid follicular cell tumor response under U.S. EPA's science policy guidance. In the case of TBZ, where there is evidence for both mutagenic and antithyroid effects, U.S. EPA's guidance recommends that both a linear and a margin of exposure approach be used in assessing the dose-response.*

DPR: A thorough discussion of the weight of evidence, including references to USEPA's science policy guidance is given in both the Hazard Identification section and the Risk Appraisal section. There was no evidence that thiabendazole caused "gene mutations and structural chromosomal aberrations". As noted above, all of the positive genotoxic effects of thiabendazole could be attributed to its ability to inhibit tubulin assembly and disrupt spindle formation. Although OEHHA uses a linear dose-response assessment for oncogenic risk as a default position, the USEPA guidance document also states: "A linear dose-response procedure should be assumed when the mode of action underlying thyroid tumors is judged to involve mutagenicity alone" (USEPA, 1998: p3 item b). The data do not support a linear approach.

It should be noted that the USEPA comments in the list of chemicals evaluated for carcinogenic potential are as follows: "CARC recommended an MOE approach for the quantification of human cancer risk. This extrapolation is supported by the weight-of-the-evidence which suggests that thiabendazole may interfere with thyroid-pituitary homeostasis. Children are not expected to be more susceptible than adults to thiabendazole-induced thyroid cancer." This is reiterated the draft RED for thiabendazole (USEPA, 2001)

3. [OEHHA] The draft RCD states "In summary, the weight of evidence does not indicate that the oncogenic potential of thiabendazole should be considered for linear response analysis. 1) Thiabendazole was genotoxic, but the genotoxic effects of thiabendazole were likely related to spindle disruption. Spindle inhibitors are known to have a threshold." The statement that spindle inhibitors are known to have a "threshold" does not represent a widely accepted viewpoint within the scientific community, and should be removed. Moreover, not all of the genotoxic effects of TBZ are related to spindle disruption. TBZ has been reported to induce mutations in Salmonella (Zeiger et al., 1988), positive results in vivo in the comet assay (indicative of DNA strand breaks), and SCEs in vivo in two independent experiments. None of these endpoints can be ascribed to spindle disruption.

DPR: A reference was cited as the basis for the statement that spindle inhibitors are known to have a threshold. OEHHA did not provide a reference to support the assertion that this statement is not widely accepted. Chemicals that cause spindle disruption can cause SCEs *in vivo*. As noted above, SCE can also be caused by a number of factors which are not even remotely mutagenic. The uncertainty of the meaning of the "positive" comet assay has been discussed above.

4. [OEHHA] The discussion of the oncogenic endpoints should be expanded to cover additional sites observed in the F344 rat bioassays. Preputial gland adenoma increased to a statistically significant extent in two separate studies in male F344 rats. Increased tumor incidence was observed in the high-dose groups, which experienced large reductions in body weight gain (i.e., 40 percent reduction). Clitoral gland adenoma increased in two separate studies in female F344 rats. In one study the increase was statistically significant. Increased tumor incidence was observed in the high-dose groups, which experienced large reductions in body weight gain (i.e., 40 percent reduction). The two series of studies conducted with F344 rats were not submitted to DPR, but were published in the scientific literature (Hayashida et al., 1985; Fuji et al., 1991). The RCD could provide more detail on the F344 rat studies. For example, it would be helpful if the RCD stated whether any effects (hyperplasia or neoplasia) were

observed in the thyroids of treated F344 rats in these studies. Much higher doses were used in the F344 rat studies than in the Sprague-Dawley rat studies. Based on reductions in body weight gain observed in the F344 rat studies in the mid- and high-dose groups (approximately 20 and 40 percent, respectively), it appears that the doses used may have exceeded the maximum tolerated dose. It would be helpful to have information on survival, as well as other toxicity parameters to validate this assumption, and rule out the possibility that the presence of TBZ in the diet reduced palatability of the food, resulting in a reduction in food consumption.

DPR: The discussion of oncogenicity in the Hazard Identification section addressed these issues adequately. A 40% decrement in weight clearly exceeds the definition of a maximum tolerated dose (Eaton, D.L., and C.D. Klaassen, 1996. Chapter 2. Principles of toxicology. *In:* Casarett and Doull's Toxicology: The Basic Science of Poisons. Fifth Edition. C.D. Klaassen, M.O. Amdur, and J. Doull, Eds. McGraw-Hill, NY, NY; Foran, J.A., 1997. Principles for the selection of doses in chronic rodent bioassays. Environ. Health Perspect. 105:18-20.).

As OEHHA noted, the studies to which they refer were published studies and the data that OEHHA wanted were not included.

5. *[OEHHA] Issues related to tumor findings, from the Proposition 65 perspective. Treatment related increases were reported for benign tumors at three sites (thyroid, preputial, and clitoral glands) in studies in rats. No treatment related increases in malignant tumors were reported. Under Proposition 65, this evidence in experimental animals, in and of itself, likely would be insufficient to identify TBZ as "clearly shown to cause cancer." However, it is possible that this evidence, taken together with positive genotoxicity data and with strong structural and functional analogies with known carcinogens, might be determined to meet the clearly shown criteria of Proposition 65. The lack of information presented in the draft RCD on structurally similar compounds, does not permit one to hazard a guess as to the likelihood of TBZ being listed as a carcinogen under Proposition 65.*

DPR: The purpose of this RCD is to characterize the risk from potential exposure to thiabendazole based on its pesticidal uses. The listing of chemicals under Proposition 65 is the responsibility of OEHHA.

Mutagenicity

I . We [OEHHA] recommend expanding the discussion of mutagenicity of TBZ to address its potential for causing aneugenic effects (aneuploidy) in experimental systems (Mailhes et al., 1997; Aardema et al., 1998). Aneuploidy is the most prevalent of the various classes of human genetic disorders. It plays a significant role in adverse human health conditions including birth defects, pregnancy wastage, and cancer. Although at present there are insufficient data to determine with certainty if chemically induced aneuploidy contributes to human disease, it is prudent to address the aneugenic potential of chemicals in the human risk assessment process.

DPR: This is an interesting research topic, but it is beyond the scope of the RCD for thiabendazole.

2. *[OEHHA] With regard to evaluating results in the Salmonella reverse mutation assay, it is important to point out that merely counting the number of positive versus negative studies fails to incorporate other potentially useful information, such as possible differences in study protocol (i.e., plate incorporation versus liquid suspension) and range of doses tested. The draft RCD appears to dismiss the positive findings reported by researchers at the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) in Zeiger et al. (1988). Although it is true that Zeiger et al. present only summary findings, rather than raw data, the criteria used to classify findings as positive (i.e., reproducibility and apparent dose-response) are stated in the report. This positive finding of mutagenicity, as reported by the NIEHS/NTP, can not be dismissed, as it was reproducible and exhibited a dose-response.*

DPR: How well the criteria were met in the Zeiger et al. (1998) study is unknown because the data were unavailable. The purity of the thiabendazole tested was unstated, and the supplier (Tokyo-Kasei) was not the same as in the submitted studies. The positive results with TA98 were achieved with Hamster liver activation (not the usual source of activation) S9 at 10% and 30%, but negative with 30% rat liver activation. The increase in revertant colonies occurred in the presence of precipitation, which confounded the interpretation of the results (There was no discussion in the text of how the precipitations were addressed, or when the precipitate was noted- preincubation or plating?). There was an earlier study, indicating that the mutagenic activity in TA98 might be due to an impurity in some lots of thiabendazole. Although it was stated that positive results were confirmed, the single table of data does not indicate the data from each trial. In the same paper, there is a table compiling chemicals for which different labs found differing results in terms of positive, negative, or weak. Consequently, we did not put as much reliance on that report as on other submitted studies, for which we had complete data, that did not report mutagenic effects. Nonetheless, it was not dismissed from consideration- as it is mentioned in the Hazard Identification section as part of the weight of evidence.

3. *[OEHHA] On page 18 the draft RCD concludes that the genotoxic effects of TBZ are consistent with mitotic spindle dysfunction, caused by an inhibition of microtubule assembly. This is true for aneuploidy and polyploidy, and may be true for micronucleus induction, but would not explain the induction of SCEs, which presumably involves breakage and rejoining of chromatids. There are at least two published articles that report TBZ induces SCEs (de Pargament et al., 1987; Ardito et al., 1996). In addition, TBZ administered orally to mice tested positive for the induction of DNA breakage in the comet assay (Sasaki et al., 1997). Therefore, its clastogenic potential should not be discounted.*

DPR: As mentioned above, SCEs could be caused by spindle disruptors.

