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OFFICE OF PREVENTION
PESTICIDES AND
TOXIC SUBSTANCES

HED DOC. NO. 014506

DATE: March 20, 2001

MEMORANDUM

SUBJECT: BENOMYL AND CARBENDAZIM- Endpoint Selection for Incidental Oral Ingestion for Carbendazim- 3rd Report of the Hazard Identification Assessment Review Committee.

FROM: Deborah Smegal, Toxicologist
Re-Registration Branch 3-
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chairman
And
Beth Doyle, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Catherine Eiden, Branch Senior Scientist
Re-Registration Branch 3
Health Effects Division (7509C)

PC Code: Benomyl: 099101
Carbendazim: 128872

BACKGROUND: On February 20, 2001, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to select toxicity endpoints for short- and intermediate-term incidental oral exposure scenarios for carbendazim (more commonly known as MBC). These endpoints were not selected previously, and are necessary to assess potential child exposures following residential uses of thiophanate methyl. MBC is the primary environmental

metabolite of thiophanate-methyl. There were no changes to the other endpoints selected in the previous HIARC document dated August 2, 1999, which include acute and chronic dietary, and dermal and inhalation exposure for risk assessment for benomyl, and its primary metabolite carbendazim. **The Committee's decisions are attached. This report supercedes the previous HIARC reports dated 9/2/99; HED Doc No. 013602, and 12/3/97; HED Doc No. 012418.**

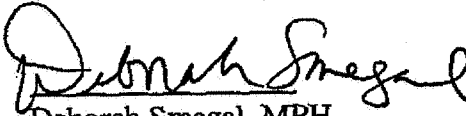
Committee Members in Attendance:

Elizabeth Doyle, Jess Rowland, Elizabeth Mendez, David Nixon, Bill Burnam, Pam Hurley, John Chen, Yung Yang, and Brenda Tarplee (Executive Secretary).

Members in Absentia were Ayaad Assaad.

Other HED staff present at the meeting were Deborah Smegal, and Gary Bangs of Re-Registration Branch 3, and Paula Deschamp.

Data Presentation:
and
Report Preparation


Deborah Smegal, MPH
Toxicologist

1. BACKGROUND

On January 9, 1997, the Health Effects Division's RfD/Peer Review Committee evaluated the toxicology data base of Benomyl and reassessed the Reference Dose but deferred to a later date the need for an additional Uncertainty Factor for the enhanced sensitivity to infants and children (as required by FQPA) as well as the final decision regarding the need for a developmental neurotoxicity study (Memorandum: G. Ghali, HED to C. Welch, RD, dated 05/28/97).

On January 14, 1997, the Health Effects Division's Toxicology Endpoint Selection Committee selected the doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments, but did not address the Margins of Exposure (MOEs) required for the various exposure scenarios.

On November 25, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to determine the Uncertainty Factors and the MOEs for dietary and non-dietary risk assessments as required by the Food Quality Protecting Act (FQPA) of 1996.

The HIARC Committee reconvened on June 1, 1999 to reassess the acute and chronic dietary RfDs as well as the dermal and inhalation endpoints for occupational and residential risk assessments for benomyl, and its primary metabolite of carbendazim or MBC. In foods and the environment, benomyl rapidly transforms to MBC. Hence, residues in food are primarily as MBC, and the EPA analytical method determines benomyl residues in food as MBC (i.e., the method involves hydrolysis, so any benomyl residue would be converted to MBC prior to analysis). Therefore, the HIARC selected doses and endpoints for risk assessment with MBC. At this meeting, the Committee also considered the Registrant's Rebuttal, dated 4/22/98, and the Registrant proposed studies for use in endpoint selection. The Registrant believes that a number of conclusions reached in the RfD Peer Review Committee review of benomyl (01/09/97) and the report of the Hazard Identification Assessment Review Committee (12/03/97) were incorrect. HED has prepared detailed responses to each of the issues identified by the Registrant in memorandum from S. Makris and N. McCarroll to D. Smegal, June 30, 1999, D248200.

On February 20, 2001, the HIARC reconvened to select toxicity endpoints for short- and intermediate-term incidental oral exposure scenarios for MBC. These endpoints were not selected previously, and are necessary to assess potential child exposures following residential uses of thiophanate-methyl. MBC is the primary environmental metabolite of thiophanate-methyl. Toxicity endpoints for short- and intermediate-term incidental oral exposure scenarios for benomyl are not necessary because benomyl does not have registered residential uses. **This report supersedes the previous HIARC document (dated August 2, 1999, HED Doc No. 013602).**

II. HAZARD IDENTIFICATION

A. BENOMYL

(1) Acute Dietary Females 13+ (One-Day)

Study Selected: Rat Developmental Studies for Benomyl

MRID. No. 00148393 (1980), 00115674, and 00126522 (1982)

Executive Summary:

In a developmental toxicity study conducted in Wistar rats (MRID 00148393), benomyl (99%) was administered at dose levels of 0, 15.6, 21.2, 62.5, or 125 mg/kg/day body weight per day on gestation days 7-16. The developmental NOAEL is 31.2 mg/kg/day and the LOAEL is 62.5 mg/kg/day based on increased fetal and litter incidence of ocular malformations (microphthalmia and anophthalmia), increased fetal mortality and significantly reduced fetal weight (percentages not provided). At 125 mg/kg/day, there were increased fetal and litter incidences of malformations of the brain (distended lateral ventricles, hydrocephaly). This study supports the findings of microphthalmia reported in the developmental study conducted in CRL:CD rats. Maternal toxicity was not present at the highest dose tested of 125 mg/kg/day.

In another developmental toxicity study in CHR:CD rats (MRID 00115674, and 00126522), benomyl (99.1%) was administered to pregnant rats on days 7-16 of gestation at gavage dose levels of 0, 3, 6.25, 10, 20, 30, or 62.5 mg/kg/day. The study was conducted to assess external hydrocephaly and microphthalmia. Incidental observations of microphthalmia and hydrocephaly were observed at 62.5 mg/kg/day, which confirmed the LOAEL established in the 1980 study. Based on the results, the NOAEL for microphthalmia is 30 mg/kg/day. Maternal toxicity was not present at the highest dose tested of 62.5 mg/kg/day.

Dose and Endpoint for Establishing the acute RfD: Developmental NOAEL = 30 mg/kg/day based on increased incidence of microphthalmia at 62.5 mg/kg/day (LOAEL).

Comments about Studies and Endpoint: The developmental effects are presumed to occur after single dose (exposure).