Developmental Toxicity

[OEHHA] The effects seen from treatment on gestational day nine are substantially different than those seen from exposure on gestational days 7 to 15 or 6 to 15. In particular, Ogata et al. (1984) in experiment number three (gestational day nine) observed fusion of vertebral arches in 34/255 fetuses at 670 mg/kg. Fusion of vertebral arches was observed at other dose levels with appreciable frequency down to 240 mg/kg, and sporadically at 60 mg/kg. In contrast, Ogata et al. (1984) in experiment number one

(gestational days 7 to 15) found 1/3 82 fetuses with fusion of vertebral arches at 700 mg/kg-day. Nakatsuka et al. (1995b) (gestational days 6 to 15) found no fusion of vertebral arches at-200 mg/kg-day. Thus, for this endpoint, the dose-response is very different for one day of exposure (gestational day nine) when compared to exposure for nine or ten days (gestational days 7 to 15 or 6 to 15). These differences in the data should be discussed and explained in the RCD, as well as the impact on the assessment of human risk.

DPR: The basis for the differences in the results was not presented in the studies, and therefor is unknown.

Reproductive Toxicity

[OEHHA] The section on reproductive toxicology appears to be complete and adequate for the purposes of the RCD. See "Specific Comments" below for additional comments. In the rat, reduced pup weight was observed with a NOAEL of 30 mg/kg-day. In the mouse, a NOAEL of 150 mg/kg-day was identified for reduced mice/litter and reduced pup weight.

DPR: No response necessary.

Children as a Sensitive Subpopulation

I . [OEHHA] The draft RCD concludes that children are more sensitive to TBZ exposure than adults. This conclusion is based on a wide spectrum of developmental toxicity in three species of laboratory animals (mouse, rat, rabbit) ranging from the induction of major malformations to fetal resorption (abortion). The lowest NOAEL identified for this type of developmental toxicity is 24 mg/kg-day based on fetal resorption and hydrocephaly in rabbits (first paragraph of page 26, page 43). The draft RCD suggests that the U.S. Environmental Protection Agency should consider an additional uncertainty factor to protect children in setting tolerances (page 43) even though the draft RCD does not include one in the assessment of dietary risk. This is an important issue and we feel that the incorporation of an additional uncertainty factor in the RCD to protect children and infants requires further discussion and consideration.

DPR: The RCD does not conclude that children are more sensitive to TBZ than adults. There are no data to support such a conclusion. TBZ does cause developmental toxicity. USEPA is governed by FQPA with regards to establishing an extra uncertainty factor for protecting children.

2. [OEHHA] Additionally, it appears that the fetus is also particularly sensitive to the adverse effects of TBZ, based on the types of developmental toxicity observed in animal studies (i.e., skeletal abnormalities, fetal resorption, and hydrocephaly). Thus, it is suggested that women of child-bearing age also be considered a sensitive subpopulation.

DPR: As stated in the Hazard Identification section: “The question of developmental anomalies amongst humans treated with thiabendazole was not addressed in any of the published papers, or in the data obtained from the Food and Drug Administration. This raises the question of whether clinical signs and symptoms, observed in human studies,

should be used as the regulatory endpoint for gauging the risks of short-term occupational and dietary exposure, when a more serious toxicological effect (teratogenicity) can be caused by a single dose of thiabendazole. The lowest NOEL and ENEL for teratogenicity in the rabbit and mouse were 24 mg/kg and 26 mg/kg, respectively. If it is assumed that humans are 10 times more sensitive to thiabendazole than the laboratory animals, the extrapolated "human equivalent" NOEL or ENEL would be 2.4 to 2.6 mg/kg, respectively. Taking into account the uncertainties involved in this cross species extrapolation, these values are probably not different from the demonstrated NOEL of 3.3 mg/kg for clinical signs and changes in blood chemistry from human studies. Consequently, the human NOEL (3.3 mg/kg) for clinical signs, symptoms, and changes in blood chemistry was used as the critical acute NOEL to assess the margins of exposure for potential acute occupational and dietary exposures to thiabendazole."

Scientifically, there is no basis for using an extra uncertainty factor for any toxicological endpoint for thiabendazole. The acute MOEs greater than 10, based on human data, are adequately protective of all population subgroups.

Pharmacokinetics

[OEHHA] This part of the draft RCD (pages 7 and 8) provides some information on the metabolism of TBZ after oral exposure to sheep, cow, goat, pig, human, and rat. It would be useful to include in the discussion any data on the toxicity of TBZ metabolites, and their role in the overall toxicological response from exposure to the parent compound. This section should also address the potential of TBZ, if any, to be distributed into milk.

DPR: There were no data on the toxicity of specific TBZ metabolites. There were no data on the amount of TBZ that might be expected to be found in milk.

Tolerance assessment

I . (OEHHA) The draft RCD provides no information on which contaminated crops could lead to human exposure (as well as the levels of TBZ contamination), including processed foods such as orange juice, orange peel and marmalade. Such information is necessary for the risk characterization and should be included in the revised RCD.

DPR: From the tolerance portion of the RCD: "…residue levels for thiabendazole were set equal to the tolerance, and the MOE, based on the upper 95th percentile for user-day exposures for each population subgroup was examined for the most highly consumed commodities (FDA, 1991). The MOEs for population subgroups theoretically exposed to tolerance levels of thiabendazole residues on label-approved commodities are presented in Table 20. Only the tolerances on the most frequently consumed commodities were examined, as it is assumed that the MOEs for lesser consumed commodities would be as great or greater." Using the tolerance on a commodity means all of the juices, peels and processed foods too, with no dilutions.

2. (OEHHA) No information is provided in the draft RCD on the types of TBZ residues considered for tolerance assessment (pages 44 to 46). We recommend that a more

specific description of the residues (e.g., parent chemical only, parent chemical and its metabolites) be included.

DPR: Unless otherwise stated in CFR40, tolerances apply to the active ingredient. Only residues of thiabendazole were considered for the tolerance assessment, as there were no data on the toxicity of any of the metabolites (what OEHHA refers to as "residues"). From the tolerance section of the RCD: "An acute exposure assessment using the residue level equal to the tolerance is conducted for each individual label-approved commodity."

3. (OEHHA) We recommend providing a table with the estimates of the theoretical maximum residue contribution (calculated by using the tolerance level and a 100 percent crop treated assumption), the anticipated residue concentrations, and their representations as percentages of the acceptable daily intake, reference dose (RfD) or NOAEL for chronic exposure.

DPR: Theoretical Maximum Residue Contribution (TMRC) is no longer performed by USEPA, as the technique is an inappropriate measure of chronic dietary exposure. TMRC assumes that all agricultural commodities (RACs) have tolerance level residues, and that all these RACs with tolerance level residues are consumed on a chronic basis. These are extremely unlikely conditions. Over the last 10 years, pesticide residue monitoring programs by DPR, FDA, and USDA's PDP have typically found that less than 2% of all RACs have residues at or above tolerances. Thus, the likelihood that one specific pesticide will have tolerance-level residues on all label-approved commodities on a chronic basis is vanishingly small.

4. (OEHHA) The tolerance assessment presented in the draft RCD qualitatively addresses the apparent greater sensitivity of children to TBZ exposure as compared to adults, but it does not quantitatively evaluate it. We recommend that the draft RCD include more discussion of whether the margin of exposure (MOE) calculations sufficiently account for the greater susceptibility of children. Current tolerances, and tolerances that take into account the greater sensitivity of children to TBZ should be presented for comparison.

DPR: There were no data indicating that children were more sensitive to thiabendazole than adults. The critical acute NOEL in humans was ten-fold below the NOEL for developmental toxicity in laboratory animals. The calculated MOEs appear to be adequate for any potential adverse effect.

Guidance and Advisories

I . (OEHHA) Guidance and advisories such as a maximum contaminant level, permissible exposure limit, health advisory, reference exposure level or threshold limit value are not available for TBZ. The only available guidance for TBZ is the World Health Organization's (WHO) RfD of 0.3 mg/kg-day (page 4, second paragraph). The draft RCD includes the WHO RfD for TBZ but did not clearly state that there are currently no other guidance or advisories established for this chemical.

DPR: Correct. The RCD only presents the standards/advisories which are available.

2. (OEHHA) It would be useful to compare the chronic NOAEL(s) identified in the RCD with the WHO RfD, discussing the toxicological bases for each one.

DPR: Unfortunately, discussion of the toxicological basis for the selection of the critical chronic NOEL used in establishing the WHO RfD was not available. DPR, however, did discuss the toxicological basis for the selection of the critical chronic NOEL used in the RCD for thiabendazole.

Environmental fate

I . [OEHHA] Some information was provided in the draft RCD on the hydrolysis, photolysis, aerobic and anaerobic soil metabolism, and soil mobility of TBZ (page 5 and 6), but there are no data on TBZ behavior in the atmosphere. We recommend including a description of any data that pertain to atmospheric transport of TBZ, or to include a statement that the data are not available (or are not needed, in the event that only post-harvest application is anticipated).

DPR: Thiabendazole is not sprayed in the fields, or in homes. It is a post-harvest fungicide used in closed chambers, and is unlikely to be a contaminant in the ambient air. As the chemical has a melting point of 300.6°C, and a vapor pressure of 4E-9 mmHg @25°C, it is unlikely to volatize from the surface of the produce, either.

2. (OEHHA) We recommend including a conclusion regarding the persistence of TBZ in particular environmental media (e.g., soil, water, and air). Our independent review of the literature indicates that the expected mobility of TBZ in soil is low to slight and the half-life is 400 days (Wauchope et al., 1991). If released into water, TBZ will be essentially non-volatile (Wauchope et al., 199 1). If released into the atmosphere, TBZ will exist primarily in the particulate phase. In the vapor phase, it will degrade in the atmosphere by reaction with photochemically produced hydroxyl radicals with an estimated half-life of six hours (Meylan and Howard, 1993).

DPR: See answer to question 1.

3. We recommend including a more complete characterization of TBZ in relation to the environment. Adverse ecological effects should be addressed. If this is outside the scope of the RCD, then a statement to this effect should be included.

DPR: Risk characterization documents for pesticides are concerned with human health consequences. At the present time, the Department does not have a legislative mandate to assess the ecological impact of a pesticide.

Risk characterization

(OEHHA) The "Risk Characterization" section of the draft RCD for TBZ (page 42) refers only to uncertainties in the current methodology and general assumptions used in the risk assessment. We recommend that this section include a discussion of the uncertainties specifically related to TBZ. These include the quality of the existing database, quality and limitations of the exposure data, data gaps (if any), and uncertainties related to toxicological responses, such as immunotoxicity and neurotoxicity for which risk assessment methodology have not been developed. The section on "Risk

Characterization" should also include a discussion on sensitive populations, including the unborn fetus, children and infants, and women of child-bearing age. Populations at special risk include people with any compromised liver functions.

DPR: Questions regarding toxicity data are more properly addressed in the toxicological portion of the Risk Appraisal. A section concerning immunotoxicity has been added. There are no neurotoxic concerns for thiabendazole, either from its pharmaceutical database, or the toxicological testing. It is true that because no specific neurotoxicity tests were required by USEPA that those tests were not performed. That does not mean that the database was inadequate. DPR is unaware of any data indicating that children and infants should be considered sensitive subpopulations. The potential hazard to women of child-bearing age was addressed in the Hazard Identification section. Whether people with compromised liver function are at special risk is not clear. The fact that thiabendazole causes cholestasis in humans and laboratory animals was discussed.

Conclusions

(OEHHA) According to the conclusions of the draft RCD, MOEs for potential acute and chronic exposures to workers handling and applying TBZ, and to the general public exposed via dietary consumption, were considered health protective. However, according to the draft RCD, the current tolerance for TBZ in apples does not provide adequate protection from the toxic effects of this chemical for certain population subgroups. Most of the currently existing tolerances may not be health protective for children since they do not take into account their greater sensitivity to this chemical as compared with adults.

DPR: There are no data to indicate that children are more sensitive to thiabendazole than adults. It is true that based on the acute tolerance analysis that MOEs for apple consumption are less than ten for two population subgroups. However, if one realizes that most of the exposure for those two population subgroups comes from processed apples (juice, primarily), and that apples that are processed are not sprayed with preservative, the MOEs are probably sufficient. However, because we did not have any specific data that would allow us to prove such a speculation, it was not included.

SPECIFIC COMMENTS

OEHHA: Page 7, first paragraph. "Thus, humans appeared to absorb at least 87% of a single oral dose of TBZ." It is not clear how this statement follows from the discussion before it.

DPR: Generally, the amount of radiolabel excreted in the urine following dosing with radiolabelled material is reflective of the absorbed dose (Rozman and Klaassen, 1996. Absorption, distribution, and excretion of toxicants. Chapter 5. Casarett & Doull's Toxicology. The Basic Science of Poisons. Fifth Edition).

OEHHA: Page 9, Table 1. Some of the categories should be IV rather than III.

DPR: Thank you. The changes have been made

OEHHA: Page 11, first paragraph. When it is stated that the liver and thyroid effects were reversible after 13 weeks, it could also be mentioned that this result supports a non-genotoxic mode of action of TBZ.

DPR: This was done in the Hazard ID and the Risk Appraisal sections, when all the data had been presented in the other studies, and were available to discuss the oncogenic potential of thiabendazole fully.

OEHHA: Page 11, first paragraph. The clearance rate of iodine was significantly elevated at the highest dose level only.

DPR: This was apparent from Table 2.

OEHHA: Page 11, Table 2. What are the units for the metabolic clearance rate of iodine?

DPR: Metabolic clearance rate is always given in the same units, volume/unit time. The table has been modified to make this clear.

OEHHA: Page 15, Table 5. For "kidney-tubular and/or ductal hyperplasia" in males, is 7/30 significantly different from 1/29 in the Fischer's exact test?

DPR: Yes. Thank you for noting the typographical error. The correction has been made in the table.

OEHHA: Page 19, first paragraph. Reproductive Toxicity/Summary. "The reproductive NOEL for mice was approximately 150 mg/kg-day, based on reduced numbers of mice formed and weaned per litter, as well as reduced weanling weight." The term "mice formed" is unclear. Does this refer to live litter size at birth, or something else? It would be helpful to use a more exact term. This change should be carried forward to the document summary on page 2.

DPR: “formed” has been changed to the study author’s term, “born”, in all the appropriate locations in the text.

OEHHA: Page 20, first paragraph. Reproductive Toxicity/Oral-Rat. "At 90 mg/kg-day, there was a significant ($P < 0.05$) decrement in pup weight gain. The NOEL for reduced pup weights was 30 mg/kg/day." It would be useful to specify when the decrement in pup weight was detected, and magnitude of decrement.

DPR: The decrements in pup body weight were only noted at the highest dose (as stated), at all time points in the F_1 generation, 14 and 21 weeks in the F_2 generation, and ranged from 6-10% in both males and females. This has been incorporated into the document.

OEHHA: Page 20, third paragraph. Reproductive toxicity/Oral-mouse. "Mice (25/sex/group) were dosed with thiabendazole (purity unstated) at concentrations of 0, 0.02, 0. 1, or 0.5% in the diet for five generations (Nessel, 1981b). The NOEL was approximately 150 mg/kg-day for reduced numbers of mice formed and weaned per litter." Include an explanation of how the dosage of 150 mg/kg-day was derived from the concentrations in feed. In addition, the term "mice formed" is unclear. It would be helpful to use a more exact term.

DPR: This appears to be a repeat of comment made above.

OEHHA: Page 20, fourth paragraph. Developmental Toxicity/Summary. "The Estimated No Effect Level (ENEL) for mice was 26 mg/kg-day, based on skeletal abnormalities." The data referred to are for a single administration of TBZ on gestational day nine (from Ogata et al. 1984, experiment number three). The endpoint and duration of exposure are different from the other mouse teratology study cited (Nakatsuka 1995b), so it is important to specify both endpoint and duration of exposure. In addition, perhaps use of the unit mg/kg should be used to denote a single exposure. The maternal and developmental NOAELs (25 mg/kg-day) and endpoints (maternal weight gain and fetal weight) for administration during gestational days 6 to 15 in mice (Nakatsuka 1995b) should be added to the summary. These changes should be carried forward to the document summary on page 2.

DPR: In this instance, the ENEL, based on skeletal abnormalities, was generated by the author of the paper. That is why it is identified in that manner. The other endpoints (decrement in maternal and fetal weight) in the other mouse study were not of major toxicological concern, and were, thus, not carried forward into the summary. Although all of the various toxicological effects of a chemical in an individual study are presented in the body of the text, DPR tries to use the summaries to emphasize the endpoints of concern.

OEHHA: Page 20, fourth paragraph. Developmental Toxicity/Summary. "The NOEL for developmental toxicity in rabbits was 24 mg/kg-day based on fetal resorption and hydrocephaly. The material NOEL in rabbits was 120 mg/kg-day based on decrement in food consumption and body weight gain." There may be some question about the reliability of the developmental NOAEL from the first rabbit developmental toxicity study. The NOAEL from the second rabbit study (150 mg/kg-day) might be more reliable. Any change in the selection of the NOAEL should be carried forward to the document summary on page 2.