Uncertainty Factor(s): 100 (10x for interspecies extrapolation and 10x for intraspecies variability).

$$\text{Benomyl Acute RfD (Females 13+)} = \frac{30 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.3 \text{ mg/kg}$$

(2) Benomyl Acute Dietary (General Population) (One-Day)

Study Selected: Hess et al. 1991

MRID. No. Published literature

Executive Summary:

Adult male Sprague-Dawley rats (approximately 100 days of age, 20 rats/dose) were given a single gavage dose of 0, 25, 50, 100, 200, 400 or 800 mg/kg body weight benomyl (95% a.i.) in corn oil. Eight animals/group were sacrificed at 2 days and 12 animals/group at 70 days (except for the 800 mg/kg group) after treatment. The testis and efferent ducts were examined each time to determine benomyl effects on spermatogenesis and on the epididymis. The primary effects seen at day 2 were testicular swelling and occlusions of the efferent ductules. Premature release of germ cells (sloughing) was the most sensitive short-term response to benomyl. At 25 and 50 mg/kg biologically significant sloughing occurred in 1% and 2.8% of the tubules, respectively. Sloughing was statistically significant ($p < 0.05$) at doses of 100 mg/kg to 800 mg/kg (approximately 25 to 55% of the tubules). Occlusions of the efferent ductules of the testis were dose dependent at 0, 0, 10, 60, 83, 93 and 92% for the 0, 25, 50, 100, 200, 400 and 800 mg/kg groups, respectively and correlated with the increase in testis weight on day 2. Occluded efferent ductules were identified by compacted luminal contents, swollen ductules and the presence of granulomas. Testes weight was significantly increased in the 200 to 800 mg/kg groups. Long-term effects (70 days) were seen in the 100, 200 and 400 mg/kg groups, e.g., decreased testis weight (400 mg/kg), dose-dependent increases in seminiferous tubular atrophy, and increases in the number of reproductive tracts containing occluded efferent ductules. No long-term effects were seen in the 0, 25 or 50 mg/kg groups. The NOAEL is 25 mg/kg/day, and the LOAEL is 50 mg/kg/day based on biologically significant sloughing and occlusions of the efferent ductules of the testes.

Dose and Endpoint for Establishing the Acute RfD: NOAEL = 25 mg/kg/day for benomyl; LOAEL of 50 mg/kg/day, based on biologically significant premature release of germ cells (sloughing) in the testes, and occlusions of the efferent ductules of the testis 2 days postexposure.

Comments about Study and Endpoint: This study identified lowest single dose associated with testicular effects. All the single dose studies submitted by the registrant evaluated higher doses.

Uncertainty Factor(s): 100 (10x for interspecies extrapolation and 10x for intraspecies variability).

$$\text{Benomyl Acute RfD (Gen Pop)} = \frac{25 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.25 \text{ mg/kg/day}$$

(3) Benomyl Chronic Dietary Risk Assessment (Reference Dose)

Study Selected: Two year Dog Study with Benomyl (Sherman et al. 1970)

MRID No. 00081913, 00097305

Executive Summary:

Groups of 4/sex/dose beagle dogs were administered a formulated product containing benomyl in the diet at dosage levels of 0, 100, 500 and 2500 ppm for 2 years. The dietary concentrations are equivalent to 0, 2.5, 12.5 and 62.5 mg/kg/day ai benomyl. There were no treatment-related effects on mortality, hematology, urinalysis, or clinical signs. Body weight gain and food consumption were decreased in the high dose group. Males in the high dose group had increased cholesterol, alkaline phosphatase and glutamic-pyruvic transaminase (GPT) values, as well as decreased total protein and albumin/globulin (A/G) ratio. Similar effects, other than cholesterol and total protein, were noted in the high dose females. The clinical chemistry observations support the adverse liver effects in the high dose group, characterized as cirrhosis and slight to marked bile duct proliferation in 4/6 dogs of the 2500 ppm (62.5 mg/kg/day ai) group. The NOAEL is 500 ppm (12.5 mg/kg/day ai) based on hepatic cirrhosis, clinical chemistry alterations as well as decreased weight gain and food consumption noted at 2500 ppm.

Dose/Endpoint for establishing the RfD: NOAEL = 12.5 mg/kg/day ai (500 ppm formulated product) based on a LOAEL of 62.5 mg/kg/day ai (2500 ppm formulated product) for hepatic cirrhosis, clinical chemistry alterations as well as decreased weight gain and food consumption.

Uncertainty Factor (UF): An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability.

$$\text{Benomyl Chronic RfD} = \frac{12.5 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.13 \text{ mg/kg/day}$$

(4) Benomyl Occupational/Residential Exposure Risk Assessments**(a). Short- and Intermediate-term incidental Oral Exposure**

Toxicity endpoints for short- and intermediate-term incidental oral exposure scenarios for benomyl are not necessary because benomyl does not have registered residential uses. Therefore, incidental oral exposures to benomyl by children are not expected to occur.

(b). Benomyl Dermal Absorption

Study Selected: Rat dermal absorption study with benomyl (1979)

MRID No: 0097287

A dermal absorption study was conducted in rats (4 rats/time point/dose) using benomyl in the form of Benlate (50% WP). The test material was applied at dose levels of 0.2, 2, 20 or 200 mg of Benlate (equivalent to 0.1, 1, 10 or 100 mg a.i. of benomyl). The exposure durations were 0, 1, 2, 4 and 10 hours. The amount of benomyl absorbed ranged from 0.031 to 3.5 percent from the highest to the lowest dose, respectively, following the maximum exposure period of 10 hour. This study is acceptable. No dermal absorption studies were located for MBC.

Dermal Absorption Factor: 3.5%

(c). Benomyl Short- Term Dermal - (1 - 7 Days)

Study Selected: 21-day Dermal Toxicity Study in Rabbits with Benomyl

MRID. No. 00097287 (Hood et al. 1969)

Executive Summary:

In a 21-day dermal study conducted in New Zealand White Rabbits, benomyl (53% a.i.) was applied dermally to abraded dorsal skin for exposure durations of six hours a day for 5 days a week, for three weeks. The doses were equivalent to 0, 50, 250, 500, 1000 and 5000 mg/kg/day ai benomyl. There were 5 animals/sex/dose except for the high dose group where 2 animals/sex were used. The test site was covered with a non-occlusive gauze pad, and all rabbits were fitted with plastic collars to prevent oral exposure. Moderate skin irritation was reported for all dose groups. At the two highest dose levels, systemic toxicity characterized by diarrhea, oliguria and hematuria were reported in females. In the 500 mg/kg/day dose group, males exhibited 19% and 20% decreases in testes weight and testes-to-body weight ratios, respectively. At 1000 mg/kg/day, males exhibited 30% and 24% decreases in testes weight and testes-to-body weight ratios, respectively (both non significant). This finding was not apparent at 5000 mg/kg/day, which may be attributed to the small number of animals evaluated at this dose (n=2 males). There were no treatment-related histopathological changes in the testes, except for one rabbit in the 5000 mg/kg/day group that had focal testicular degeneration. This study identifies a NOAEL and LOAEL of 500 and 1000 mg/kg/day, respectively based on biologically significant decreased relative and absolute testes weights.

Dose and Endpoint for Risk Assessment: NOAEL = 500 mg/kg/day ai for benomyl based on decreases in relative and absolute testes weights at 1000 mg/kg/day ai (LOAEL).

Comments about Study and Endpoint: The testicular effects following dermal exposure are of a concern since this was one of the target organ following oral exposure in other species (rats and dogs). The lack of effects at the highest dose tested (5000 mg/kg/day) may be due to the low number of animals (2/sex) evaluated at this dose. This endpoint is protective of developmental effects (i.e., developmental NOAEL of 30 mg/kg/day / 0.035 (dermal absorption) = 860 mg/kg/day).

(d). Benomyl Intermediate-Term Dermal - (7 days to Several Months)

Study Selected: 21-day Dermal Toxicity Study in Rabbits with Benomyl

MRID No. 00097287 (Hood et al. 1969)

Executive Summary: See Short-Term

Dose and Endpoint for Risk Assessment: NOAEL = 500 mg/kg/day ai for benomyl based on decreases in relative and absolute testes weights at 1000 mg/kg/day ai (LOAEL).

Comments about Study and Endpoint: The testicular effects following dermal exposure are of a concern since this was one of the target organs following oral exposure in other species (rats and dogs). The lack of effects at the highest dose tested (5000 mg/kg/day) may be due to the low number of animals (2/sex) evaluated at this dose. This endpoint is protective of developmental effects (i.e., developmental NOAEL of 30 mg/kg/day / 0.035 (dermal absorption) = 860 mg/kg/day).

(e). Benomyl Long-Term Dermal (Several months to lifetime)

Study Selected: Two year Dog Study with Benomyl (Sherman et al. 1970)

MRID No. 00081913, 00097305

Executive Summary: See Chronic Dietary for Benomyl

Dose and Endpoint for Risk Assessment: NOAEL= 500 ppm formulated product (12.5 mg/kg/day ai) for benomyl based on hepatic cirrhosis, clinical chemistry alterations as well as decreased weight gain and food consumption at 2500 ppm (62.5 mg/kg/day ai) (LOAEL). assessments.

Comments about Study and Endpoint: This dose was also used in establishing the benomyl RfD. Since a dose from an oral study (i.e., oral NOAEL) was selected, a dermal absorption rate of 3.5% should be used for these risk.

(f). Benomyl Inhalation Exposure (any time period; 1 Day to Several Months)

Study Selected: 90-day rat inhalation study with Benomyl (Warheit 1987)

MRID No(s). 40399501

Executive Summary

In a subchronic inhalation study, benomyl (95% a.i.) was administered to Crl:CDBR rats (Sprag Dawley) at concentrations of 0, 10, 50 and 200 mg/m³ for 4 hours/day for 90 days. These concentrations are equivalent to doses of 0.96, 4.8, 19.2 mg/kg/day in males and 1.4, 7, and 28.8 mg/kg/day in females based on the average body weights of 300 and 220 grams for males and females, respectively in the study. The mass median aerodynamic diameters (MMAD) were in the range of 1.7 to 2.3 microns, with the smaller MMADs being reported at the lowest concentration therefore, an adequate concentration of benomyl reached the lungs. Histological lesions suggestive of olfactory degeneration, characterized by necrosis, chronic and acute inflammation and loss of olfactory epithelium was observed at the highest dose tested in females and at 50 mg/m³ in males. At 200 mg/m³, males also had decreased body weights (10.8%) and body weight gains (13.5%). The NOAEL is 10 mg/m³ (0.96 mg/kg/day) for males. The LOAEL is 50 mg/m³ (4.8 mg/kg/day) based on olfactory degeneration in the nasal cavity.

Dose and Endpoint for Risk Assessment: NOAEL=10 mg/m³ (0.96 mg/kg/day) based on olfactory degeneration in the nasal cavity at 50 mg/m³ (4.8 mg/kg/day) (LOAEL).

Comments about Study and Endpoint: This dose/endpoint should be used for short, intermediate and long-term exposure risk assessments. HIARC recommends an additional uncertainty factor 3 be applied to the NOAEL (i.e., MOE = 300).

B. CARBENDAZIM (MBC)**(1) MBC Acute Dietary Females 13+ (One-Day)**

Study Selected: Rat Developmental Study for Carbendazim (MBC)

MRID. No. 40438001 (Alvarez 1987)

Executive Summary:

In a developmental toxicity study (MRID No.: 40438001), 25 CrI:CE BR strain presumed pregnant rats per dose group were dosed with 0, 5, 10, 20 or 90 mg/kg/day of carbendazim (MBC, 98.8% a.i. in 0.5% methyl cellulose) by gavage on days 7 through 16 of gestation. The rats were sacrificed on day 22 of gestation.

There were 24, 23, 24, 22 and 15 dams that delivered viable fetuses for the control, 5, 10, 20 and 90 mg/kg/day dose groups, respectively. The low number of dams delivering pups in the high dose group was attributed to the lower pregnancy rate (only 19 of 25 dams, not related to treatment), one death (by mechanical dosing trauma) and three dams that had total resorptions. Since there were no dams with total resorptions in the other groups, the resorptions are considered to be related to treatment, but not specifically maternal toxicity. There was a lower (32%, $p < 0.05$) mean dam body weight gain for days 17-22 of gestation and absolute liver weight was increased 10% ($p < 0.05$, with a positive trend for relative liver weight) at day 22 among the 15 high dose dams that delivered. **The maternal LOAEL is 90 mg/kg/day based on decrease weight gain and increased liver weight. The NOAEL is 20 mg/kg/day.**