DPR: If the rabbit studies were examined individually, in isolation from all other developmental toxicity studies, we might agree with OEHHA. However, similar skeletal abnormalities associated with thiabendazole treatment occur in mice, rats, and rabbits. In order to be adequately health protective, DPR emphasized the No Observed Effect Level (NOEL), 24 mg/kg-day, for skeletal abnormalities in the former study (acceptable under FIFRA guideline requirements), rather than the NOEL of 150 mg/kg-day for decrement in fetal weight in the latter study (acceptable under FIFRA guideline requirements). On what basis does OEHHA find the latter study more reliable than the former study?

OEHHA: Pages 20, fourth paragraph. Developmental Toxicity/Summary. "In the rat gavage study, the NOEL for decreased maternal food consumption was 10 mg/kg-day." It appears that this NOAEL is for decreased maternal weight gain as well as food consumption.

DPR: The decrement in maternal weight gain, 4.8%, occurred at the high dose only. Significantly decreased food consumption occurred at the both the mid- and high dose levels.

OEHHA: Page 20, fifth paragraph. Developmental Toxicity/Gavage-mouse. "In the second regime, a single dosage of 2400 mg/kg-day was used on any one of days 6-12 of gestation. The third dosage regime was to give one of 17 dosages of thiabendazole, ranging from 30 to 2400 mg/kg-day, on day 9 of gestation." The units mg/kg-day usually refer to multiple exposures, for a single exposure the units mg/kg is more appropriate.

DPR: In the text of the Hazard ID, where the logic for the selection of the critical acute NOEL discusses which endpoint will be used, and why, the units of the endpoints from all developmental toxicity studies are expressed as mg/kg. In the study summary, the units are all kept the same to preclude confusion over units.

OEHHA: Page 20, fifth paragraph. Developmental Toxicity/Gavage-mouse. "The estimated no effect level (ENEL) (EDO I determined by probit analysis by the authors) for the incidence of 9 litters with fetuses having skeletal fusion was 26 mg/kg-day." The citation of "9 litters" appears to be an interpretation of Figure I from Ogata et al. (1984), which shows "probit" analysis, The "9" appears to come from the number of open circles associated with the line for limb deformities. However, closer inspection of this figure indicates that each data point represents all the litters at a given dose. For example, the solid black dot at about 2,400 mg/kg represents about 65 percent of all the litters at that dose having fetuses with skeletal fusion. This corresponds with the entry for 2,400 mg/kg in Table 7. There were 18 litters examined at 2,400 mg/kg, and a range of 18 to 28 litters at other doses. According to Table 7, there are 20 doses in the range of 30 to 2,400 mg/kg. Not all are apparent on Figure I because some data points coincide, and others are difficult to see because they fall on the X axis. The total litters analyzed would be about 20 x 20, or 400 litters. Deletion of "9" from the cited sentence would avoid confusion.

DPR: The text has modified to take OEHHA's concerns into account.

OEHHA: Pages 20 and 21, fifth paragraph. Developmental Toxicity/Gavage-mouse. "In a separate experiment, maternal weight loss was induced by starvation to see if weight loss alone would cause the appearance of skeletal malformations... " The term "starvation- is misleading. The more correct term is pair-feeding. It should be specifically pointed out in this paragraph that mice were pair-fed to thiabendazole-treated mice.

DPR: Thank you for your suggestion.

OEHHA: Page 21, second paragraph. Developmental Toxicity/Gavage-mouse "There were decrements in maternal body weight at 200 (15.6%), 400 (30.2%), and 800 mg/kg-day (39%), as well as reduced RBC counts, hemoglobin, and hematocrit." This sentence could be further clarified by noting that the numbers in parenthesis actually refer to the decrement in maternal body weight gain during treatment (i.e., on days 6 to 15 of gestation). There were also small decrements in maternal weight gain during treatment at 25 and 100 mg/kg-day, although these were not statistically significant. If the decrements at 25 and 100 mg/kg-day are not mentioned, then the qualifier "statistically significant" should be added to the above sentence.

DPR: The text has been modified to add statistically significant.

OEHHA: Page 21, third paragraph. Developmental Toxicity/Gavage-mouse "There were slight decrements in body weight gain of the pregnant females at the high and middle doses in the first four days of the study." This paragraph omits the important observation that there were statistically significant decrements in maternal body weight gain during treatment in the 100 mg/kg-day (15 percent) and 200 mg/kg-day (24 percent) doses. This should be added.

DPR: The observation of "*statistically significant decrements in maternal body weight gain during treatment in the 100 mg/kg-day (15 percent) and 200 mg/kg-day (24 percent) doses*" is not particularly important when one realizes that "Differences in litter sizes, which were not due to treatment effects, caused the decrement in body weight gain to be more pronounced over the course of the study."

OEHHA: Page 21, third paragraph. Developmental Toxicity/Gavage-mouse "Differences in litter sizes, which were not due to treatment effects, caused the decrement in body weight gain to be more pronounced over the course of the study." The study cited (Nakatsuka 1995b) does not report extra-gestational weight gains. Thus, in the absence of further analysis, the above-cited sentence appears speculative and could be misleading in regard to the impact of litter sizes on body weight gains. It could well be that the change of extra-gestational weight gain was greater than of gestational weight gain. Consideration should be given to omitting the phrase "caused the decrement in body weight gain to be more pronounced over the course of the study."

DPR: OEHHA's concerns have been noted, and the text has been modified to read "..may have caused.."

OEHHA: Page 21, paragraph 4. Developmental Toxicity/Gavage-rabbit "The NOEL for developmental toxicity was 24 mg/kg-day based on fetal resorption (4/18 litters resorbed with whole litter resorption at 120 mg/kg-day) and hydrocephaly (2 fetuses in 2 litters at 600 mg/kg-day and one fetus at 120 mg/kg-day)." It appears that the data cited in this study (Hoberman, 1989) are the same data as the "first" rabbit developmental study cited in the published report Lankas and Wise (1993). Based on these data, interpretation of the whole litter fetal resorptions observed at 120 mg/kg-day appears problematic. First, there were no whole litter fetal resorptions at the high dose in this study (600 mg/kg-day). Although it could be hypothesized that the abortions observed at 600 mg/kg-day were etiologically related, it is not clear that this is the case. Also, even if one assumes that they are related, there would be little dose-response effect. At 120 mg/kg-day, there were 4/18 whole litter resorptions (no abortions), and at 600 mg/kg-day there were 4/13 abortions (no whole litter resorptions). Thus, increasing the dose by five times had little effect on the frequency of the whole litter resorptions plus abortions. While this is possible, it appears to leave a question about the biological meaning of the effects at 120 mg/kg-day. Second, in a subsequent study (cited in the draft RCD as Lankas and Wise 1991, apparently the same data as the "second" rabbit developmental study in Lankas and Wise 1993), which was nearly identical to the first study, there were no whole litter resorptions at 150 or 600 mg/kg-day. Finally, the frequency of whole litter resorptions at 120 mg/kg-day in the first study was not statistically significant ($p = 0.066$ by Fisher Exact test). Some of the same concerns apply to the observations of hydrocephaly. The small number of observations of the effect is far from statistically significant, either on a per litter or per fetus basis. Also, there were no observations of hydrocephalus in the second rabbit study at either 150 or

600 mg/kg-day. Overall, the results from the first study are difficult to interpret. Although there are indications of adverse developmental effects at the middle dose (120 mg/kg-day), various factors, including lack of statistical significance, lack of dose response, and lack of corresponding effects in the second study make interpretation difficult. The NOAELs from the second study appear to be more reliable for use in risk assessment.

DPR: The issue of the NOELs in the rabbit studies submitted by the registrant was dealt with above. With regard to reconciling the submitted results with the published results, there is one major difference between the two types of "results". The published results represent the author(s)' interpretation and analysis of the experimental data. Neither the reviewers nor the readers ever get to see the raw data to determine whether the author(s)' opinions are correct. When FIFRA studies are submitted to DPR, we have the raw data and make our own interpretation and analyses of the data.

OEHHA: Page 22, paragraph 2. Developmental Toxicity/Gavage-rat "A slight decrement in body weight gain (1.7 to 4.8%) was seen in the high dosage rats (80 mg/kg-day) on days 8 through 14. Food consumption was significantly (P<0.05) reduced at dosages of 40 (11-15%) or 80 mg/kg-day (22-28%) compared to controls. The NOEL for decreased maternal food consumption was 10 mg/kg-day." In addition to the study which is cited in the draft RCD as Wise 1990, there is a published report, Lankas and Wise (1993), which appears to present either the same or a very similar study. In the latter report, it is stated that "There were statistically significant (P = 0.05) decreases in average maternal body weight gain in the 40 and 80 mg/kg/day groups between GD 6 and 18 (12% and 26% below control, respectively ...)." It would be helpful to reconcile the Lankas and Wise (1993) report with Wise (1990) article, particularly since the former report would indicate that the NOAEL should be for reduced food consumption and reduced maternal body weight gain.