There were a total of 312, 310, 281, 288 and 149 fetuses for the control to high dose groups, respectively available for examination. At 20 mg/kg/day there was a decrease in fetal weight (5% $p < 0.05$ for combined sexes). The mean percent of fetuses with variations due to retarded development was 22.9%, 25.0%, 19.5%, 41.6% ($p < 0.5$) and 52.5% ($p < 0.05$) for the control to high dose groups, respectively. At 20 mg/kg/day the vertebrae showed increases in bipartite ossification (21 incidents in 8 litters) and dumbbelled centrum (44 incidents in 13 litters) due to retarded development as well as misaligned sternbrae and extra ossification of the ribs that were not described as being related to retarded growth. At 90 mg/kg/day, there were a variety of developmental effects including decreases in mean live fetuses per litter (-24%, $p < 0.05$), early and late resorptions, and decreased fetal weight (-26%, $p < 0.05$, both sexes combined). There were 3/2, 1/1, 1/1, 3/3, and 91/15 ($p < 0.01$) fetuses/litters affected with malformations in the control to high dose groups, respectively. These malformations included a variety of conditions mainly the head (exencephaly, domed head), eyes (none, small or bulge), paws (clubbed) and skeleton (fused vertebrae, ribs and sternum or malformed scapula). Some of these malformations were seen in the three fetuses affected in the 20 mg/kg/day dose group and not in the lower doses or controls. Thus, 20 mg/kg/day is considered a threshold for malformations. **The LOAEL is 20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a**

threshold for malformations. The NOAEL is 10 mg/kg/day.

Dose and Endpoint for Establishing the acute RfD: Developmental NOAEL = 10 mg/kg/day for MBC based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations in dams exposed to 20 mg/kg/day (LOAEL). MBC is the primary metabolite of benomyl.

Comments about Study and Endpoint: HIARC concluded that the NOAEL is appropriate for the exposure period (i.e., after a single dose). The acute RfD is based on MBC, the primary metabolite of benomyl. The developmental NOAEL of 10 mg/kg/day for MBC is lower than the developmental NOAEL of 30 mg/kg/day for benomyl. Fetuses of pregnant dams exposed to 62.5 mg/kg/day benomyl during gestation days 7 through 16 had an increased incidence of microphthalmia. In the environment, benomyl rapidly transforms to MBC. Hence, residues in food are primarily as MBC, and the EPA analytical method developed to determine benomyl residues in food only measures MBC (i.e., the method involves hydrolysis, so any benomyl residue would be converted to MBC prior to analysis).

Uncertainty Factor(s): 100 (10x for interspecies extrapolation and 10x for intraspecies variability).

$$\text{MBC Acute RfD (Females 13+)} = \frac{10 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.1 \text{ mg/kg}$$

(2) MBC Acute Dietary (General Population) (One-Day)

Study Selected: Nakai et al. 1992

MRID. No. Published literature

Executive Summary:

Groups of male rats (n=20/dose between 97 and 105 days of age) were treated with a single oral dose of 0, 50, 100, 200, 400 or 800 mg/kg MBC and killed on day 2 or 70 post-treatment. On day 2, at 50 mg/kg, round spermatids were sloughed (prematurely released) from stage I and II epithelium and elongated spermatids were sloughed from stage VII epithelium. In addition a dose-dependent increase in testicular weight was seen at dose levels of 100 mg/kg and higher this was accompanied by significant increases in mean seminiferous tubular diameter at 400 and 800 mg/kg. At 100 mg/kg, the disappearance of germ cells was more severe and statistically significant and sloughing of elongated spermatids extended into stages XII and XIV. In animals treated with 100 mg/kg or more, there was a dose-dependent increased incidence of occlusions in the efferent ductules of the testes. The rete testis was swollen with sloughed germ cells indicating that ductal blockage had occurred further down the tract. At doses of 200 mg/kg and above, missing germ cells extended into all stages except stages IX-XI, while, at doses of 400-800 mg/kg, some of the seminiferous epithelia were damaged so severely that it was difficult to identify the stage.

On day 70, tubule diameter was significantly decreased at all doses in a dose-dependent relationship. Histologically, these decreases were associated with a dose-dependent increase in seminiferous tubular atrophy (significant at 100 mg/kg and higher). No atrophic tubules were seen in the control rats, however, atrophy of a few seminiferous tubules in one testicle was noted at 50 mg/kg. The atrophied tubules contained primarily Sertoli cells and occasional spermatogonia and were surrounded by a thickened basement membrane. Pathological alterations were also noted in the efferent ductules of the treated animals, 50% or more of the ducts being occluded in rats dosed with 100 mg/kg or more. Minimal effects were seen at 50 mg/kg, where slight abnormal growth of the efferent ductules was seen in only one specimen. The occlusions were characterized as compacted luminal contents, spermatocytic granulomas, mineralizations and obliterations of the original lumen by fibrotic connective tissue. In addition, mean testis weight showed a dose-dependent decrease that was statistically significant at doses of 100 mg/kg and greater.

Dose and Endpoint for Establishing the acute RfD: LOAEL = 50 mg/kg/day for MBC; no NOAEL was identified based on sloughing (premature release) of immature germ cells 2 days postexposure; and atrophy of a few seminiferous tubules in one testicle, significant decrease in seminiferous tubule diameter, and slight abnormal growth of the efferent ductules at 70 days postexposure. The subtle effects detected in the epididymal sperm at 50 mg/kg may be attributed to the direct effect of MBC on the seminiferous epithelium.

Comments about Study and Endpoint: The testicular effects were seen 2 days post exposure and this study identified lowest single dose associated with testicular effects. All the single dose studies submitted by the registrant evaluated higher doses.

Uncertainty Factor(s): 100 (10x for interspecies extrapolation and 10x for intraspecies variability 3x for lack of a NOAEL).

$$\text{MBC Acute RfD (Gen Pop)} = \frac{50 \text{ mg/kg/day (LOAEL)}}{300 \text{ (UF)}} = 0.17 \text{ mg/kg/day}$$

(1) MBC Chronic Dietary Risk Assessment (Reference Dose)

The chronic MBC RfD established in December 3, 1997 by the HIARC was re-assessed and the NOAELs and LOAELs were reaffirmed by the HIARC.

Study Selected: Chronic toxicity study in Dogs with MBC (Sherman et al. 1972)

MRID No. 00088333

Executive Summary:

Beagle dogs (4/sex/dose) were administered a product formulation containing 53% a.i. carbendazim, a primary metabolite of benomyl at dietary dose levels of 0, 100, 500 or 2500 ppm for two years. This is equivalent to 0, 2.5, 12.5 or 62.5 mg/kg/day ai MBC. No treatment-related effects were noted in dogs fed 100 ppm (2.5 ai mg/kg/day). Dogs of both sexes in the mid dose group (500 ppm or 12.5 ai mg/kg/day) exhibited liver pathology characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis. At 500 ppm, there were also reported increases in cholesterol, total protein, SGPT and alkaline phosphatase, none of which were biologically or statistically significant. At 2500 ppm (62.5 mg/kg/day ai), anorexia, distended abdomens and poor nutritional condition were reported.

The NOAEL is 100 ppm (2.5 mg/kg/day ai). The LOAEL is 500 ppm (12.5 mg/kg/day ai) based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes of dogs.

Dose/Endpoint for establishing the RfD: NOAEL = 2.5 mg/kg/day ai for MBC based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes of dogs at 12.5 mg/kg/day ai (LOAEL).

Comments about Study and Endpoint: The chronic RfD is based on MBC, the primary metabolite of benomyl. In foods and the environment, benomyl rapidly transforms to MBC. Hence, residues in food are primarily as MBC, and the EPA analytical method determines benomyl residues in food as MBC (i.e., the method involves hydrolysis, so any benomyl residue would be converted to MBC prior to analysis).

Uncertainty Factor (UF): An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability.

$$\text{MBC Chronic RfD} = \frac{2.5 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.025 \text{ mg/kg/day}$$

(2) MBC Occupational/Residential Exposure Risk Assessments(a). Short-term incidental oral (1-7 days)

Study Selected: Developmental toxicity in rabbits with Thiophanate-methyl. Guideline #: 83-3(b)

MRID No.: 45051001

Executive Summary:

In a developmental toxicity study (MRID 45051001) thiophanate-methyl (97.28% purity) was administered to groups of 20 New Zealand White Rabbits by gavage in a 1% aqueous methyl cellulose vehicle (at a rate of 10 mL/kg) at dose levels of 0, 5, 10, 20 or 40 mg/kg/day on gestation days 6 to 28. The rabbits were sacrificed on day 29 and the does were subjected to uterine examination and the pups subjected to external, visceral and skeletal examination.

- At 20 mg/kg/day there was decreased body weight gain (56%, $p < 0.05$) for the interval days 12-15 and body weight gain was decreased 13% for the entire dosing period. At 40 mg/kg/day, body weight gain was decreased and there was actual body weight loss for the interval days 6-9 (i.e. the controls gained 80 ± 40 g while the 40 mg/kg/day dose group actually lost 110 ± 100 g). Final (day 29) body weight of the does in the high dose group was 6% less than the control. Decreased food consumption accompanied the decrease in body weight with there being 13 to 20% decrease in the 20 mg/kg/day dose group and 24 to 70% decreased in the high dose group. The high dose group also had more does with scant or no feces. There were no abortions. The LOAEL for maternal toxicity is 20 mg/kg/day based on body weight and food consumption decreases. The NOAEL is 10 mg/kg/day.

At 40 mg/kg/day, there were statistically significant ($p < 0.01$) increases in the mean number of ossification sites in the thoracic vertebrae (+3.12%) and ribs-pairs (+3.21%) as well as a decrease in lumbar vertebrae (-6%) and the differences were in excess of or less than the historical control range respectively. These conditions were collectively referred to as an increase in "supernumerary ribs" by the study author and were described as a reversible condition. There were also decreases (not statistically significant) in fetal weight (-9.6% for males and -6.6% for females). The LOAEL is 40 mg/kg/day based on supernumerary ribs and decreased fetal weight. The NOAEL is 20 mg/kg/day.

Classification: This study is classified as ACCEPTABLE/GUIDELINE and satisfies the requirement for a series 83-3 developmental toxicity study in rabbits.

Dose and Endpoint Selected for Risk Assessment: NOAEL = 10 mg/kg/day based on decreases in body weight gain and food consumption at 20 mg/kg/day thiophanate-methyl.

Comments about Study/Endpoint: The decreases in body weight gain and food consumption are considered appropriate endpoints for the population (toddlers and young children) and duration (1-7 days) of concern. Thiophanate methyl data were used as a surrogate for this endpoint for MBC because thiophanate methyl transforms in the environment to MBC following lawn application, and no appropriate endpoint was identified for infants and children in the available MBC studies. The adverse testicular effects noted following a single oral dose of MBC were not considered to be applicable for young children, that have not reached puberty, and are only considered relevant for mature males (i.e., adolescents and adults).

(b). Intermediate--term incidental oral (7 days to several months)

Study Selected: 90 day dog study with MBC

MRID No.: 00091130

Executive Summary:

In a subchronic oral toxicity study in dogs (MRID 00091130), carbendazim (53 % a.i.) was administered in the diet to 4 beagle dogs/sex/dose at dose levels of 0, 100, 500, 2500/1500 ppm for 13 weeks. The 2500 ppm dose was lowered to 1500 ppm due to weight loss. These exposures are equivalent to a time-weighted average of 0, 2.7 (both sexes), 14.4 (M)/11.3 (F), or 40.7 (M)/35 (F) mg ai/kg/day, respectively.

There were no treatment-related effects on mortality, clinical signs, hematologic or urinalysis parameters. Body weight in the high dose males decreased about 6.8%, while all other groups gained weight similar to controls. Food consumption was decreased in the 2500 ppm group, but returned to control values after the dietary level was reduced to 1500 ppm. Adverse liver effects included hepatic cirrhosis with hepatic cell necrosis, tubular collapse and increased fibrous connective tissue around the triads, which were noted in one male and one female of the high-dose group. Other indications of liver effects included elevated alkaline phosphatase (AP) and glutamic-pyruvic transaminase (GPT) activity in high dose males; decreased albumin in high dose males and females; and elevated cholesterol in mid and high dose males and females. There were no other treatment-related changes in clinical chemistry parameters. In the high-dose males, the mean testes weights were reduced 17%, and diffuse testicular degeneration was noted in one male. **The NOAEL and LOAEL for liver and testicular effects are 500 and 1,500 ppm, respectively (equivalent to 14(M)/11 (F) and 41(M)/35(F) mg ai/kg/day, respectively).**

Classification: This subchronic toxicity in dogs is classified as unacceptable-guideline and does not satisfy the guideline requirements 82-1 or 870.3150 for a subchronic oral study in dogs because not all required hematological (i.e., platelet count) and biochemical parameters (i.e., sodium, calcium, phosphorus, bilirubin, aspartate aminotransferase, alanine aminotransferase) were measured. However, HIARC concluded that this study is acceptable for use in risk assessment.

Dose and Endpoint Selected for Risk Assessment: NOAEL = 11 mg/kg/day [rounded to 10 mg/kg/day based on consideration of the short-term oral endpoint] based on adverse liver effects in females at 35 mg/kg/day.