DPR: They are one and the same study. However, the data that they supplied to DPR did not indicate the decrements in bodyweight gain that were cited in the published paper.

OEHHA: Pages 22 to 24, Developmental Toxicity/Diet-rat. The results of the two rat dietary studies are difficult to reconcile. Both were conducted with Wistar rats, the first for gestational days 6 to 17 and the second for gestational days 7 to 17, but with very different concentrations of TBZ in the feed (up to 100 ppm in the first, and up to 10,000 ppm in the second). The results of the first study indicated reduced fetal body weights at 50 ppm but the results of the second study indicated no reduction at 1,250 and 2,500 ppm, but only at 5,000 and 10,000 ppm. Furthermore, the results first study indicated increased major skeletal malformations (including cleft palate) at 100 ppm, but the results of the second study did not indicate any skeletal malformations. Given that these effects are characteristic of a fairly developed embryo or fetus, it does not seem likely that these differences would result from one study starting on gestational day six and the other on gestational day seven. For these reasons, it may be appropriate to reconsider whether the results from the first (low concentration) study should be carried forward to the summary.

DPR: We agree that it is difficult to reconcile the results. Since we couldn't account for the difference in response, we simply presented it.

OEHHA: Page 22, last paragraph. The number of animals used per dose level is not indicated.

DPR: The number of animals has been added.

OEHHA: Page 24, Table 11. For skull bone hypoplasia, is 15 significantly different than 0?

DPR: We thank OEHHA for pointing out a typographical error.

OEHHA: Page 25, last paragraph. Three clinical studies are cited in which TBZ was administered acutely to treat parasitic infections. Is this a sufficient number, considering the large number of studies in the literature? In some of these studies the drug was administered for longer periods of time.

DPR: There were not a large number of studies that dealt with dosing and side effects published in the open literature. The ones cited were the only ones that dealt with side effects from acute dosing. No chronic human dosing studies were identified. As there were only acute and a chronic regulatory endpoints required, the acute studies were discussed.

Page 25, last paragraph. "The NOEL in a third clinical study involving 42 male subjects was 3.3 mg/kg." What toxicity endpoint was this "NOEL" based upon?

DPR: The lack of side effects described in the other studies at higher doses.

Page 26, third paragraph. Since platelet counts were not elevated in the mouse, does this suggest that the thrombi were due to other factors?

DPR: Don’t know.

OEHHA: Page 27, top paragraph. "through disruption of tubulin formation" should read "through disruption of microtubule formation."

DPR: Thank you for the suggested grammatical correction.

OEHHA: Page 35, Table 16. For some categories the numbers in the third column do not equal the sum of the first and second columns.

DPR: Only the first row does not add up, ostensibly. However, the first column consists of numbers rounded to the nearest whole number.

OEHHA: Page 40, last paragraph. "but the increased clearance of iodinated compounds indicated an increased turnover rate for T3 and T4." This was only true at the highest dose level, not at the second highest dose level, where the effects of the test article on liver and thyroid weights and on TSH levels were also observed.

DPR: We thank OEHHA for the comment, but the text will not be changed as the data speak for themselves. What, if any, are the potential implications here?

OEHHA: Page 41, second paragraph. "All other genotoxic effects involved spindle disruption ..." This is not the case for SCE induction, which presumably involves breakage and rejoining of chromatids.

DPR: The genotoxic implications of SCE are unknown at this time.

OEHHA: Page 41, third paragraph, first sentence. It could also be added that according to Casarett and Doull's Toxicology (fifth edition, pages 617 to 62 1), the induction of thyroid adenomas by elevated TSH, resulting from liver stimulation, does not occur in humans.

DPR: We thank OEHHA for supplying a fourth reference which suggests that the chemical induction of thyroid follicular tumors in rodents has no relevance to human health concerns.

(OEHHA) Appendix, page 30, Table 2. The total dermal exposures for the citrus workers are not the sums of the hands, arms and T-shirt values.

DPR: This will addressed by WH&S in a separate memorandum.

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The following references were not cited in the draft RCD:

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TOXICITY PROFILE

A. GENERAL COMMENTS

Novartis respectfully submits that California DPR's conclusions on the endocrine effects of thiabendazole are not fully supported by the data. Novartis also submits that the conclusions on the developmental toxicity of thiabendazole are not well founded based on non adverse developmental findings from GLP compliant investigations, and the methodological deficiencies of an earlier study (Ogata et al., 1984) relied on for this interpretation.

DPR: Presumably, the endocrine effects of thiabendazole (TBZ) referred to are the stimulatory effect of TBZ on plasma TSH. In as much as Novartis submitted a study (Lankas, 1995) which clearly indicates a dose-related, statistically significant increase in plasma TSH in the rat, DPR believes that there are effects on the endocrine system. Novartis goes into detail on the reasons for differences in interpretation of developmental studies later, and DPR will respond to the specifics in the appropriate place later in this document.

In several locations including the Summary Section, the document contains language to describe the NOEL that Novartis believes could be misinterpreted. For example, the draft document states that "In a 14 week dietary study, the NOEL for hepatotoxicity and thyrotoxicity in rats was 10 mg/kg/day". Novartis believes that a more accurate representation of the study data would be; "In a 14-week dietary study in rats, the NOEL was 10 mg/kg/day based on hepatotoxicity and thyrotoxicity at higher dose levels". Several such citations occur in the Chronic and Subchronic Toxicity Sections of the draft document.

DPR: We thank Novartis for their suggestion; however, we do not believe that it will be misinterpreted.

B. GENOTOXICITY COMMENTS

(Novartis) The draft document states that the genotoxicity potential for thiabendazole has been demonstrated in laboratory studies. Novartis believes that this statement is not fully supported by the evidence presented. For example, consider the statement in lines 5-8 of the same Genotoxicity subsection: "..positive results were reportedly obtained in Salmonella strains TA98 and TA99 in a study published in summary form. In the absence of data from this study, it was not possible to evaluate the mutagenic potential of thiabendazole". Therefore a more accurate and better introduction would be "All acceptable regulatory toxicology studies on thiabendazole, conducted under GLP guidelines, demonstrate that the compound is not mutagenic in bacteria or clastogenic in vitro in mammalian cells conducted without S(activation". Incidentally, the USEPA has also reached a similar conclusion.

DPR: In the Hazard Identification section, in which the weight of evidence for oncogenicity was examined, we stated: "All of the submitted genotoxicity tests for thiabendazole were negative."" Even though published studies do not necessarily meet GLP criteria, that does not render those studies scientifically invalid. Consequently, the results of those studies must be added to the total

toxicological database for consideration. DPR is well aware of the short-comings of some of the studies, and we so state in the text: "…positive results were reportedly obtained in Salmonella strains TA98 and TA99 in a study published in summary form. In the absence of data from this study, it was not possible to evaluate the mutagenic potential of thiabendazole."

(Novartis) In Section E. Genotoxicity (Summary) found on page 18, lines 1-2 state: "…Genotoxicity potential for thiabendazole has been demonstrated in laboratory studies". Novartis suggests that this sentence be changed or deleted, since the statement is incorrect or misleading. See also the comment above for details.

DPR: We do not feel that the statement is incorrect or misleading for the reasons stated above.

C. CHRONIC TOXICITY COMMENTS

(Novartis) As previously mentioned in the General Comments above, Novartis notes that the NOELs for several chronic toxicity studies have been described in a manner that could be misinterpreted and respectfully suggests that these should be revised as indicated above.

DPR: Again, we appreciate the suggested stylistic changes, but we do not feel that the endpoints will be misinterpreted.

D. PHARMACOKINETICS COMMENTS

(Novartis) In Section A. Pharmacokinetics (Summary) found on page 7, line 1 states: "…absorbed oral dose." Novartis suggests that this phrase be changed to "…administered oral dose."

DPR: Thank you. The change has been made.

E. SUBCHRONIC TOXICITY COMMENTS

(Novartis) As previously mentioned in the General Comments above, Novartis notes that the NOELS for several subchronic toxicity studies have been described in a manner that could be misinterpreted and respectfully suggest that these should be revised as indicated above.

DPR: Again, we appreciated the suggest stylistic changes, but we do not feel that the endpoints will be misinterpreted.

(Novartis) in Section C. Subchronic Toxicity (Oral-Rat study) found on page 11, the last line of the paragraph states: "…inanition…" Novartis suggests that the word be changed to: "…metabolic enzyme induction…"

DPR: In as much as the increased catabolism of T3 and T4 could be due to decreased food consumption, rather than a direct stimulation of the liver by TBZ, the term inanition was used to indicate that possibility.

F. DEVELOPMENTAL AND REPRODUCTIVE TOXICITY COMMENTS

(Novartis) With regards to developmental toxicity, the draft document concluded that thiabendazole caused major malformations of the skeletal system in mice, rabbits and rats and defined an Estimated No Effect Level (ENEL) for mice of 26 mg/kg-day based on skeletal abnormalities. Novartis believes that these studies demonstrate that the skeletal variations observed in mice, rabbits and rats all occurred within the context of maternal toxicity- a position also consistent with the conclusions of US EPA. Also the term "Estimated No Effect Level (ENEL)" is very subjective and is ill defined for use in regulatory decision making. A more objective quantitative approach, such as benchmark dose, would have been more appropriate.

DPR: There is a major difference between malformations and variations. The former are terata, the latter are developmental anomalies. Thiabendazole causes terata. DPR has not yet adopted a comprehensive policy on the use of an approach to estimating a No Effect Level when there are effects at the lowest dose level tested. Currently, we use a default procedure of dividing the LOEL by a factor of 10. The ENEL in question was derived by the authors of that study. As stated in the text: "The estimated no effect level (ENEL) (ED_{01} determined by probit analysis by the authors)…" Whether this is more or less valid than using the lower bound of the ED_{05} or ED_{10}, as recommended by the "benchmark dose" approach suggested by USEPA, could be the subject of extensive debate. However, the number was used strictly for comparison with the critical acute human NOEL to get a measure of the adequacy of the selected endpoint to be fully health protective.

(Novartis) In the Conclusions of the Summary found on page 3, lines 4-5 of the second paragraphs state "…Thiabendazole has adverse prenatal effects and causes disruption of endocrine levels associated with body metabolism…." Novartis suggests that the entire sentence be deleted since it is factually incorrect. there are no experimental data available that point to the interpretation that thiabendazole causes endocrine disruption. It is also unclear from the draft document which endocrine levels are being referred to. Even the most conservative review of the chronic developmental and pharmacokinetic data fail to show any association between thiabendazole administration and endocrine effects. For prenatal effects, the same lack of, or misinterpretation, of data also applies. (See also the general comments on developmental effects in the next page(s).

DPR: As DPR believes that thiabendazole is a teratogen, the first part of the phrase "adverse pre-natal effects" is correct. Clearly, thiabendazole causes changes in plasma levels of Thyroid Stimulating Hormone (TSH), an endocrine polypeptide. As changes in TSH levels affect the circulating levels of hormones involved in body metabolism, the second part of the phrase is correct. We therefor disagree with the interpretation of Novartis.

(Novartis) In section F. <u>Reproductive Toxicity</u> (Oral-Rat study) found on page 20, the first line of the second paragraph states: "…Thiabendazole (98.8%) was… Novartis suggests that the following phrase be inserted before the sentence: "In another multigenerational reproductive study (Vogin, 1968),

DPR: The sentence has been modified.

(Novartis) In section G. Developmental Toxicity (Summary) found on page 20, lines 1-3 state "Thiabenzazole caused major malformations of the skeletal system in mice, rabbits and rats. The Estimated No Effect Level (ENEL) for mice was 26 mg/kg-day based on skeletal abnormalities:. Novartis suggests that the entire sentence be deleted for the following reasons:

* *The Skeletal variations observed in mice, rabbits and rats all occurred within the context of maternal toxicity. Therefor, thiabendazole is not selectively toxic to fetuses.*
* *The term "Estimated No Effect Level (ENEL) is very subjective and is ill defined for use in regulatory decision making. A more objective quantitative approach, such as benchmark dose would have been more appropriate.*

DPR: In the mouse (Ogata *et al.,* 1984), the NOEL for maternal toxicity was 965 mg/kg-d. The LOEL for skeletal fusion was 30 mg/kg-day. The NOELs for maternal toxicity (decrement in weight gain) were the same as the NOELs for hydrocephaly and skeletal malformations in rabbits (Hoberman, 1989; Lankas and Wise, 1991), and retardation of ossification in rats (Tanaka *et al*., 1982).

As stated above, DPR has not yet adopted a comprehensive policy on the use of an approach to estimating a No Effect Level when there are effects at the lowest dose level tested. Currently, we use a default procedure of dividing the LOEL by a factor of 10. The ENEL in question was derived by the authors of that study. As stated in the text: "The estimated no effect level (ENEL) (ED_{01} determined by probit analysis by the authors)…" Whether this is more or less valid than using the lower bound of the ED_{05} or ED_{10}, as recommended by the "benchmark dose" approach suggested by USEPA, could be the subject of extensive debate. However, the number was used strictly for comparison with the critical acute human NOEL to get a measure of the adequacy of the selected endpoint to be fully health protective.

(Novartis) In Section G. <u>Developmental Toxicity</u> (Summary) found on page 20, lines 7-10 state: "…However, in two studies in which pregnant rats were exposed to thiabendazole…" Novartis suggests that the entire sentence be deleted for the following reasons, also stated above:

* *The skeletal variations observed in rats all occurred within the context of maternal toxicity.*
* *In GLP compliant regulatory studies, thiabendazole is not selectively toxic to rat fetuses.*

DPR: As noted above, the developmental effects of concern are skeletal malformations, not just skeletal variations, although they may be part of the spectrum of toxic effects. In the rat developmental studies, with dietary exposure, there were not indications of maternal toxicity reported. Yet, the skeletal malformations and variations were reported to have occurred. True, these dietary exposure studies were not FIFRA compliant, but that did not eliminate their scientific validity. The difficulty is in reconciling the skeletal effects in those studies with the lack of developmental effects at higher dose in the gavage dosing study.

GENERAL COMMENTS ON APPARENT DEVELOPMENTAL TOXICITY

(Novartis) The apparent developmental effects of thiabendazole is based on data from a poorly conducted study - namely experiment #3 of a 1984 study with Jcl:ICR mice (Ogata et al, 1984). However, in view of the critical deficiencies in this 1984 study and the new 1995, GLP and guideline compliant, mouse study that was conducted later (Nakatsuka, 1995a, b), there is no evidence that thiabendazole meets the criteria to be referred to as a developmental toxicant.

DPR: The Ogata *et al,* 1984 study was not conducted under FIFRA guidelines; however that does not invalidate it as a scientific study. Most scientific studies are not GLP and/or guideline compliant. The Nakatsuka 1995a,b studies, though conducted in the same strain of mouse, were done more than 10 years later. Lower doses were used in the Nakasuka studies, perhaps because NOEL for maternal toxicity (indicated by decrement in maternal weight) in these studies was 25 mg/kg-day, while the maternal NOEL for the same endpoint was reported to be 965 mg/kg-day in the Ogata study. Nonetheless, at 800 mg/kg-day in the Nakatsuka 1995a range finding study, "…there was an increased incidence of cleft palate (15 fetuses in 4 litters) compared to controls (1 fetus in 1 litter)." The highest dose tested in the Nakasuka 1995b FIFRA guideline study was 200 mg/kg-day.

(Novartis) The 1984 mouse study by the Ogata group can not be considered a "core-grade minimal" regulatory study due to its many methodological and reporting deficiencies. The publication provided no information on the randomization of animals, no information on the time of dosing, no food consumption measurement, and no chemical verification of test substance concentration and homogeneity of the suspension. While some apparent developmental effects were noted in the experiment #3, these were inconsistent with experiment #1 of the same study - which is distinctly odd for a scientific study with same mouse strain, same investigators, and same laboratory environment. In addition, the important maternal effects usually associated with thiabendazole in humans and rodents (diarrhea, epigastric distress, hemoglobin level, erythrocyte count, hematocrit, food consumption, and body weight) (e.g., Physician's Desk Reference, 1998) were not evaluated or fully reported and the actual dose levels are unknown since the non-homogenous dosing mixture was not analyzed. The observed fetal effects are a set of meaningless data without a full knowledge of the dose levels actually applied and the maternal context of observation. The effects observed in experiment #3 of the 1984 Ogata Study are, therefore, not appropriate for hazard identification and do not constitute sufficient evidence of developmental effects for regulatory consideration.