Comments about Study/Endpoint: The adverse liver effects are considered an appropriate endpoint for the population (toddlers and young children) and duration (1 week to several months) of concern. The liver is a known target organ of MBC based on chronic studies. The available data demonstrate that MBC residues are present for up to 14 days following treatment of lawns with thiophanate-methyl.

(c). Dermal Absorption

No dermal absorption studies are available for MBC, therefore, the dermal absorption factor of 3.5% for benomyl should be used.

(d). MBC Short-Term Dermal - (1 - 7 days)

Study Selected: Rat Developmental Study for MBC

MRID No. 40438001 (Alvarez 1987)

Executive Summary: See MBC Acute Dietary for Females 13+

Dose and Endpoint for Risk Assessment: Developmental NOAEL = 10 mg/kg/day for MBC based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations in dams exposed to 20 mg/kg/day (LOAEL). MBC is the primary metabolite of benomyl. Since a dose from an oral study (i.e., oral NOAEL) was selected, a dermal absorption rate of 3.5% should be used for these risk assessments.

Comments about Study and Endpoint: No dermal toxicity studies were located for MBC. The oral (developmental) NOAEL was selected because of the concern for developmental effects seen with MBC as well as the parent compound Benomyl. The HIARC requests that the registrant submit a 21-day dermal toxicity study in rats with MBC. Although developmental effects are not applicable to young children, this endpoint was selected to be protective of the most sensitive population (i.e., pregnant females), and is to be used to assess all dermal exposure scenarios (including children).

In the environment, benomyl rapidly transforms to MBC. Hence, workers and residents are likely to be exposed to MBC following occupational and residential uses of MBC.

Since an oral value was selected, 3.5% dermal absorption factor should be used in risk assessments.

(e). MBC Intermediate -Term Dermal - (7 days to Several Months)

Study Selected: Rat Developmental Study for MBC

MRID No. 40438001 (Alvarez 1987)

Executive Summary: See MBC Acute Dietary for Females 13+

Dose and Endpoint for Risk Assessment: Developmental NOAEL = 10 mg/kg/day for MBC based on decreased fetal body weight and increases in skeletal variations and a threshold for

malformations in dams exposed to 20 mg/kg/day (LOAEL). MBC is the primary metabolite of benomyl. Since a dose from an oral study (i.e., oral NOAEL) was selected, a dermal absorption rate of 3.5% should be used for these risk assessments.

Comments about Study and Endpoint: No dermal toxicity studies were located for MBC. The oral (developmental) NOAEL was selected because of the concern for developmental effects see with MBC as well as the parent compound Benomyl. The HIARC requests that the registrant submit a 21-day dermal toxicity study in rats with MBC. Although developmental effects are not applicable to young children, this endpoint was selected to be protective of the most sensitive population (i.e., pregnant females), and is to be used to assess all dermal exposure scenarios (including children).

In the environment, benomyl rapidly transforms to MBC. Hence, workers and residents are likely to be exposed to MBC following occupational and residential uses of MBC.

Since an oral value was selected, 3.5% dermal absorption factor should be used in risk assessments.

(f). MBC Long-Term Dermal (Several months to lifetime)

Study Selected: Chronic toxicity study in Dogs with MBC (Sherman et al. 1972)

MRID No. 00088333

Executive Summary: See Chronic Dietary for MBC

Dose and Endpoint for Risk Assessment: NOAEL= 100 ppm (2.5 mg/kg/day ai) for MBC based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes at 500 ppm (12.5 mg/kg/day) (LOAEL).

Comments about Study and Endpoint: This dose/endpoint was also used in establishing the MBC RfD. Since a dose from an oral study (i.e., oral NOAEL) was selected, a dermal absorption rate of 3.5% should be used for these risk assessments.

(g). MBC Inhalation Exposure (any time period; 1 Day to Several Months)

Study Selected: 90-day rat inhalation study with Benomyl (Warheit 1987)

MRID No(s). 40399501

Executive Summary See Benomyl Inhalation Exposure

Dose and Endpoint for Risk Assessment: NOAEL= 0.96 mg/kg/day based on olfactory degeneration in the nasal cavity. This dose is lower than the developmental NOAEL for MBC of 10 mg/kg/day, and therefore would be protective of the *in utero* developmental effects of concern.

Comments about Study and Endpoint: There are no inhalation studies available for MBC, therefore, the benomyl inhalation study is used to assess MBC inhalation exposures. For long-term exposures (> several months), HIARC recommends an additional uncertainty factor of 3 be applied to the NOAEL (i.e., MOE = 300).

C. Margins of Exposure for Occupational/Residential Exposures:

A MOE of 100 should be used for all of the occupational risk assessment scenarios with benomyl and MBC because these endpoints were based on NOAELs from animal studies, except for the long-term inhalation exposures, where a MOE of 300 should be used. An additional uncertainty factor of 3 was applied to the subchronic inhalation study to be protective of longer-term exposure more than several months. The MOEs for residential exposure risk assessment scenarios will be determined by the FQPA Safety Factor Committee.

D. Recommendations for Aggregate Exposure Risk Assessments

For both benomyl and MBC **acute** aggregate exposure risk assessments, combine the high end exposure values from food + water for the population of concern (i.e., females 13+, or the general population) and compare it to the appropriate acute RfD.

Short- or Intermediate-Term aggregate exposure risk assessment is not appropriate for benomyl or MBC because the endpoints are different for dermal (testicular effects for benomyl and developmental for MBC), inhalation (respiratory effects), and oral (decreased body weight/food consumption and liver effects for MBC) exposure.

For **Long-Term** aggregate exposure risk assessment, the oral and dermal exposures, which are both based on liver effects, should be aggregated. The dermal exposure should be converted to an oral equivalent dose (using 3.5% dermal absorption) and compared to the oral NOAEL. Inhalation effects are not aggregated because the endpoint is based on respiratory tract effects.

III. FQPA CONSIDERATIONS

1. Neurotoxicity Data

This issue was previously addressed in the December 3, 1997 HIARC Report (HED Document No. 012418), and is discussed below under Determination of Susceptibility and Recommendation for a Developmental Neurotoxicity Study.

2. Determination of Susceptibility.

- (i) There is increased sensitivity of rat fetuses as compared to maternal animals following *in utero* exposure in a prenatal developmental toxicity study in rats for benomyl. Increased sensitivity manifested as developmental anomalies (decreased fetal body weight and ocular and/or cerebral malformations) at doses which were found to be not maternally toxic. For developmental toxicity the NOAEL was 30 mg/kg/day whereas for maternal toxicity, the NOAEL was ≥ 125 mg/kg/day (highest dose tested).
- (ii) There is concern for the developmental neurotoxic potential of Benomyl.
 - a) In a pre-natal developmental toxicity study conducted under Subdivision F Guidelines, malformations of the CNS (e.g., anophthalmia, microphthalmia, and hydrocephaly) were observed in rat fetuses following prenatal exposure to benomyl.
 - b) In addition, there is extensive evidence from the published literature which indicates that benomyl produces CNS anomalies in rats when administered during gestation, including some studies which suggest that this effect is enhanced by dosing in late gestation.
 - c) These concerns are also supported by the evidence of neurotoxic effects in the acute and subchronic neurotoxicity (Subdivision F Guideline) studies
 - d) Developmental neurotoxicity studies with benomyl and MBC are required. The absence of these studies results in uncertainties regarding the evaluation of hazard to infants and children.
- (iii) There is increased sensitivity of rat and rabbit fetuses as compared to maternal animals following *in utero* exposure to MBC, the primary metabolite of benomyl, in prenatal developmental toxicity studies. In the MBC rat study, increased sensitivity manifested as developmental anomalies (decreased fetal body weight and increases in skeletal variations and a threshold for malformations) at doses which were not maternally toxic. For developmental toxicity the NOAEL was 10 mg/kg/day, whereas for maternal toxicity, the NOAEL was 20 mg/kg/day (based on a slight increase in liver weight at 90 mg/kg/day).

In the rabbit developmental study with MBC, increased sensitivity manifested as decreased implantations and litter size, and increased resorptions at 20 mg/kg/day the NOAEL is 10 mg/kg/day. Maternal toxicity was not observed until higher doses of 125 mg/kg/day, based on abortions and decreased maternal body weight; the maternal NOAEL is 20 mg/kg/day.

- (iii) Mutagenicity studies with benomyl and MBC provide evidence of aneuploidy induction following oral dosing in mice. The mutagenicity data support the evidence of developmental anomalies in rats.

3. Recommendation for a Developmental Neurotoxicity Study

BENOMYL

The previous decision by HIARC on December 3, 1997 to require a developmental neurotoxicity study for benomyl was re-assessed based on the registrant's rebuttal Dated April 22, 1998, and re-affirmed by HIARC on June 1, 1999. The following weight-of-the-evidence was considered by the committee:

- The prenatal developmental toxicity study in rats with benomyl demonstrated central nervous system (CNS) anomalies in the fetuses following maternal exposure during gestation. The CNS anomalies included anophthalmia, microphthalmia, and hydrocephaly (MRID No. 00148393 and 0015764).
- A number of other studies on benomyl available in the literature have also demonstrated similar observations (Zeman et al., 1986; Ellis et al., 1987, 1988; Hess et al., 1987; Hoogenboom et al., 1991 and Lu et al., 1994).
- There is a suggestion that administration of Benomyl in late gestation, as opposed to administration only during the period of major organogenesis, enhances the incidences of CNS anomalies in rats (Zeman et al., 1987 and Ellis et al., 1988).
- In mutagenicity studies with benomyl, there is evidence of aneuploidy induction following oral dosing in mice (MRID No. 42911601, 42911602). Mutagenicity data support the evidence of developmental anomalies in rats. Hoogenboom et al. (1991) postulated that the known antitubulin action of Benomyl may impair microtubule formation and produce brain and ocular malformations by disruption of neuronal proliferation and migration.
- In an acute neurotoxicity study a single dose of Benomyl at 2000 mg/kg caused a decrease in motor activity in females along with a decrease in body weight gain. Therefore, the former effect was not considered to be evidence of neurotoxicity. On the other hand, the decrease (6%) in absolute brain weight in males at 500 or 2000 mg/kg was considered to be a possible indicator of neurotoxicity (MRID No 42817003).

- In a subchronic neurotoxicity study in rats, the increased motor activity observed in females given repeated oral administration of Benomyl at 578 mg/kg/day was considered to be indicative of a possible neurotoxic effect in light of FQPA. The Committee noted that functional effects were not measured in this study (MRID No. 43277901).

MBC

The HIARC determined that a developmental neurotoxicity study *is required* for MBC. The following weight-of-the-evidence was considered by the committee:

- Developmental CNS malformations. In a prenatal developmental toxicity study in rats with MBC, treatment-related malformations of the CNS were observed. These included exencephaly, domed head, anophthalmia, microphthalmia and bulged eyes.
- There is increased sensitivity of rat and rabbit fetuses as compared to maternal animals following *in utero* exposure to MBC, the primary metabolite of benomyl in prenatal developmental toxicity studies.
- In mutagenicity studies with MBC, there is evidence of aneuploidy induction following oral dosing in mice (MRID No. 42911602). Mutagenicity data support the evidence of developmental anomalies in rats.

The Committee recommended that highest dose level tested in the developmental neurotoxicity studies should be sufficiently high to demonstrate the CNS defects observed in other studies. A clear difference in fetal response to gavage versus dietary exposure to Benomyl has been demonstrated, with gavage dosing producing anomalies at approximately one-tenth of the dietary level (Kavlock et al., 1982; Chernoff, 1985). This would need to be considered when the protocol is designed and dose levels are selected for the developmental neurotoxicity study. Due to greater exposure concerns for MBC, HIARC would prefer that the registrant give higher priority to conducting the developmental neurotoxicity study for MBC.

The HED FQPA Safety Factor Committee met on June 7, 1999 to evaluate the hazard and exposure data for benomyl and its primary metabolite, MBC, and recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) should be retained at 10x in assessing the risk posed by these chemicals. The FQPA SFC concluded (See memo from B. Tarplee July 1, 1999 HE Do No. 013544) that the FQPA safety factor be retained at 10x for benomyl and its primary metabolite, MBC, due to:

- ▶ evidence of increased susceptibility following *in utero* exposure of benomyl in the prenatal developmental toxicity study in rats;
- ▶ evidence of increased susceptibility following *in utero* exposure of carbendazim, the primary metabolite of benomyl, in the prenatal developmental toxicity study in rats and rabbits; and

- ▶ the need for developmental neurotoxicity study in rats for both benomyl and carbendazim

The Committee determined that 10x FQPA safety factor for benomyl and its primary metabolite, carbendazim, is applicable for the following subpopulations:

- ▶ Females 13-50 since increased susceptibility was demonstrated following *in utero* exposure and
- ▶ Infants, Children (1 - 6 years), and Children (7 - 12 years) due to the uncertainty resulting from data gaps for the developmental neurotoxicity study in rats.