DPR: The difference between experiment 1 and experiment 3 in the Ogata study was the dosing regimen. In experiment 1, the dams were dosed repeatedly from day 7 to day 15. In experiment 3, the dams were dosed only on day 9. Although skeletal malformations did occur in experiment 3, it should not be a surprise that there were fewer effects than with multiple dosing. We did not consider the Ogata *et al.,* 1984 study to be a FIFRA compliant study. That did not detract from the scientific value of the study- showing that a single dose of thiabendazole on a single day could elicit specific teratogenic effects. Further, that these

specific teratogenic effects were chemically related, and not due solely to maternal toxicity. As in any published study, the data were limited to summaries and specific information selected by the authors to prove the point they wished to make.

(Novartis) Two new mouse teratogenicity studies were done in 1995 (Nakatsuka, 1995a -range finder, 1995b - definitive) using the same strain of mice and dosing vehicle. The definitive study (1995b; the "Nakatsuka Definitive Study") was a GLP compliant study conducted and reported exactly according to USEPA guidelines. The 24% decrease in maternal body weight gain and the average 7% drop in food consumption at the top dose of 200 mg/kg in the definitive study demonstrate the sufficiency of this dose level and its adequacy for risk assessment. The slight decrease in pup birth weight (by 4-5%) at this dose level in the definitive study is not considered indicative of unique fetal toxicity but is rather an expected secondary effect due to the reduced maternal food consumption, low maternal weight gain, and other maternal toxic effects such as the strong binding of thiabendazole to proteins, including the possibility of digestive proteases. The results of this valid GLP study demonstrate that thiabendazole is not developmentally toxic to mice and contradict the findings of the poorly conducted 1984 study by Ogata's group. Consequently, thiabendazole should not be described as a developmental or reproductive toxicant because the flawed data source do not constitute sufficient evidence of such physiological lesions. The developmental effects of thiabendazole are adequately described by the Nakatsuka Definitive Study.

DPR: As noted above, DPR is aware of the differences in the studies. If Novartis has data which conclusively show that the effects noted in the Ogata study are solely due to the binding of thiabendazole to digestive proteases, DPR would be willing to take such data into consideration in evaluating the developmental toxicity of thiabendazole.

(Novartis) In summary, therefore, thiabendazole cannot be considered a developmental toxicant for the following reasons:

1. *Additional analysis of the data, particularly those of experiment #3, from the 1984 Ogata Study, demonstrate that no part of the 1984 Ogata Study can be relied upon for hazard identification.*

2. *Scientific literature and USEPA reviews support the interpretation of low birth weight as being secondary to low maternal food consumption, body weight, anemia, and other maternal toxic effects. Thus, low birth weight observed at the top dose of the Nakatsuka range finding study (Nakatsuka, 1995a) are secondary to adverse maternal effects.*

3. *Additional analysis of data from the Nakatsuka Definitive Study demonstrate that developmental findings were limited to slight delay in fetal growth secondary to the effects on maternal weight gain, food consumption, and other toxicity (Le., no unique or direct developmental toxicity) in this GLP compliant study with thiabendazole.*

4. *The third experiment in the Ogata Study should not be used for hazard identification since the non-homogenous dosing mixture was not analyzed (actual dose levels are unknown) and important maternal effects or endpoints (including hemoglobin, erythrocyte and hematocrit levels, hypoxia, diarrhea, food consumption, and body weight changes) were not evaluated or fully reported. The findings in the third experiment are inconsistent with the Nakatsuka Definitive Study, which is scientifically more rigorous and GLP guideline compliant.*

5. *The developmental findings in the third experiment are inconsistent with the first experiment of the same study. These internal inconsistencies within the Ogata Study further highlights the unreliability of the dose given in this study. It is inconceivable that any developmental study will be considered valid for scientific or regulatory purposes without reliable information on the administered dose.*

6. *Thiabendazole is a unique zwitterionic compound (see structure below) and is most reliably analyzed by ion exchange systems, rather than the conventional normal or reversed phase chromatography. Even limited analytical work would have revealed that quantitative determinations of thiabendazole in solvents other than acids or bases are highly erratic and unreliable. Peer reviewed publications on thiabendazole have therefore generally included detailed information on analytical or separation methods if chemical analysis was done (e.g., Rosenblum, 1977; Chukwudebe et al, 1994). Consequently, the absence of such important information must be taken to indicate that the analysis of concentration and homogeneity was not part of the study design.*

DPR: We, respectfully, disagree with Novartis's contention that thiabendazole is not a teratogen. Aside from the Ogata et al., 1984 study, there are similar terata identified in mice in Nakatsuka, 1995a; in rabbits in Hoberman, 1989 and Lankas and Wise, 1991; and in rats in IPTP, 1985.

G. RISK ASSESSMENT COMMENTS

(Novartis) In Section A. Hazard Identification of the Risk Assessment portion found on page 25, line 2 states: "...and developmental toxicity". Novartis suggests that "developmental toxicity" be deleted since thiabendazole is not developmentally toxic.

DPR: As thiabendazole produces malformations in three different species, it is developmentally toxic.

(Novartis) In the same section, line 6 states: "Thiabendazole was genotoxic". Novartis suggests that the phrase: "Thiabendazole was genotoxic" be deleted since thiabendazole has not been demonstrated to be a genotoxin.

DPR: As several studies have shown (Table 8. Genotoxicity studies with thiabendazole), thiabendazole causes spindle disruption both *in vitro* and *in vivo*, and is considered genotoxic.

(Novartis) In Section A. Hazard Identification (Acute Toxicity) of the Risk Assessment portion found on page 25, the second and third paragraphs contain statements that Novartis believes should be deleted for the following reasons: Novartis

suggests that all statements to the effect that thiabendazole may be a teratogen be deleted. These were based on the discredited 1984 Ogata Study. The US EPA reviewed the study in 1991 before they had the opportunity to also review the methodologically correct and GLP compliant Nakatsuka Definitive Study. The USEPA has since come to the conclusion that the developmental potential of thiabendazole is more adequately described by the Nakatsuka Definitive Study.

DPR: USEPA and DPR have agreed to disagree on several occasions.

III. **EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION**

Novartis agrees with the Department's conclusions that margins of exposure (MOEs) for potential daily and annual exposure to workers handling and applying thiabendazole are greater than those conventionally recommended to protect people from hazardous effects of a pesticide. We encourage the Department to include a subsequent statement in their report that helps readers better understand the implications of having MOEs that exceed those required. For example, a statement such as "Therefore, there is reasonable certainty that no harm will result to individuals from applying thiabendazole-containing products or from coming into contact with treated surfaces." would be helpful.

DPR: We thank Novartis for their suggestion; however, the description of the MOE is sufficient.

Novartis wishes to emphasize that the risk assessments presented in the Department's Risk Characterization document are highly conservative and that actual MOEs are likely to be substantially higher than those calculated. Several of the assumptions incorporated into the risk assessments contribute to this conservativeness. For example, in the absence of dermal absorption data for thiabendazole, it was assumed that dermal absorption would be 100%. CDPR acknowledges that this assumption probably results in an overestimation of exposure. It has been Novartis' experience that in the absence of dermal absorption data, CDPR traditionally has used a default value of 50% dermal absorption in risk assessments rather than 100%. CDPR also acknowledges that there are a number of conservative factors built into the Pesticide Handlers Exposure Database (PHED), which was used as the basis for estimating some exposures, that result in overestimation of exposure.

DPR: Novartis is correct in noting a great many uncertainties exist on the exposure side of characterizing the risk in the RCD. Many of these uncertainties arose due to the lack of chemical specific exposure data. If the degree of uncertainty in each of the noted parameters were known, quantitative corrections in the exposure estimates would have been made.

Novartis would also like to request clarification within the document regarding non-occupational exposures to thiabendazole. On page 31 of the Risk Characterization document, at the end of section 1. Occupational Exposure, the document states "There are no non-occupational exposures to thiabendazole, except through the diet." A similar statement is included on page 43, section D. Federal Food Quality Protection Act, Aggregate Exposure. However, on page 42, section B. Exposure, Combined Dietary/Occupational, a statement is made that

"it is unlikely that the agricultural workers or residential applicators engaged in thiabendazole application would also..." The reference to residential applicators in this latter sentence can create some confusion regarding residential uses of thiabendazole. We request a clarification of this latter sentence so it is clear that this refers to professional workers applying thiabendazole to residential properties, and not to homeowners applying thiabendazole to their residences.

DPR: Novartis is correct. There are no residential applications. The text has been modified to reflect the current usage of thiabendazole.