The Committee determined that 10x FQPA safety factor for benomyl and its primary metabolite, carbendazim, is applicable for the following risk assessment scenarios:

- ▶ all risk assessments (acute/chronic dietary and residential scenarios for all durations) since increased susceptibility was seen following *in utero* exposure (which could occur after a single dose) and since there is uncertainty resulting from the need for developmental neurotoxicity study in rats. This study may provide data that could be used in the toxicology endpoint selection for dietary and nondietary exposure risk assessments.

IV. RECOMMENDATION FOR ADDITIONAL STUDIES

The HIARC recommended that the following additional studies be conducted: (1) 870.3200 21-day dermal toxicity study in rats with MBC; (2) 870.6300- Developmental neurotoxicity study in the rat with benomyl; and (3) 870.6300- Developmental neurotoxicity study in the rat with MBC. The rationale for requiring developmental neurotoxicity studies for benomyl and MBC is provided in Section III under "Recommendations for a Developmental Neurotoxicity Study."

V. ACUTE TOXICITY

Acute Toxicity of Benomyl					
Guideline No.	Study Type	% a.i.	MRID #	Results	Toxicity Category
81-1	Acute Oral, Rat	75	00064819	LD ₅₀ = >5000 mg/kg,	IV
81-2	Acute Dermal, Rat	75	243043	LD ₅₀ = >2000 mg/kg,	III
81-3	Acute Inhalation, Rat	50	00097599	LC ₅₀ >4.01 mg/L	III
81-4	Primary Eye Irritation, Rabbit	75	00064820	irritant	II
81-5	Primary Skin Irritation, Rabbit	75	243043	Non-irritant	IV
81-6	Dermal Sensitization, Guinea Pig	not given	050427	mild to moderate dermal sensitizer	N/A
81-7	Delayed neurotoxicity, hen	not given	241930	NOAEL = 2500 mg/kg	N/A
81-8	Acute Neurotoxicity, Rat	97.4	42817003	NOAEL >2000 mg/kg	N/A

N/A Not applicable

VI. SUMMARY OF TOXICOLOGY ENDPOINTS SELECTION: BENOMYL

The doses and toxicological endpoints selected for various exposure scenarios are summarized below:

Summary of RfDs and Toxicological Endpoints for Benomyl			
EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary, Females 13+	NOAEL=30 UF = 100	Increased incidence of microphthalmia at 62.5 mg/kg/day (LOAEL) in pregnant rats given oral administrations of Benomyl at during gestation days 7 through 16.	Rat Developmental Study with Benomyl
Acute Dietary, General Population	NOAEL=25 UF =100	LOAEL=50 mg/kg/day based on biologically significant premature release of germ cells (sloughing) in the testes, and occlusions of the efferent ductules of the testis 2 days postexposure	Single Dose Rat Study (Hess et al. 1991)
Benomyl Acute RfD (Females 13+) = 0.3 mg/kg/day Benomyl Acute RfD (General Population) = 0.25 mg/kg/day			
Chronic Dietary	NOAEL= 12.5 UF= 100	LOAEL=62.5 mg/kg/day based on hepatic cirrhosis, clinical chemistry alterations as well as decreased weight gain and food consumption.	2 year dog study with benomyl
	Benomyl Chronic RfD =0.13 mg/kg/day		
Short-and Intermediate Term Dermal	Dermal NOAEL = 500	LOAEL= 1,000 mg/kg/day based on decreases in relative and absolute testes weights	21 Day Dermal Rabbit Study
Long-Term Dermal *	Oral NOAEL =12.5	LOAEL=62.5 mg/kg/day based on hepatic cirrhosis, clinical chemistry alterations as well as decreased weight gain and food consumption	2 year dog study with benomyl
Short-, Intermediate- and Long Term Inhalation	Inhalation NOAEL= 0.96 (10 mg/m ³)	LOAEL=4.8 mg/kg/day based on olfactory degeneration in the nasal cavity	90 day rat inhalation study

a = Since an oral value was selected, 3.5% dermal absorption factor should be used for route-to-route extrapolation.

VII. SUMMARY OF TOXICOLOGY ENDPOINTS SELECTION: CARBENDAZIM

The doses and toxicological endpoints selected for various exposure scenarios are summarized below:

Summary of RfDs and Toxicological Endpoints for CARBENDAZIM (MBC)			
EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary, Females 13+	NOAEL=10 UF = 100	LOAEL=20 based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations	Rat Developmental Study with MBC
Acute Dietary, General Population	LOAEL=50 UF = 300	Sloughing (premature release) of immature germ cells 2 days postexposure, atrophy of a few seminiferous tubules in one testicle, significant decrease in seminiferous tubule diameter, and slight abnormal growth of the efferent ductules at 70 days postexposure.	Single Dose Rat Study (Nakai et al. 1992)
MBC Acute RfD(Females 13+) =0.1 mg/kg/day MBC Acute RfD(General Population) =0.17 mg/kg/day			
Chronic Dietary	NOAEL= 2.5 UF= 100	LOAEL=12.5 mg/kg/day based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes of dogs	2 year dog study with MBC
	MBC Chronic RfD =0.025 mg/kg/day		
Short-term Incidental Oral Exposure	Oral NOAEL=10	LOAEL= 20 mg/kg/day based on decreased maternal body weight and food consumption.	1997 Rabbit Developmental Study with Thiophanate-methyl
Intermediate-term Incidental Oral Exposure	Oral NOAEL=11 (round to 10)	LOAEL=35 mg/kg/day based on histopathological lesions of the liver characterized as hepatic cirrhosis with hepatic cell necrosis, tubular collapse and increased fibrous connective tissue around the triads, in addition to altered clinical chemistry in both sexes.	90 day dog study with MBC
Short-and Intermediate Term Dermal ^a	Oral NOAEL =10	LOAEL=20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations in dams	Rat Developmental Study with MBC
Long-Term Dermal ^a	Oral NOAEL =2.5	LOAEL=12.5 mg/kg/day based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes of dogs	2 year dog study with MBC
Short-, Intermediate- and Long Term Inhalation	Inhalation NOAEL= 0.96 (10 mg/m ³)	LOAEL= 4.8 mg/kg/day based on olfactory degeneration in the nasal cavity	90 day rat inhalation study

^a = Since an oral value was selected, 3.5% dermal absorption factor should be used for route-to-route extrapolation.

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