Finally, Novartis wishes to comment regarding the aggregation of dietary and occupational exposure. Although CDPR's aggregate assessment indicates that MOEs are higher than those recommended, Novartis finds the Department's approach to aggregate risk assessment to be unconventional. The pathways of exposure typically considered in an aggregate exposure and risk assessment include the potential for pesticide residues in food, drinking water and from residential, non-occupational pesticide use. Occupational exposures are not typically aggregated with these other sources of potential exposure. Furthermore, acute aggregate risk assessments typically combine dietary exposures from food and water only. Short- and intermediate-term aggregate risk assessments are done only when a potential for residential exposure exists and chronic aggregate assessments are performed for long-term durations of exposure. CDPR has conducted an acute and annual aggregate risk assessment in which dietary exposures have been combined with occupational exposure. Some reconciliation of the traditional approach and procedures for performing aggregate exposure and risk assessment with CDPR's approach or the basis for taking an approach that differs from the traditional would be very helpful.

DPR: To the best of our knowledge, persons engaged in the application of thiabendazole are as likely to consume agricultural commodities treated with thiabendazole as the general public. We have always included an estimate of aggregate exposure for workers in an RCD, unless the exposure data were derived from biological monitoring of the workers.

IV. **DIETARY ASSESSMENT**

(Novartis) The California Department of Pesticide Regulation (CDPR) completed a draft document entitled "Thiabendazole - Risk Characterization Document" dated June 16, 2000. In this document the Agency thoroughly reviewed the toxicity of thiabendazole (TBZ) and assessed occupational and dietary exposures separately as well as a combined occupational and dietary exposure assessment. The Agency used two approaches to evaluate acute and chronic dietary exposure to TBZ: 1) a refined estimate was made utilizing field trial residues and monitoring data, and 2) a conservative worst case estimate was made on individual highly-consumed commodities utilizing tolerance values to evaluate the risk of each selected commodity. The acute dietary exposure analyses were conducted by using the Exposure-4 TM software program, and the chronic dietary exposure analyses were conducted by using the Exposure- 1 TM software program both developed by Technical Assessment Systems, Inc (TAS). The consumption information was derived from the 1989-91 Continuing Survey of Food Intake by Individuals (CSFII). An acute No-Observable Effect Level (NOEL) of 3.3 mg/kg-bw/day was used and is based on clinical signs and blood chemistry changes in humans. A chronic NOEL of 10 mg/kg-bw/day was used and is based on a long term exposure study in dogs. The results of the Agency's refined acute dietary assessment showed that exposure at the 95 th percentile ranged from 27 to 81 pg/kg-bw/day corresponding to Margins of Exposure (MOEs) of 123 - 41 for all population subgroups. The refined chronic analysis provided MOE values of 7,700 'o 2,200 for all population subgroups. Therefore, evaluation of both acute and chronic dietary exposure using a refined approach results in an adequate margin of safety. The Agency also conducted acute analyses using tolerance values for individual highly-consumed commodities. Assuming a tolerance residue level on apples and with 100% of crop treated, the MOEs ranged from 4 to 83 for all population subgroups. With the exception of apples, the use of U.S. EPA tolerance levels provided a sufficient safety margin for all individual commodities evaluated.

To investigate the margin of safety on TBZ-treated apples, Novartis Crop Protection, Inc. conducted an acute dietary assessment utilizing the Dietary Exposure Evaluation Model (DEEM™) from Novigen Sciences, Inc., and food consumption information from USDA's 1994-96 CSFII. The same acute NOEL of 3.3 mg/kg-bw/day was used as in the Agency's assessment. The results show that non-nursing infants are the most sensitive sub-population, and these results are summarized in Table 1.

Table 1. Exposures and MOEs for Non-Nursing Infants Resulting from an Acute Dietary Intake of TBZ Treated Apples

	Apple Residue Value		
	TOLERANCE (0 ppm) 100% CT	TOLERANCE (0 ppm) 62% CT	PDP-DATA (5xl 0-4 _ 10 ppm) 62% CT
Exposure (mg/kg-bw/day	0.361346a	0.268028a	0.053597u-
MOEc	9.13	12	61

a/ Calculated at the 95th percentile of exposure.
b/ Calculated at the 99th percentile of exposure.
c/ MOE = NOEL (3.3 mg/kg)/Exposure

(Novartis) Using the 10 ppm tolerance residue level and assuming that 100% of the crop is treated, an MOE value of 9.13 was obtained at the 95 th percentile for the most sensitive population subgroup (non-nursing infants). Using U.S. EPA's estimate of 62% for the percent of crop treated, the MOE increases to 12 for the same population subgroup. In order to obtain the most realistic estimate, an additional assessment was made utilizing data from USDA's Pesticide Data Program (PDP) database. The PDP data contains information on composited apples; therefore, the distribution of single servings was estimated using the Maximum Likelihood Imputation Procedure (MAXLIP). Since the imputation procedure provided residue values greater than the tolerance, the distribution was truncated at the tolerance level (10 ppm). Apple juice residue data was also available from the PDP database and apple juice residue values were directly incorporated into the residue distribution file. Each residue distribution was adjusted for percent of crop treated by adding zeroes to the distribution to account for the percent of crop not treated. As a result, an MOE of 61 was obtained at the 99.9th percentile of exposure for the most sensitive population subgroup (non-nursing infants).

Using the DEEM™ software and contemporary food consumption information, an MOE value of 9 was obtained with a tolerance level residue and 100% crop treated. In addition, utilizing data from USDA's PDP database results in a margin of safety that is greater than 60. Therefore, our analyses showed that the tolerance for TBZ on apples provides a sufficient safety margin when using conservative assumptions.

DPR: In California, USEPA established tolerances are evaluated under the mandate of Assembly Bill 2161, generally referred to as the Food Safety Act (Bronzan and Jones, 1989). The Act requires DPR to conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides. In these assessments, the tolerance for each specific commodity is evaluated individually. An acute exposure assessment using the residue level equal to the tolerance is conducted for each individual label-approved commodity. An annual exposure assessment using residues equal to the established tolerances for individual or combinations of commodities was not conducted because it is highly improbable that an individual would chronically consume single or multiple commodities with pesticide residues at the tolerance levels.

The evaluation of tolerances is wholly separate from the dietary analyses (acute and chronic) which are conducted in an earlier section of the risk characterization document. DPR possesses, and can utilize DEEM when appropriate. When the characterization of risk from dietary exposures derived earlier from analyses by TAS indicate adequate MOEs, those analyses are not revisited. Again, this is a tolerance assessment. If dietary residues at the tolerance level are not adequately protective, then the evaluation may be considered by USEPA as part of their tolerance reassessment.

V. CONCLUSION

Novartis respectfully re-emphasizes that fully acceptable GLP compliant guideline studies have demonstrated that thiabendazole is not mutagenic and therefore not genotoxic. In addition, the apparent developmental effects of thiabendazole described in this draft document is based on data from a poorly conducted study - namely experiment #3 of a 1984 study with Jcl:ICR mice (Ogata et al, 1984). However, in view of the critical deficiencies in this 1984 study and the new 1995, GLP and guideline compliant, mouse study that was conducted later (Nakatsuka, 1995a, b), there is no evidence that thiabendazole meets the criteria to be referred to as a developmental toxicant. The draft document also contains statements indicating that thiabendazole may be a teratogen which are also based on the discredited 1984 Ogata Study. The methodologically correct and GLP compliant Nakatsuka Definitive Study has been determined to more adequately describe the developmental potential of thiabendazole.

DPR: As we do not agree with Novartis's conclusions regarding either genotoxicity or developmental toxicity, the RCD will not be modified in those regards.

Novartis agrees with the Department's conclusions that margins of exposure (MOEs) for potential daily and annual exposure to workers handling and applying thiabendazole are greater than those conventionally recommended to protect people from hazardous effects of a pesticide. Nonetheless, Novartis wishes to emphasize that the risk assessments presented in the Department's Risk Characterization document are highly conservative and that actual MOEs are likely to be substantially higher than those calculated.

DPR: We agree that the MOEs are likely to be underestimates of the "true" MOEs because of uncertainties in the estimates of exposure. However, we have no data which would allow us to estimate the magnitude of the uncertainty. As a consequence, adverbial phrases such as "substantially higher" or "greatly overestimate" cannot be justified.

Novartis wishes to re-emphasize the revised dietary risk assessment that is presented using the DEEM™ software and contemporary food consumption information. Based on this data, an MOE value of 9 was obtained with a tolerance level residue and 100% crop treated. In addition, utilizing data from USDA's PDP database results in a margin of safety that is greater than 60. Therefore, our analyses showed that the tolerance for TBZ on apples provides a sufficient safety margin when using conservative assumptions.

DPR: Novartis did not provide us with an indication of what percentile of acute exposure they used in their DEEM analysis. Generally, DPR uses the 95th percentile of exposure for the TAS program.